Bournemouth University

An evaluation of passive recumbent quantitative fluoroscopy to measure mid-lumbar intervertebral motion in patients with chronic non-specific low back pain and healthy volunteers

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A thesis submitted in partial fulfilment of the requirements of Bournemouth University for the degree of Doctor of Philosophy (PhD)

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Title. An evaluation of passive recumbent quantitative fluoroscopy to measure mid-lumbar intervertebral motion in patients with chronic non-specific low back pain and healthy volunteers.   Fiona Elizabeth Mellor

Abstract

Introduction: The biomechanical model of back pain has failed to find distinct relationships between intervertebral movement and pain due to limitations and variation in methods, and errors in measurement. Quantitative fluoroscopy (QF) reduces variation and error and measures dynamic intervertebral motion *in vivo*. This thesis used recumbent QF to examine continuous mid-lumbar intervertebral motion (L2 to L5) in patients with assumed mechanical chronic non-specific low back pain (CNSLBP) that had been clinically diagnosed. It aimed to develop kinematic parameters from the continuous data and determine whether these could detect subtle mechanical differences by comparing this to data obtained from healthy volunteers.

Methods: This was a prospective cross sectional study. Forty patients with CNSLBP (age 21 to 51 years), and 40 healthy volunteers matched for gender, age and body mass index underwent passive recumbent QF in the coronal and sagittal planes. The patient group completed questionnaires for pain and disability. Four kinematic parameters were developed and compared for differences and diagnostic accuracy. Reference intervals were developed for three of the parameters and reproducibility of two were assessed. The radiation dose was compared to lumbar spine radiographs and diagnostic reference levels were established. Finally, relationships between patient's pain and disability and one of the kinematic parameters (continuous proportional motion CPM) were explored.

Results: Reproducibility was high. There were some differences in the coronal plane and flexion for each kinematic parameter, but no consistency across segments and none had high diagnostic accuracy. Radiation dose for QF is of the same magnitude as radiographs, and there were no associations between patient characteristics of pain and disability and CPM.

Conclusion: Although the kinematic differences were weak, they indicate that biomechanics may be partly responsible for clinically diagnosed mechanical CNSLBP, but this is not detectable by any one kinematic parameter. It is likely that other factors such as loading, central sensitisation and motor control may also be responsible for back pain that is considered mechanical. QF is easily adapted to clinical practice and is recommended to replace functional radiography, but further work is needed to determine which kinematic parameters are clinically useful.

Table of Contents

List of figures

List of tables

Author's declaration

Content from this thesis has been published in the following peer reviewed journals

1. Mellor, F. E., Thomas, P., and Breen, A., 2014. Moving back: The radiation dose received from lumbar spine quantitative fluoroscopy compared to lumbar spine radiographs with suggestions for further dose reduction. *Radiography,* 20(3), 251-257 http://authors.elsevier.com/sd/article/S1078817414000418

2. Mellor, F. E., Thomas, P., Thompson, P., and Breen, A., 2014. Proportional lumbar spine intervertebral motion patterns: A comparison of patients with chronic, non-specific low back pain and healthy controls *European Spine Journal,* (10) Oct
http://link.springer.com/article/10.1007%2Fs00586-014-3273-3

Additionally it has been presented at the following conferences

3. Mellor, F.E., 2014. Back to the Future. Quantitative fluoroscopy versus functional radiographs in the lumbar spine. Invited Keynote Lecture (the William Stripp Memorial Lecture) United Kingdom Radiological Congress. Manchester.

4. Mellor, F.E., 2014. Does your spine move differently if you have mechanical low back pain? Centre for Postgraduate Medical Research and Education. Annual Symposium. Bournemouth University. UK.

5. Mellor, F. E., and Breen, A. C., 2014. Discrimination of biomechanical back pain patient subgroups from continuous intervertebral motion data: A protocol. *Bone & Joint Journal Orthopaedic Proceedings Supplement,* 96-B (Supp 4), 5 Society for Back Pain Research. London. UK.

6. Mellor, F.E., and Breen, A.C. 2013. Measuring low back intervertebral motion patterns with quantitative fluoroscopy. NIHR Statistics Group – Imaging in Translational Research, Pembroke College, University of Oxford. U.K.

7. Mellor, F.E., 2013. Moving back with x-ray vision; intervertebral motion *In vivo* measured with quantitative fluoroscopy. Christchurch Hospital Rheumatology meeting. Christchurch hospital. UK.

8. Mellor, F.E., 2012.Measuring IV-RoM. How, why and clinical examples. State University of New York. Grand Rounds presentation. Syracuse hospital. U.S.A.

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14. Breen, A. C., Teyhen, D. S., Mellor, F. E., Breen, A. C., Wong, K., and Deitz, A., 2012. Measurement of intervertebral motion using quantitative fluoroscopy: Report of an international forum and proposal for use in the assessment of degenerative disc disease in the lumbar spine. *Advances in Orthopaedics*, 1-10.

15. England, A., and Mellor, F. E., 2012. Incidental findings detected during imaging for research purposes. *Radiography,* 18 (3), 150-152.

16. Mellor, F.E., Breen, A., 2009. Objective assessment of spinal motion: The future? *Imaging and Oncology,* 3, 34-41

17. Deitz, A. K., Mellor, F.E., Teyhan, D.S., Panjabi, M.M., Wong, K.W.M., 2010. Kinematics of the aging spine: A review of past knowledge and survey of recent developments, with a focus on patient-management implications for the clinical practitioner. Yue, Guyer, Johnson, Khoo & Hochschuler (eds)

18. Mellor, F. E., Muggleton, J. M., Bagust, J., Mason, W. M. A., Thomas, P. W., and Breen, A. C., 2009. Mid-lumbar lateral flexion stability measured in healthy volunteers by *In vivo* fluoroscopy. *Spine,* 34 (22), E811-E817

Acknowledgements

Glossary

AD	Absorbed dose	The amount of energy that ionising radiation imparts to a given mass of matter
AECC	Anglo-European College of Chiropractic	The host institution and sponsor of this research
AHP	Allied health professions	A wide range of professions (currently 12 in the UK), other than nursing or medicine, relating to healthcare
BMI	Body mass index	$$\mathrm{BMI} = \frac{\mathrm{mass(kg)}}{(\mathrm{height\,(m))}^2}$$
C.I.	Confidence interval	A range of values within which, the observed value may lie.
CI	Chief investigator	The author of this thesis
cIVR	Continuous intervertebral rotation	Intervertebral rotation captured at 15 frames per second
CNSLBP	Chronic non-specific low back pain	LBP that has no known biological or pathological cause
COSHH	Control of substances hazardous to health regulations (2005)	2005 Health and safety regulations which include radiation emissions
CPG	Chronic pain grade	A questionnaire that measures the level of chronic pain (scale 0-4)
CPM	Continuous proportional motion	Intervertebral continuous motion expressed as a percentage.
CPRV	Combined proportional range variance	A mid-range continuous kinematic parameter which is the sum of proportional range variance (PRV) for each direction
CT	Computed Tomography	An ionising medical imaging procedure
DAP	Dose Area Product	Measured in Grays.cm^2 this is the amount of radiation that leaves the x-ray tube measured in a set volume of air. It is a measurement of the absorbed dose (AD)
DICOM	Digital Imaging and Communications in Medicine	A method of standardising medical images to allow viewing on multiple platforms

DRL	Diagnostic reference levels	Upper 1/3 quartile of a range of radiation doses. They can reflect absorbed dose, effective dose or skin entrance dose
ED	Effective dose	The tissue-weighted radiation dose in all specified tissues and organs of the body. The ED represents risk, which the probability of cancer induction and genetic effects.
ESD	Entrance skin dose	The absorbed dose in the skin at a given location on the patient. It includes the backscattered radiation from the patient
Hypermobility		An increase in the range of movement of which a bodily part and especially a joint is capable (Merriam Webster Dictionary). In this thesis it relates to excessive intervertebral motion than would be expected in 95% of the normal population, and is not to be confused with hypermobility syndrome. (Participants with hypermobility syndrome were excluded from this study)
Hypo mobility		A spinal segment which is capable of a smaller range or frequency of movement than would be expected in 95% of the normal population
ICC	Intra class correlations	A measurement of reliability
ICR	Instantaneous centre of rotation	A kinematic measurement from functional or dynamic studies
II	Image Intensifier	Also known as a fluoroscope, although the II is the part of the fluoroscope that produces the radiographic image.
IMRCI	Institute for Musculoskeletal Research and Clinical Implementation	The host institution of the CI
IR(ME)R	Ionising radiation (medical exposure) regulations	UK statutory regulations that state the responsibilities of practitioners working with medical ionising radiation
kVp	kilo Voltage peak	A measure of the speed of radiation that leaves the x-ray tube

IVR	Intervertebral rotation	Rotation between two vertebrae, also called segmental rotation
LBP	Low back pain	Pain between the lower crease of the buttocks and lower border of the ribs
mAs	Milli-amperes per second	An exposure factor that determines image quality and radiation dose.
mIVR	Maximum intervertebral rotation	The range between the minimum and maximum y value measured from continuous intervertebral rotation. (These measurements are not the maximum attainable because trunk bending is restricted to 40°).
SDC	Smallest detectable change	The difference between two scores that indicates a change has occurred (SEM*2)
MRI	Magnetic Resonance Imaging	A non-ionising medical imaging procedure
mSv	Milli-Sieverts	The S.I. unit for measuring effective dose and communicating risk from ionising radiation
NHS	National Health Service	The United Kingdom publicly funded healthcare system
NIHR	National Institute for Health Research	United Kingdom government body that coordinates and funds research for the National Health Service
NZ	neutral zone	A defined zone of mid-range motion in cadaveric spines. Sometimes applied to *in vivo* studies
PRV	Proportional range variance	A kinematic parameter created in this thesis. The variance of the proportional ranges throughout a continuous motion sequence
QF	Quantitative fluoroscopy	Fluoroscopy combined with automated measurements of intervertebral motion
RIDDOR	Reporting of injuries, Diseases and Dangerous Occurrences regulations	2013 Statutory Instrument that regulates the statutory obligation to report deaths, injuries, diseases and dangerous occurrences that take place at work.
RSA	Roentgen Stereophotogrammetric Analysis	An invasive but highly accurate technique used to measure three dimensional vertebral motions *in vivo*.
RMDQ	Roland Morris Disability Questionnaire	A self-administered disability questionnaire in which greater levels of disability are reflected by higher numbers on a 24 point scale.

SEM	Standard error of measurement	Estimates how repeated measures of a person on the same instrument tend to be distributed around the "true" score.
Sensitivity		Sensitivity is the true positive rate (i.e those who have the condition and for whom the test is positive). In this thesis it relates to patients with CNSLBP who also demonstrated abnormal motion. It is complementary to the false negative rate.
Specificity		Specificity is the true negative rate, which is the proportion of negatives that are correctly identified as such (e.g., the percentage of healthy people who are correctly identified as not having the condition). It is complementary to the false positive rate
Tracking templates		Automated measurement of rotation of the vertebral bodies throughout the fluoroscopic sequences was achieved by the manual placement of two templates per vertebral body in the first image. The first template was a four point template that registered the x, y position of the vertebra and the second template register the depth, density and position of each pixel within its border. Throughout this thesis they are collectively called tracking templates
VESC	Vertebral endplate signal changes	An MRI parameter that may indicate early disc degeneration

Chapter 1   Introduction

The purpose of this thesis is to evaluate mid lumbar intervertebral kinematics in the coronal and sagittal planes (see Figure 1-1 p4) using passive recumbent quantitative fluoroscopy (QF) in a group of patients with assumed mechanical chronic non-specific low back pain (CNSLBP) (n=40) which had been clinically diagnosed, and healthy volunteers (n=40). Four kinematic parameters, developed from continuous in vivo intervertebral motion were evaluated, however it is not the intention of this PhD to suggest that QF is a suitable clinical tool as this would require further study into its economic effects against current alternatives, such as flexion –extension radiographs (functional views).

1.1   Organisation of the thesis

This thesis is organised as a series of studies that examine kinematic parameters obtained from continuous motion data (chapter 5 through to chapter 9). A general literature review and overall discussion are presented as separate chapters (2 and 11) and where necessary, individual chapters contain a focussed literature review and discussion.

The contents of each chapter are detailed below.

Chapter 1 provides the rationale for the study and describes the development of the QF method and analyses that led to the research question in this thesis then states the role of the funding source.

Chapter 2 details the research questions, aims and objectives and includes an overall review of the literature associated with mechanical CNSLBP. This focusses on the variation in measurement techniques and outcomes, and the difficulties in defining abnormal intervertebral motion.

Chapter 3 details the passive motion QF methodology and outlines the procedure for data acquisition and analysis.

Chapter 4 features the demographics of both groups (patients (n=40) and controls (n=40)). Groups were matched for gender, age and body mass index (BMI) to reduce the influence of these variables.

Chapter 5 is concerned with the reproducibility of the two *a priori* measurements; maximum intervertebral rotation (mIVR) and initial intervertebral attainment rate,

reporting both intra and inter observer standard errors of measurement (SEM) and intra-class correlations (ICC).

Chapter 6 describes the method of measuring the maximum intervertebral rotation (mIVR) using continuous motion data, and assesses these for differences between groups, diagnostic accuracy, and the creation of exploratory reference limits to define hyper and hypo mobility. Data from an independent yet similar quantitative fluoroscopy (QF) study is presented and used to create independent reference intervals by which to compare both groups from this thesis.

Chapter 7 introduces the measurement of mid-range motion from continuous data, specifically the initial gradient of intervertebral rotation over its corresponding 10° passive table rotation. This is called initial intervertebral attainment rate and is a ratio of the gradient of intervertebral rotation (IVR) to the gradient of passive table rotation. Differences between groups and diagnostic accuracy are assessed, along with the creation of an upper reference limit and an examination of the proportions in both groups that exceed the limit. The clinical usefulness of attainment rate in passive motion and its similarity in concept to the neutral zone (NZ) theory is discussed.

Chapter 8 is an exploration of the measurement of continuous intervertebral rotation (cIVR) patterns and advances the use of reference interval data in Chapter 6 by creating and applying these to continuous data. Differences in the proportions of participants in each group whose motion patterns move outside the reference intervals are statistically analysed, and the proportions also used to calculate sensitivity and specificity..

Chapter 9 builds upon Chapter 8 by presenting proportional continuous motion patterns (CPM). It introduces a new independent kinematic parameter, known as the proportional range variance (PRV), and the combined proportional range variance (CPRV). Differences between groups, and diagnostic accuracy were examined and subsequently published in the European Spine Journal (Mellor et al. 2014b).

Chapter 10 specifies the radiation dose for QF and compares this to the nearest comparators of other QF studies; local data for functional radiography; and published data for AP and lateral radiographs. Suggestions for further dose reduction are given and this work was accepted for publication in Radiography journal (Mellor et al. 2014a). The main body of this publication is reproduced, with additional information on the establishment of local diagnostic reference levels for passive recumbent QF.

Chapter 11 is the overall discussion that brings together the kinematic parameters and evaluates them in light of current and previous research findings. Limitations of the

passive recumbent QF method and limitations of the development of kinematic parameters from continuous intervertebral data are discussed, before suggestions for future research are given.

Chapter 12 is the conclusion to the thesis in light of the overall hypothesis and research questions.

Chapter 13 contains the appendices for each chapter.

1.2   Rationale of the thesis

Chronic non-specific low back pain is poorly understood. It is theorised that mechanical disruptions may play a part although such disruptions may be subtle and are not readily detectable. This is because existing methods are invasive, produce inadequate information, and have poor measurement precision and accuracy. Additionally, there is extraneous variability between and within participants that swamps subtle movement abnormalities and renders them undetectable.

Since the mid 1990' s, a technique called quantitative fluoroscopy (QF) has been in development which uses standardised passive recumbent patient motion during fluoroscopy to reduce the variability that comes from confounders such as uncontrolled muscle contractions, axial loading and fear avoidance behaviour.

This thesis aims to determine if passive recumbent intervertebral motion, measured from QF outputs, is related to CNSLBP when these confounders are removed. If passive recumbent intervertebral motion is different in 'non-specific' back pain in patients and healthy volunteers, this would prove that subtle mechanical disruption can play a role. However it is noted that, by its nature, QF cannot accurately measure axial motion (see Figure 1.1) and this exclusion may provide an incomplete picture of passive in vivo biomechanics in these two groups. It is also noted that the selection of participants with CNSLBP thought to be mechanical is based upon clinical examination and that this may not be an accurate assessment.
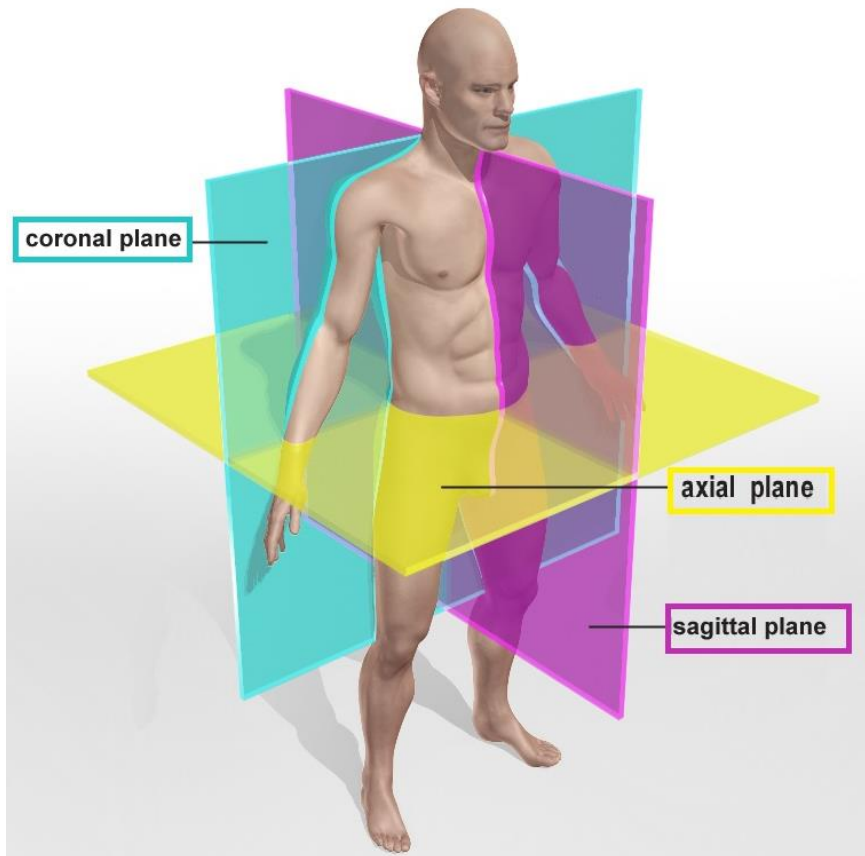
Figure 1-1 Planes of motion

1.3   Background to the PhD

1.3.1 Development of the research question

The research question evolved from observation of continuous motion patterns from two previous recumbent passive QF studies. The first study of healthy volunteers (n=30) provided data from segments in the coronal plane (Breen et al. 2006) which was compared to a subsequent baseline population of patients in a surgical study (n=10) and revealed subjective differences in coronal motion patterns in the surgical population (Mellor et al. 2009). Both these studies were recumbent and only passive motion was studied in this thesis because at this conception of this thesis weight-bearing motion had not been sufficiently studied for reproducibility. Furthermore, cadaveric studies indicate differences in biomechanical subsystems which by their nature are passive. Thus studying passive motion in vivo may help confirm the presence of absence of these in the population.

Ensuing conversations with clinical colleagues guided the study towards investigating passive recumbent motion in CNSLBP because it is commonly believed that this

represents 75% - 85% of sufferers for whom no patho-anatomical cause can currently be found (Deyo 2002a), although this is disputed (Abraham and Killackey-Jones 2002), and because this group includes mechanical LBP, which is defined as pain made worse by movement or position (NICE 2013).

1.3.2 Development of the image acquisition protocol

In this thesis, further standardisation of initial participant position was achieved with L3/4 positioned over the fulcrum of the motion table. As in previous studies (Breen et al. 2006; Mellor et al. 2009), movement entailed the upper body remaining static while the lower body was moved through a range of 80^0 in the coronal and sagittal planes (see Figure 1-2 p6). It was an assumption from previous studies that 80° was sufficient global motion to detect differences in intervertebral motion. Participants lay in a supine or in a lateral decubitus position and knees and hips were flexed to flatten the lumbar lordosis. The development in this thesis separated left and right, flexion and extension into four individual sequences to allow accurate calculation of initial intervertebral attainment rates (Mellor et al. 2009; Breen et al. 2012) (see Chapter 7 p129).
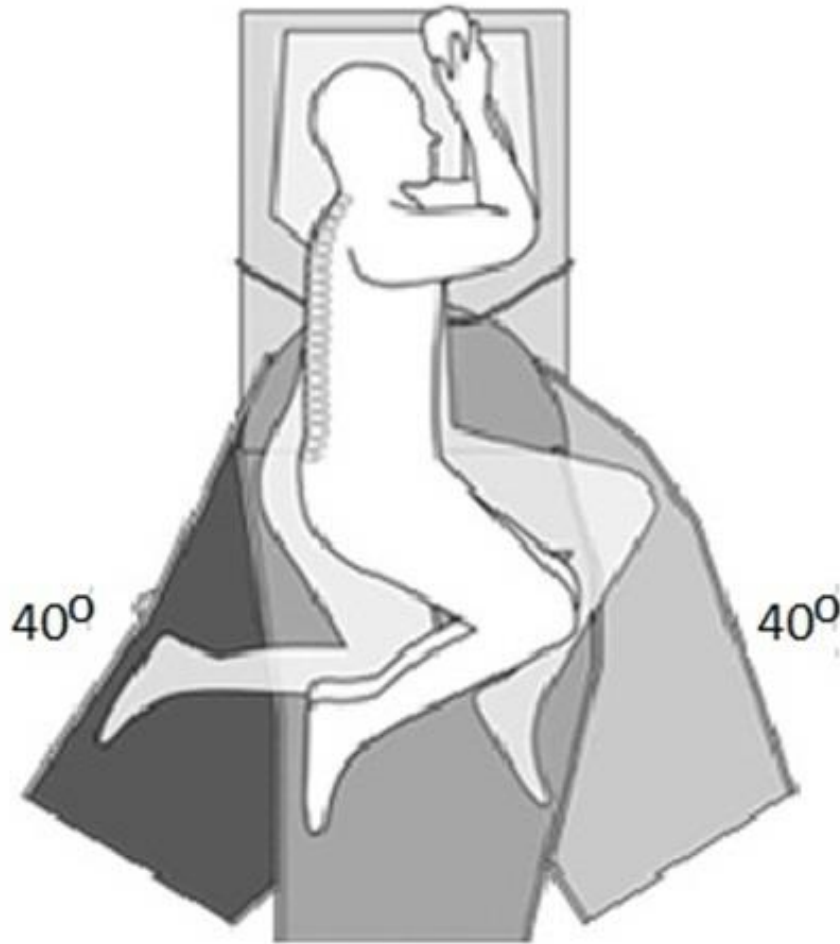
Figure 1-2 Diagram of passive motion table and hip swing protocol for sagittal motion.

1.3.3 Development of the data analyses

Improvements in image acquisition included an upgrade from analogue to DICOM standard digital images on a 1024*1024 matrix. This enabled more information per pixel (contrast, density, depth and sharpness) upon which the automated tracking templates depend. There were also improvements made to the bespoke imaging analysis software, such as improving the graphic user interface and the introduction of parallel processing, which resulted in faster outputs.

A description of all the improvements are beyond the scope of this thesis, but included an option to select 1/6 possible edge enhancements and replace templates at any point throughout the motion if they were deemed to no longer be tracking vertebral bodies. These changes were designed to decrease the probability of tracking template failure and were mainly of benefit for S1, which is not included in this analysis. Table 1.1 p7 shows the improvements made by the team at the IMRCI which were utilised in this PhD.

Changes made for the passive motion QF technology and used in this thesis. These changes were created by the team at IMRCI
1. An upgrade from analogue to DICOM standard digital images on a 1024*1024 matrix
2. Improvement to bespoke imaging software: a) Graphic user interface update   b) Introduction of parallel processing to allow faster output of vertebral angles   c) Edge enhancement of fluoroscopic images   d) Replacement of tracking templates that were not following the vertebral bodies at any point during the sequence
3 Separating coronal motion into separate left and right sequences, and sagittal motion in flexion extension sequences. This allowed the beginning of each sequence to be labelled as zero for the purpose of calculating initial segmental attainment rate (See Chapter 7)
4 Standardising patient positioning so that L3/4 was centred over the fulcrum of the passive motion table

Table 1-1 Changes made to the QF technology by the team at IMRCI and used in this PhD.

The QF procedure is capable of creating translation and instantaneous centre of rotation (ICR) as outputs but, at the start of this thesis, they had not been validated. Hence intervertebral rotation was selected which included *a priori* analyses of the maximum intervertebral rotation (mIVR) and initial intervertebral attainment rate. Exploratory data analyses include the development of reference intervals for continuous intervertebral rotation (cIVR), and an objective measurement for the variability of continuous proportional motion (CPM).

Secondary studies included the measurement of radiation dose and establishment of diagnostic reference levels (DRL's) and the relationship of patient characteristics of pain and disability to continuous proportional motion.

1.4   Role of the funding source

The CI also received funding from the Bournemouth University Santander Travel Award fellowship which facilitated a five day visit to Southern Upstate New York University, Syracuse, USA in 2012.

This study is registered on the UK Clinical Research Network: Portfolio database, UKCRN Study ID: 11478.

Chapter 2   Aims, objectives, and literature review

2.1 Chapter overview

The hypothesis, aims, objectives, and research questions are stated, and the literature pertaining to the measurement of intervertebral motion and chronic non-specific low back pain (CNSLBP) is examined in this chapter.

The relationship between intervertebral motion and CNSLBP remains an enigma. This chapter reviews methods of measuring *in vivo* intervertebral motion and discusses studies that have investigated altered intervertebral motion in CNSLBP and other LBP disorders. However, comparisons across studies are difficult, due in part to the complexities of, and differences between methods.

The literature review begins with the global problem of chronic non-specific low back pain (CNSLBP) and leads into the debate of variability which has plagued back pain research, treatment and diagnosis. The theories and models of back pain that are most pertinent to this thesis are introduced and linked to how these may relate to abnormal motion or 'instability' of the spine. The history of measuring intervertebral motion is presented along with a discussion of techniques for *in vivo* intervertebral motion measurements.

Finally, Quantitative fluoroscopy (QF), the technique used in this study, is introduced along with justification for continuous automated output and a standardised procedure to reduce variability. This could potentially increase the clinical utility of *in vivo* intervertebral motion measurements by identifying the presence of subtle mechanical problems in the passive holding elements such as the discs and ligaments. QF may be a suitable replacement for functional radiographs (weight-bearing static end of range sagittal radiographs, see Figure 2-1 p10) if it can be proven to be reproducible and the kinematic parameters clinically meaningful.
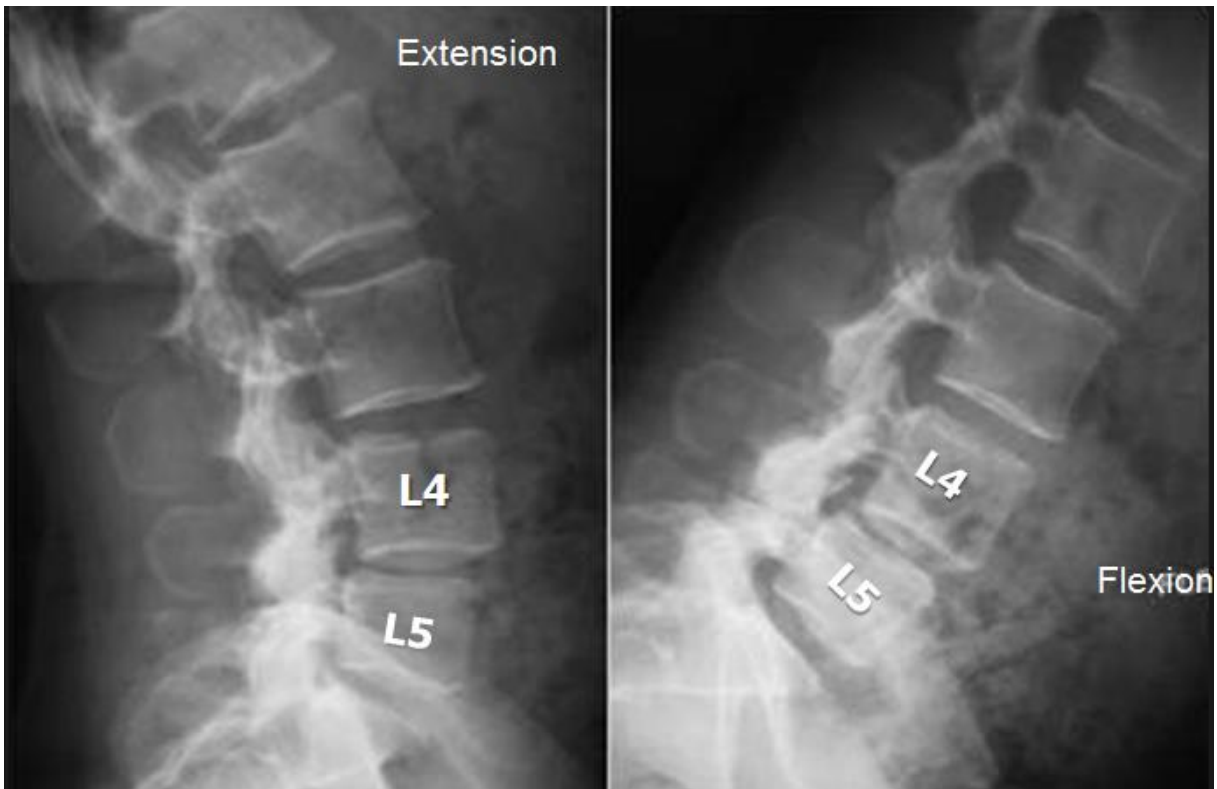
Figure 2-1 Functional radiographic views of the lumbar spine

2.2 Hypothesis

Patients with clinically diagnosed mechanical chronic non-specific low back pain (CNSLBP) will have different passive recumbent intervertebral motion patterns[1] to healthy volunteers.

2.3 Aim

The overall aim of this thesis is to explore the ability of kinematic parameters derived from passive recumbent QF to differentiate between patients with mechanical low back pain and healthy volunteers.

2.3.1 Secondary aims

a) To further validate passive recumbent QF as a clinical tool by developing kinematic parameters for measuring differences in mid spine lumbar intervertebral motion in patients with CNSLBP versus healthy volunteers (Chapters 5 to 9)

b) To establish any relationship between pain and disability for patients and continuous proportional motion (Chapter 9 p159).

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[1] Measureable from passive motion quantitative fluoroscopy

c) To determine the mean radiation dose for passive recumbent QF with comparisons to published and local data for lumbar spine radiographs and calculate the upper 1/3 quartile Dose Area Product (DAP Gy.cm^2) for use as a local diagnostic reference level see Chapter 10 p177).

2.4 Objectives

1. Determine the agreement (standard error of measurement (SEM $_{agreement}$) and repeatability (inter and intra observer intra class correlations (ICCs)) of the analysis of two kinematic parameters (maximum intervertebral rotation (mIVR) and initial intervertebral attainment rate. See Chapter 5 p79).

2. Explore the kinematic parameters for the ability to differentiate between CNSLBP and healthy volunteers (diagnostic accuracy) and differences in mean values between groups, establish reference intervals from healthy volunteers and compare data from both groups to these.

3. Measure the absorbed dose (AD) for passive recumbent QF and compare this to existing standards for lumbar spine and functional radiography.

2.5 Research question:

- Can passive recumbent quantitative fluoroscopy (QF) discriminate between people with clinically diagnosed mechanical CNSLBP and healthy volunteers?

The hypothesis states there will be difference in the motion patterns of patients compared to healthy volunteers. However, it became evident that kinematic parameters derived from continuous data and the determination of abnormal motion required further investigation. Consequently two pre-determined kinematic parameters of maximum intervertebral rotation mIVR and initial intervertebral attainment rate were compared between groups, and two exploratory parameters, continuous intervertebral rotation (cIVR) and continuous proportional motion (CPM) were developed and compared.

Secondary research questions relating to these are detailed below:

2.5.1 Secondary research questions

- How reproducible are the measurements of mIVR and initial intervertebral attainment rate from the image analysis procedures?
- Can any of the kinematic parameters distinguish between patients and healthy volunteers?

- Are there any statistically significant differences for intervertebral motion for each kinematic parameter between groups?
- Do more patients than healthy volunteers exceed reference limits for mIVR, attainment rate and cIVR?

Additionally, because this study uses ionising radiation it was important to understand the risks. Thus another research question was:

- Is the radiation dose for QF of the same magnitude as functional radiographs?

And finally, because data were collected on the pain score and disability of patients, the research question asked was:

- Is there a relationship between pain and disability for the kinematic parameter of CPM?

2.6 Anticipated benefits

Knowing if CNSLBP is mechanical or not will facilitate treatment allowing better selection of stabilisation or mobilisation treatment. However, if the mechanical disruptions are subtle then a method which reduces variability (from muscle and motor control) and decreases measurment errors is required to detect these.

If such differences are detected, it will lead to better decisions and reduce the amount of ineffective treatment. It will also lead to further research to determine the relationships between failure of passive structures and abnormal intervertebral motion in different directions, allowing insights into which tissues are disrupted when passive motion is disordered. Additionally there is the identification of kinematic parameters obtained from continous motion that would be useful for identifying subtle mechanical differences. Such advances in the clinical utility of passive motion QF would require independent replication of these results.

If no differences are found in passive recumbent intervertebral motion then the quest to determine the link between motion and pain should instead focus on muscular and motor control, with an emphasis on loading. If the passive subsystem does not yield differences then explanations within the biomechanical model, for the link between movement and pain, should be sought from chemical and neurological hypotheses.

2.7   Method of literature review

A broad range of literature was examined and included peer reviewed journal papers, conference proceedings and grey literature (unpublished MSc and PhD theses). A number of databases were searched using MeSH terms when necessary and detailed below. Citation alerts were attached to research which used quantitative fluoroscopy or measured *in vivo* intervertebral motion. Additionally individual researchers were contacted to discuss ideas and concepts which developed into an international forum to discuss the use of QF and kinematic parameters (Breen et al. 2012).

Databases included were both public and private; PubMed, Scopus, Web of science, COCHRANE, CINAHL, Embase, Science Direct, Elsevier, Springerlink and Google Scholar. The private databases included an existing Endnote library within the chief investigator's (CI) home institution (the Institute for Musculoskeletal Research and Clinical Implementation IMRCI) and Heritage, which searched the host institution's library. The search dates were from inception until May 2014 and articles were accessed in English, German and French with translation provided by the host institute.

Different keywords and terms were used to identify appropriate literature; an example of a search strategy for a PubMed email alert is given below:

("Joint Instability/classification"[Mesh] OR "Joint Instability/complications"[Mesh] OR "Joint Instability/diagnosis"[Mesh] OR "Joint Instability/ethnology"[Mesh] OR "Joint Instability/history"[Mesh] OR "Joint Instability/mortality"[Mesh] OR "Joint Instability/nursing"[Mesh] OR "Joint Instability/pathology"[Mesh] OR "Joint Instability/physiopathology"[Mesh] OR "Joint Instability/prevention and control"[Mesh] OR "Joint Instability/radiography"[Mesh] OR "Joint Instability/rehabilitation"[Mesh] OR "Joint Instability/surgery"[Mesh] OR "Joint Instability/ultrasonography"[Mesh])) AND "Radiologic Health"[Mesh]) OR ("Radiography"[Mesh] OR "Radiology"[Mesh] OR "radiography "[Subheading])) OR ("Radiography, Dual-Energy Scanned Projection"[Mesh] OR "Technology, Radiologic"[Mesh] OR "Radiographic Image Enhancement"[Mesh])) OR ("Radiology Department, Hospital"[Mesh] OR "Radiographic Magnification"[Mesh] OR "Radiology, Interventional"[Mesh] OR "Radiography, Interventional"[Mesh] OR "Radiography, Abdominal"[Mesh] OR "Radiographic Image Interpretation, Computer-Assisted"[Mesh])) OR "Radiologic Health"[Mesh]) AND ("Lumbosacral Region"[Mesh] OR "Lumbar Vertebrae"[Mesh] OR "Osteoarthritis, Spine"[Mesh] OR "Manipulation, Spinal"[Mesh])

RSS feeds and/ or email alerts were created for the table of contents for relevant journals which included; *The Spine Journal, Spine, European Spine Journal, Clinical*

Biomechanics, Manual Therapy, BMC Musculoskeletal Disorders, Radiology and the Journal of Bone and Joint Surgery. Finally, all retrieved articles were hand searched to identify further references and grey literature.

2.8   Introduction to the literature review

The human spine is strong but not static. The contrary requirements of strength and mobility are met by combining strong individual intervertebral joints allowing limited movement with a large number of motion segments which collectively provide large ranges of movement (Taylor and Twomey 2000)

A motion segment consists of two adjacent vertebral bodies, the intervertebral disc and associated ligaments (Figure 2-2 p14). These allow for intervertebral motion which includes both rotation and translation in three planes (see Figure 2-3 p15), thus the spine is said to have 6 degrees of freedom.

Intervertebral motion has historically signified maximum end of trunk range intervertebral rotation, although some studies have reported rotation at points throughout the bend. More recently, continuous intervertebral motion and three dimensional (3D) studies have reported translation, or combined translation and rotation which yield the instantaneous centre of rotation (ICR).
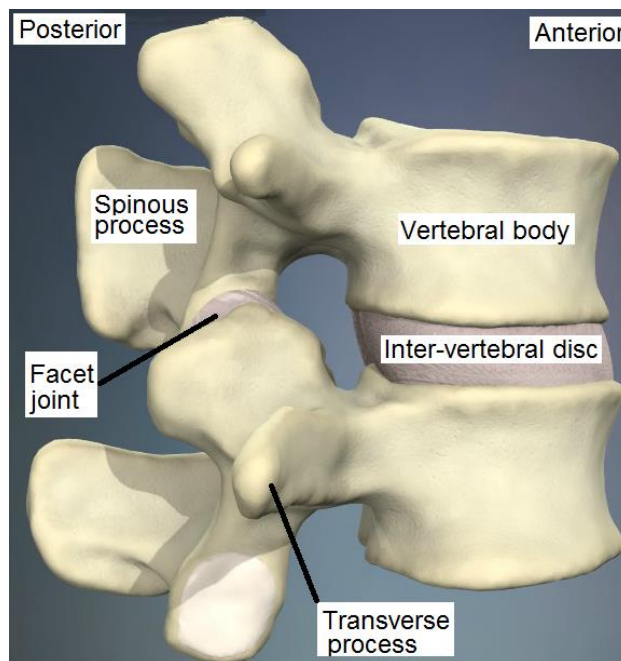
Figure 2-2 A functional spinal unit without muscles or ligaments

For clarity, this thesis relates purely to intervertebral rotation (IVR). The terms used to describe the different kinematic parameters derived from this are below.

- Maximum intervertebral rotation (mIVR). The range between minimum and maximum intervertebral rotation from any point throughout the bend (see Chapter 6 p95 and Figure 5-1 p83). This is not the maximum achievable rotation because trunk rotation is restricted.

- Initial intervertebral attainment rate. The gradient of initial intervertebral rotation during the corresponding 10° of trunk rotation (see Chapter 7 p129)

- Continuous intervertebral rotation (cIVR) The measurement of intervertebral rotation from every point throughout the bend (see Chapter 8 p143)

- Continuous proportional motion (CPM). The percentage contribution of each intervertebral segment at every point throughout the bend (Chapter 9 p159)
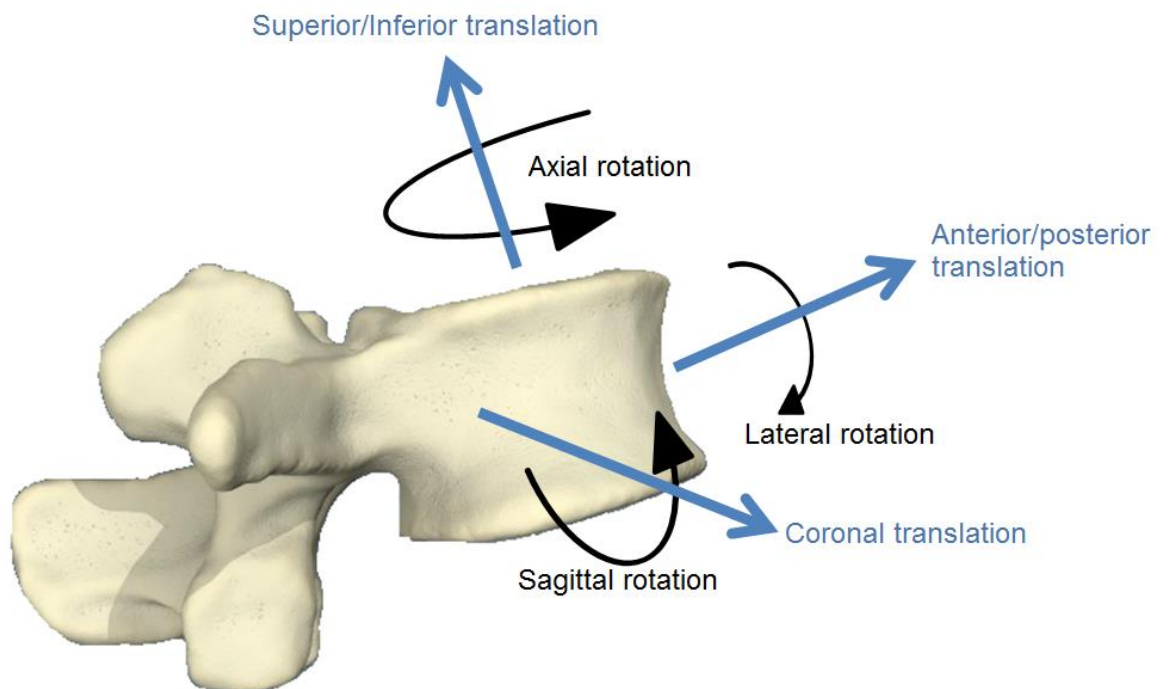
Figure 2-3 Intervertebral range of motion (rotation and translation) in three planes

2.9   The global problem of chronic non-specific low back pain (CNSLBP)

The majority of literature regarding chronic non-specific low back pain (CNSLBP) defines the issue in a global sense and debates the fact that incidence and prevalence have remained constant (Deyo et al. 2006) but costs in terms of treatment and disability have risen (Dagenais 2008; Deyo et al. 2009). Interpretations range from over-diagnosis and over-treatment (Deyo et al. 2009), to links between pain beliefs and ethnic identity (Rogers 2004), and patient expectations for their own healthcare (Main 2010; Georgy 2011).

The approach to CNSLBP is variable with different definitions and criteria used to subgroup and classify (O'Sullivan 2005; Karayannis et al. 2012). The only agreement between researchers and clinicians is that low back pain (LBP) refers to pain between the bottom of the rib cage and the buttock crease (NICE 2009), but that covers a large area of the torso and includes abdominal structures which can be responsible for pain in the same region.

Incidence and prevalence of CNSLBP are variously quoted. Nachemson et al (Nachemson 1985), supported by Coste et al (Coste 1994) noted that only 10% suffer disabling back pain after six weeks, although more recent studies calculated recovery to be only 76% at three months (Grotle et al. 2005) with one third of people still not recovered a year later (Henschke 2006).

Whether pain is labelled as chronic depends upon the definition, which may be based upon its persistence (NICE 2009) such as the number of pain days over the last year or month (Von Korff 1994), or its duration. Nachemson and Bigos provided the definition that pain present for more than three months is chronic, declaring it to be different than recurrent LBP (Nachemson and Bigos 1984), but Von Korff questioned whether pain would also be classed as chronic if it had been present for every day for five months, and then only experienced on 15-50 days in subsequent months (Von Korff 1994).

Non-specific' is used when there is no definitive cause for the pain (N.H.S 2010) although this is contentious. Using disc degeneration to illustrate the point, a degenerate intervertebral disc can be a source of pain (Takatalo et al. 2011; Hughes et al. 2012), but conversely there are a high number of asymptomatic individuals with degenerate discs, ranging from 7% to 85%, with a combined estimate of prevalence of 54% (Endean et al. 2011). Thus when understanding 'non-specific' it is more useful to think of it as a symptom; a vague term concealing a multitude of conditions with different aetiologies (Leboeuf-Yde et al. 1997), including mechanical low back pain.

While the global problem of CNSLBP may be seen in terms of prevalence, incidence and cost; one of the basic issues in care is that of definitions (Dionne et al. 2008). For the purpose of this thesis, pain was labelled as chronic if it was present for three months or more, or if it was present for more than half the days of the previous year (Mason 1994)

2.10 Models of chronic non-specific low back pain

The response to increasing costs has centred upon outcomes of treatment, with a move away from the medicalisation of LBP towards a greater understanding of the role

of psychological, social, occupational and lifestyle dimensions in chronic pain (Deyo et al. 2009).

In the early 1990's there was a paradigm shift from the 'biomedical' or 'patho-anatomical' model of back pain (identifying physical and structural abnormalities as the pain source) towards a multi-factorial bio psychosocial pain syndrome with increasing evidence that chronicity was associated more with psycho-social factors (Waddell 1998). However, O' Sullivan reported an increasing tendency to classify patients with CNSLBP as primarily psycho-social due to a lack of an alternative diagnosis (O'Sullivan 2005) and debate continues regarding the relative contribution of these factors and whether they predispose, or are as a result of chronic pain.

O' Sullivan (O'Sullivan 2005) provides a good overview of models for the diagnosis and classification of low back pain which include: The signs and symptoms model, which encompasses changes in intervertebral spinal movement as well as pain in response to mechanical stress (provocation tests) (Abbott et al. 2009); the mechanical loading model, which states both high and low levels of physical activity are risk factors for LBP (Kopec 2004); and the motor control model, which is impairment of movement due to pain (Dankaerts et al. 2007). These three models appear intrinsically linked because motor control impairments result in ongoing abnormal tissue loading which manifest as changes in intervertebral motion (Sahrmann 2002; Karayannis et al. 2012).

Karayannis et al identified five classification approaches to LBP, all of which have aberrant motion as a component (Karayannis et al. 2012).

1. The mechanical diagnosis and treatment classification of which categories include: Derangement, defined as displacement of the intervertebral disc, dysfunction, where tissue has undergone detrimental change to its function such as scarring, and postural, which assumes joint capsule and ligament ischemia is responsible.

2. The treatment based classification system which uses observation to detect the presence or absence of aberrant motion and uses tests such as the prone instability test (Wadsworth 1988; McGill 2007).

3. The patho-anatomical model which uses signs and symptoms in a hierarchical approach including response to mechanical aggravating factors, which it presumes are linked to structure (Cieza et al. 2004).

4. The movement system impairment model (Sahrmann 2002) which presumes that prolonged postures and repeated movements cause tissue adaptations that eventually lead to a joint developing susceptibility to abnormal motion;

5. The O' Sullivan classification system which separates central and peripheral nerve disorders, acknowledging that peripheral disorders can be influenced by mechanical factors (O'Sullivan 2005).

In contrast to O' Sullivan, Karayannis et al stated that a biomechanical assessment predominated in most of the approaches with limited consideration of the psycho-social aspects (Karayannis et al. 2012). They went on to review the reliability of the clinical tests used within these models and noted that percentage agreement ranged from 50% to 100% (kappa statistic).

It is now well established that CNSLBP is a multi-dimensional problem consisting of patho-anatomical, neurophysiologic, physical and psychosocial factors (Borkan et al. 2002) of which the biomechanical subsystem is just one component. Thus mechanical low back pain is just one aspect of CNSLBP. Additionally it is unlikely to exist to the exclusion of other biological factors, such as chemical pain stimuli, central sensitisation, and abnormal muscle recruitment patterns during active motion (Mellor et al. 2014b).

This thesis lies within the biomechanical framework by focussing on mechanical low back pain and its link to passive recumbent motion. While it is an accepted criticism that focussing on a single dimension limits the validity of the results (O'Sullivan 2005) the counter argument is that each dimension needs to be fully understood before it can be incorporated into the bigger picture.

2.11 The biomechanical model of low back pain

In a summary of spinal biomechanics in 1978, White and Panjabi delineated the terms and definitions relating to measurements of spinal motion. It was acknowledged that these were based on *in vitro* studies and that a more refined model *in vivo* was needed (White and Panjabi 1978).

2.11.1 The Neutral Zone Theory

Their model (see Figure 2-4 p19), the biomechanical hypothesis, demonstrated that continuous intervertebral motion was not linear in cadavers (Panjabi 1992b) and they defined the Neutral Zone and Elastic Zone (EZ and NZ) respectively as;

> "That part of the range of physiological intervertebral motion, measured from the neutral position, within which the spinal motion is produced with a minimal internal resistance. It is the zone of high flexibility or laxity".

> "That part of the physiological intervertebral motion, measured from the end of the neutral zone up to the physiological limit. Within the elastic zone, spinal motion is produced against a significant internal resistance"

Range of motion
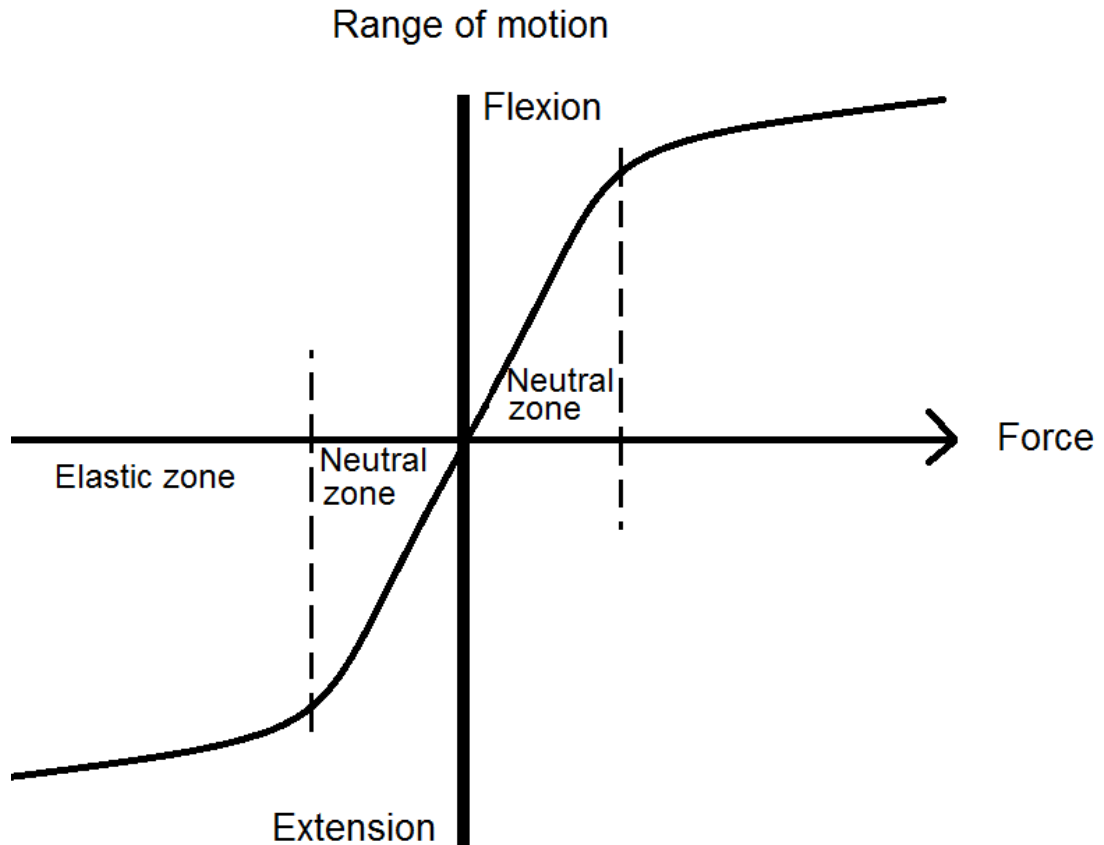
Figure 2-4 Neutral Zone Theory

The theory of NZ has since advanced and Wilke et al (Wilke et al. 1998) in their recommendations for *in vitro* spinal testing parameters defined it as

> "A measurement of the laxity of the spinal specimen. It describes the range over which the specimen moves essentially free of applied loading, for instance under its own weight. NZ is defined as the difference in angulation at zero load between the two phases of motion".

The definition of 'between two phases of motion' makes this essentially different to the zone of minimal resistance (Smit et al. 2011) and, strictly speaking, the NZ is an *in vitro* measurement from cadaveric (Mimura et al. 1994; Crawford et al. 1998; Cannella et al. 2008; Kettler et al. 2011) or animal models (Oxland 1992; Thompson et al. 2003). Although it has been likened to joint laxity *in vivo* (Crawford et al. 1998) (Kumar and Panjabi 1995) and some authors have claimed to measure the neutral zone *in vivo* (Kumar and Panjabi 1995; Hasegewa et al. 2009; Mellor et al. 2009; Breen et al. 2012).

2.11.2 Biomechanical subsystems

In addition to the NZ, Panjabi (Panjabi 1992a) hypothesised that the stability of the spine is dependent upon three subsystems:

- The passive subsystem comprising the vertebrae, discs and ligaments.
- The active subsystem including muscles and tendons that supply force to the spine.
- The neural subsystem which is the motor control aspect of movement.
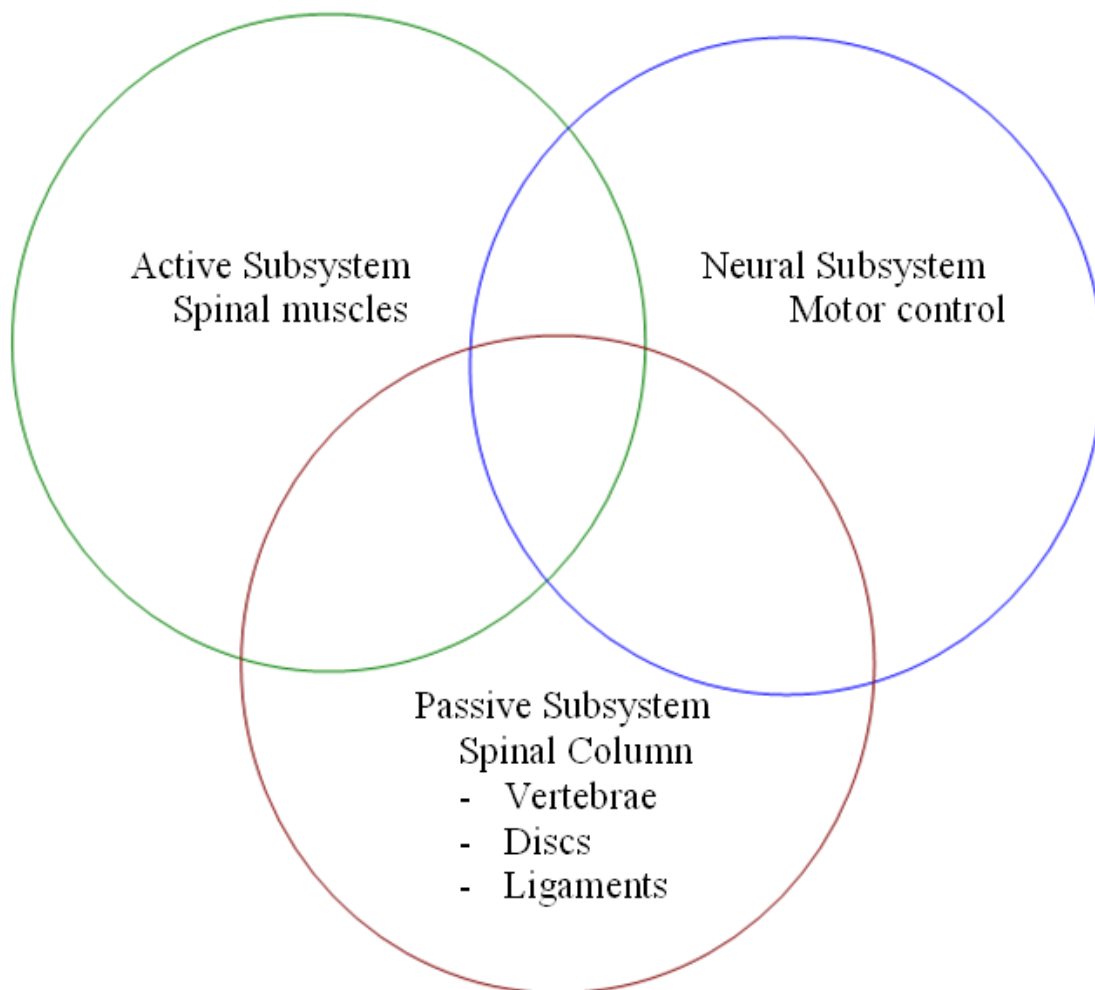
Figure 2-5 Subsystems of spinal motion

It is proposed that any of these subsystems have the potential to generate pain if they become disordered. If this is true previous attempts to measure *in vivo* biomechanics, where the patient begins from an erect weight-bearing posture with no standardisation of range and velocity, would be influenced by all three subsystems and would not accurately identify the link between any one of these and pain (see Figure 2-5 p20).

In contrast, cadaveric studies measure passive motion so information about the passive subsystem *in vitro* is well known, but there are issues with applying these findings *in vivo*. There is a need to study each subsystem independently, as agreed at the first forum for QF study of spinal biomechanics (Breen et al. 2012) and previous work by Breen at al has made this possible by developing a method for measuring the passive subsystem (Breen et al. 2006).

Motion abnormalities noticed in the passive subsystem will likely be due to changes in the passive holding elements and it is theorised that an increased NZ and hypo mobility may respectively represent the early and late stages of disc degeneration. Knutsson suggests the initial stages begin with increased intervertebral motion as the disc loses height, and ends with stiffness as the sclerotic changes and reduced disc height restrict movement (stabilisation phase) (Knutsson 1944). This fits with theories advanced by Kirkaldy Willis and Farfan who described the patho-mechanical sequence of instability (Kirkaldy-Willis and Farfan 1982) which has since been revised by Kettler et al (Kettler et al. 2011).

2.12 Debating instability in the spine

Disordered spinal biomechanics have long been suspected of causing pain although understanding the relationship between abnormal motion and pain have been challenging. While some studies claim there is a relationship between intervertebral motion and disorders thought to cause pain such as disc degeneration (Mimura et al. 1994; Iguchi et al. 2003), facet joint fluid (Rihn et al. 2007), and spondylolysis/spondylolisthesis (Schneider et al. 2005), others have found no relationship (McGregor et al. 2002b; Axelsson and Karlsson 2004).

Clinicians and researchers may label motion disorders as instability, but while some argue this is measureable and provable (Nachemson 1981) others state there is no credible support for such a diagnosis in the literature (McKenzie 2000). Hence instability of the spine remains an enigma. Part of the problem lies in the definition (Farfan and Graceovetsky 1984) which varies for specialists such as radiologists, bio-engineers, and clinicians (Cook et al. 2006; Demoulin et al. 2007; Leone et al. 2007; Reeves et al. 2007; Alqarni et al. 2011) although it seems to be agreed that abnormal intervertebral motion plays a part. Radiological instability is a subject of considerable debate. Static end of range radiographs (functional radiography see Figure 2-1 p10) remain the most common method of measuring this *in vivo* (Leone et al. 2009) but this has low reliability and validity (Hayes et al. 1989; Soini et al. 1991; Boden 1996).However, the ease of accessibility allows its continued clinical and research use.

A biomechanical definition of instability is

> "a lack of resistance to force while the spine is at, or near, the neutral position" (Panjabi 1992b).

This is linked to the neutral zone (NZ) theory and has been validated from cadaveric studies (Crawford et al. 1998; Gay et al. 2008) (see Figure 2-4 Neutral Zone Theory p19), although it has been difficult to demonstrate *in vivo* with functional radiography or other static imaging methods because they take an anatomical snapshot of a physiological problem and cannot measure mid-range motion.

Clinical instability is a concept based on the patients signs, symptoms and examination measures (Cook et al. 2006; Alqarni et al. 2011) such as palpation (Abbott et al. 2009) and 'instability tests' (Wadsworth 1988; Delitto et al. 1995; McGill 2007; Cook and Hegedus 2011). While such tests are uncertain (Lee 1995; Beneck et al. 2005) these measures have received the most attention in the recent literature (Hicks et al. 2003) and led to classification systems for LBP. These 'subgroups' (Brennan et al. 2006) include instability (Delitto et al. 1995; Fritz et al. 2005; McGill 2007), and the relationship between clinical and radiographic instability has been investigated (Fritz et al. 2005) but using functional radiography as the gold standard questions the validity of these results.

Radiographic instability, measured from functional radiographs, also has varying definitions for normal and abnormal rotation and translation in the sagittal plane which is further discussed in the literature review for Chapter 6 (see Defining abnormal intervertebral motion *in vivo*.p97). The lack of consensus on instability is partly down to missing information on spinal motion *in vivo*. Having a universally accepted definition and classification system for instability would help understand this sub category of LBP (Morris 2006) but currently this would be difficult; it is generally accepted that instability consists of both mechanical derangement and clinical consequences (Panjabi et al. 2004) but the relationships between these are still unknown.

2.13 The history of measuring *In vivo* intervertebral motion and its significance in low back pain.

Willheim Roentgen discovered x-rays in 1896 (Roentgen 1896), 60 years after the first study of cadaveric spinal biomechanics was published (Weber and Weber 1836). Within 10 years the disciplines had combined and advanced to a stage where 'radiograms' were used to study the lumbar spine *in vivo* (Fick 1904). This led to disorders thought previously rare, such as spondylolisthesis, to be observed with

increasing frequency and associated with 'chronic backache' (Lovett 1905; Meyerding 1932).

Up until this point all knowledge of lumbar spine biomechanics had come from cadaveric studies (Knutsson 1944; Naderi et al. 2007) but the discovery of x-rays led to biomechanical studies *in vivo* (Brailsford 1934) and one early method, functional radiography (flexion extension radiographs of the lumbar spine in the sagittal plane), remains as a method of studying *in vivo* spinal biomechanics (Stewart Whitley et al. 2005) .

The first functional radiographic studies appeared three decades after the discovery of x-rays (Bakke 1931; Wiles 1935; Guntz 1937; Ferguson 1938) and the oldest surviving functional radiograms depict views from four female acrobats (Welcome Trust 2013). The images were created by Brailsford who, two years later, described a technique to record motion with x-rays at 16 frames per second (Brailsford 1934). He called this direct cine-radiography, but stated that -

> "While the method may be used for the production of teaching films it can never come into general use in radiographic examination".

This was due to the high radiation doses both to the patient and the operator. In the same year, Reynolds gave a demonstration of x-ray cinematography, the forefather of fluoroscopy, and declared it to be safe (Reynolds 1934), but the radiation doses were still high and it did not appear in general use.

Historically, certain motion features were often associated with LBP, such as excessive intervertebral translation (IVT) (Meyerding 1932; Smith 1934; Ferguson 1938). In fact Morgan and King suggested this was the commonest cause, labelling it primary instability (Morgan and King 1957). Other motion features included stiffness (Hasner et al. 1952); hyper mobility (excessive intervertebral rotation (IVR)) (Knutsson 1944; Tanz 1953), and paradoxical motion between vertebrae (motion in the opposite direction to the trunk bend) (Knutsson 1944; Hasner et al. 1952), primarily because these features had not been observed in healthy volunteers.

Gianturco claimed to be the first to study healthy volunteers using functional radiography (Gianturco 1944). They derived values from 20 healthy volunteers and compared these with 35 LBP patients, describing a method of measuring the fulcrum, rather than angles, to depict rotation. Forty two percent of the patients showed abnormal fulcrums when compared to the healthy volunteers and they concluded that lesions such as bony spurs and spondylolisthesis affected intervertebral motion. Of note is that the majority of the patients did not show abnormal motion although this is

not discussed in this paper. False positives and negatives were often ignored or misinterpreted and movement abnormalities in the healthy population were believed to be an indicator of pre-disposition to LBP (Smith 1934; Tanz 1953; Jirout 1957; Mensor and Duvall 1959). Conversely the absence of abnormal movement in those with LBP was interpreted as being due to small changes not demonstrated (Hasner et al. 1952).

From these early studies the link between motion features and pain became difficult to define, with disagreement over which features were significant. The prevalence of stiffness in people without back pain was shown to be 20%, 11% and 15% respectively (Tanz 1953; Jirout 1957; Mensor and Duvall 1959) and Knuttson could not decide whether hyper mobility was pathological or not (Knutsson 1944). Paradoxical motion, only rarely observed, continued to remain an indicator of abnormal motion, as did retrolisthesis (Smith 1934; Knutsson 1944; Fletcher 1947). However Melamed and Ansfield suggested these could be due to inaccurate radiographic positioning, interpretation and anatomical variations (Melamed and Ansfield 1947).

Begg and Falconer concluded that the high daily variance in spine mobility meant absolute measurements were of little value (Begg and Falconer 1949) and Tanz agreed that high variance in people without back pain meant a normal range could not be produced (Tanz 1953). This variation was also evident in groups compared by Aho (Aho et al. 1955) but despite this, relationships between intervertebral motion and back pain continued to be suggested, with reports of abnormal intervertebral motion being associated with features thought to cause pain such as disc degeneration (Knutsson 1944), and spondylolisthesis (Schalimtzek 1954).

Today this view remains contentious with research neither proving nor refuting the theory. In fact, relatively recent advances in medical imaging such as magnetic resonance imaging, (MRI), and computed tomography (CT) have allowed for better visualisation and classification of anatomy and pathology which has led to a revival of the original theory that structural changes affect intervertebral motion, and is somehow linked to mechanical LBP. However, the answer that any one change is responsible for LBP remains inconclusive (Endean et al. 2011).

Such advances in medical imaging have allowed deeper study into the relationships between anatomy, pathologies, and pain, and this has led to greater diagnostic subgrouping of features such as disc degeneration (Pfirrmann et al. 2001). This needs to be balanced against a risk of over-diagnosis and a need to understand the normal aging process (Sheehan 2010). Consequently the National Institute for Health and Care Excellence (NICE) produced guidelines for CNSLBP encouraging the judicious use of MRI within the first 12 months (NICE 2009).

Conversely, these advances have also added to the variation in measurement techniques and outcomes, making comparisons more complex. Most continue to measure intervertebral motion in a static way, which is analogous to a picture describing a scene that a video would depict in greater detail. In contrast, dynamic intervertebral motion has been studied using quantitative fluoroscopy (QF) and kinetic MRI, although the latter is a series of semi-static images so not truly dynamic. These imaging methods are relatively recent and they reignite the interest in the relationship between LBP and the biomechanical model.

The last word is given to Brailsford (Brailsford 1934) who considered the advantages of radiograms (a new technique in 1934) for studying the spine and observed that -

 "It was necessary for individuals to learn the radiological anatomy of normal before attempting to interpret pathology".

The same holds true for new imaging techniques (i.e. kinetic MRI and QF) because, despite nearly 100 years of research into spinal motion, there are still no universally accepted definitions for abnormal motion and how this should be measured.

2.14 Intervertebral kinematic parameters

The majority of intervertebral measurements concentrate on the sagittal plane, the coronal and axial planes have been less studied. This was previously due to errors associated with contamination from coupled motion (associated motion in a different plane) (Vrtovec et al. 2009a) which occurred less in the sagittal plane, although recent imaging advances have begun to address this. Measurements traditionally focused on end of range and include rotation and translation (see Figure 2-3 p15). Recently, continuous intervertebral motion has gained in popularity because it has higher agreement and reliability than traditional methods and provides functional information. Kinematic parameters from this data has included gradients (slopes) of the motion curve (Teyhen et al. 2005; Wong et al. 2006; Mellor et al. 2009) but these have yet to be validated.

2.14.1 Sagittal rotation

A frequently measured kinematic parameter from functional radiographs is sagittal rotation, however, variation and errors are high and there are many ways to calculate the outcome, ranging from superimposition of radiographs (Lee 1995) to complex

computer assisted digital measurements[2] (Yeager et al. 2014). Sagittal rotation is later discussed in Difficulties in measuring intervertebral motion (p31).

2.14.2   Sagittal translation

Morgan and King (Morgan and King 1957) first described a method for measuring static displacement on a single radiograph, which involved drawing a line along the anterior border of the inferior vertebrae. The magnitude of a line then drawn perpendicular from this line to the inferior anterior corner of the superior vertebrae indicated the measure of instability (see Figure 2-6 p26).

Shaffer et al (Shaffer et al. 1990) compared seven different measurements for sagittal translation in a cadaveric model and radiographs. Morgan and Kings' method was the most accurate, and the only one to use the anterior border as a fundamental landmark. Other methods used posterior borders and were affected by posterior margin overlap and projectional errors. Unsurprisingly lower quality films were associated with significantly higher rates of error.

1.7mm
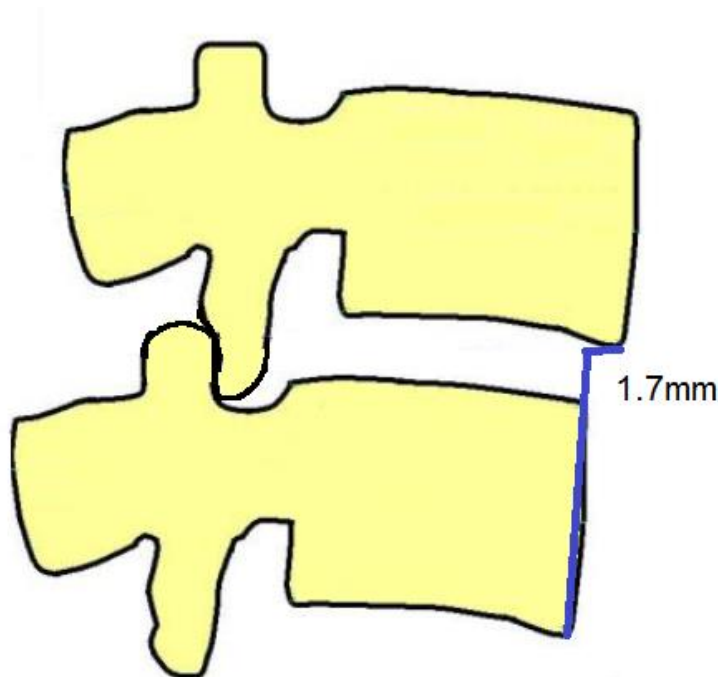
Figure 2-6 Morgan and King's measurement of translation

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[2] Computer assisted digital images are where the observer uses computer software to make measurements on digitally enhanced images, which account for magnification and to some extent out-of-plane rotations..

2.14.3   Instantaneous centres of rotation

In recognition of the fact that rotation and translation occur simultaneously in the sagittal plane, researchers adopted the instantaneous centre of rotation (ICR) as a measurement parameter. This has been variously described as the instantaneous axis of rotation (IAR) (Yoshioka 1990; Breen 2011), centre of rotation (CoR) (Schulze et al. 2011) and the finite centre of rotation (FCR) (Gertzbein et al. 1984). ICRs have been measured in the lumbar spine (Pearcy and Bogduk 1988; Yoshioka 1990; McCane et al. 2006) although most authors have not published accuracy or reproducibility. Instead they have presented average locations in populations, usually in the sagittal plane (Gertzbein et al. 1986; Ogston et al. 1986; Yoshioka 1990; Rousseau 2006)

In each of these studies, with the exception of McCane et al (McCane et al. 2006), Breen (Breen 2011), and Van Mameren et al. (van Mameren 1992), ICRs are manually calculated from functional radiographs. Furthermore, the minimum amount of intervertebral rotation needed to accurately measure rotation in the cervical spine is 7° (Van Mameren 1992). An unpublished study was able to discern ICR's from QF in the lumbar spine with a minimum IVR of 5° (Breen 2011) although reproducibility could not be calculated due to a limited sample size.

While ICR's are useful in a research setting, their clinical implications are little understood thus they are not routinely measured. Additionally they are a function of loading, hence are of no clinical significance if measured from recumbent passive motion.

2.14.4   Lateral rotation

Lateral bending has been more frequently examined than axial rotation (Duncan and Hoen 1942; Hasner et al. 1952; Tanz 1953; Schalimtzek 1954; Cassidy 1976; Dimnet 1978; Weitz 1981; Dupuis et al. 1985; Dvorak et al. 1991a) because it does not rely on 3D imaging. However, due to a belief that the spine cannot bend in the coronal plane without associated coupled axial motion, studies in this plane have been harder to interpret.

Coupled axial motion in lateral bending was first noted in cadaveric studies by Lovett (Lovett 1905) and Roaf (Roaf 1958) and *in vivo* by Tanz (Tanz 1953). Both Lovett and Roaf studied scoliosis but reached different conclusions on whether axial rotation always accompanied lateral bending and Tanz declared it un-measurable with any accuracy from radiograms. Miles and Sullivan (Miles and Sullivan 1961) were the first to point out the different results may be due to the different methods of positioning patients and acquiring images, consequently they used the term lateral bending rather

than lateral flexion in recognition that, if undertaken in the erect position, lateral bending is limited by a combination of abduction and axial twisting due to loading of the facet joints. This is apparent in results from Cosentino et al who showed greater rotation at the L4/5 level when participants lay supine with hips and knees flexed to eliminate the lumbar lordosis (Consentino et al. 1982).

White and Panjabi (White and Panjabi 1990) believe that lateral bending *in vivo* is always associated with a degree of axial rotation which according to Cholewicki et al is 1° for every 2° of lateral flexion (Cholewicki et al. 1996). This coupling motion has led some researchers to declare that 2D measurement of lateral bending will always be subject to error whereas others believe it is a useful measurement (Pearcy 1985; Yamamoto et al. 1989; White and Panjabi 1990; Dvorak et al. 1991a). Pearcy et al (Pearcy 1984) published normative values for lateral bending and coupled rotations, showing little consistency and no correlation between the magnitudes of primary and coupled rotations. This was later supported by research using skin surface measurements (Hindle et al. 1990), and Ha et al, who used the same, concluded again that the magnitude and direction is different for individuals (Ha et al. 2013), although skin markers are not accurate for intervertebral motion (Yang et al. 2008).

Panjabi et al (Panjabi 1989) advanced the work of Miles and Sullivan (Miles and Sullivan 1961) by perceiving that the conflicting results on coupled motion and lateral bending were a function of posture. They demonstrated that a neutral spine produced the least amount of coupled rotation. This had also been demonstrated earlier by Bronfort et al (Bronfort 1984) who used functional radiography in both sitting and standing positions in the coronal and sagittal plane, and concluded that the least amount of coupled motion in lateral bending occurred when sitting with a flattened lordosis. Additionally this technique produced fewer errors in measurement due to the straightening of the lumbar lordosis allowing easier discernment of vertebral bodies. Cholewicki et al (Cholewicki et al. 1996) also demonstrated the effect of posture on coupled motion, and reported that intrinsic mechanical properties, such as the orientation of the facet joints, were equally responsible for the magnitude and direction. Bergmark (Bergmark 1989) demonstrated that an unloaded spine model produced fewer coupled rotations.

In terms of clinical significance, Weitz (Weitz 1981) believed restricted uni or bi lateral flexion was symptomatic of lumbar disc herniation and called this the 'lateral bending sign'. This supported earlier findings by Duncan and Hoen (Duncan and Hoen 1942) although Weitz was more cautious and acknowledged this sign its own was not diagnostic. Goel et al studied coronal motion *in vitro* and observed increased lateral

RoM (rotation and translation) after induced injuries such as partial and total discectomy (Goel 1985). This was supported *in vivo* by Tibrewal et al who also showed hyper mobility in lateral bending following discectomy (Tibrewal 1985).

Despite these findings lateral bending abnormalities have not been pursued thus the clinical utility of motion in the coronal plane is unknown. Pitkanen and Manninen (Pitkanen and Manninen 1994) directly compared sagittal functional radiographs with coronal bending radiographs to correlate the signs of instability. Although the relationship was statistically significant, instability was more readily diagnosed from sagittal views and hence they stated that coronal bending should not be routinely used. They did not discuss the fact signs of instability were only evident in the coronal plane and that this was subjectively analysed.

Given the findings of previous research into the relationship between coupled motion, posture and lateral bending it would be reasonable to conclude that measuring lateral rotation in a supine position with knees bent would reduce the degree of coupled rotation by both reducing the load, and disengaging the facet joints. If a new method with high validity and reliability is available, such as passive recumbent quantitative fluoroscopy (QF), there is a case to re-examine coronal motion and its contribution to CNSLBP and determine the clinical utility of motion defects in this plane.

2.14.5   Axial rotation

Axial motion has gained more popularity with the advancement and accessibility of 3D imaging such as computed tomography (CT) (Rogers et al. 2005) and MRI (Haughton et al. 2002), although these modalities are limited to static, recumbent, and mainly non-load bearing positions. While this is useful for the determination of gross spinal deformities (Newton 2002), they are limited in their usefulness for assessing mid-range biomechanics.

QF is unable to measure axial rotation, although Pearcy et al attempted to measure this with a bi-planar radiographic technique in a group of 20 healthy adult males. They also addressed coupled motion in lateral bending and published their normative values (Pearcy 1984). However, contrasting findings regarding the direction and magnitude of coupled motions have since been reported in the literature (Cholewicki et al. 1996). Bifulco et at tried to reconcile the out-of-plane axial rotations in coronal bending from fluoroscopic images using a CT reconstructed method. Although they reported advancement on current techniques, they also acknowledge further work is needed (Bifulco et al. 2002).

Attempts to mimic the effects of load bearing on axial rotation have included the development of compression devices as a proxy for *in vivo* spinal loading (Cartolari 1997; Kimura et al. 2001; Willen and Danielson 2001). Additionally, open upright MRI scanners have enabled researchers to study axial motion in true physiological states (Saifuddin et al. 2003) although caution in the interpretation of false positives is advised for this relatively new imaging method (Khalil et al. 2012). Upright MRI introduces new challenges for interpreting weight-bearing anatomy and physiology, bringing to mind Brailsford's observation in 1934 (that it is necessary to understand what is normal before attempting to interpret pathology (Brailsford 1934)). Further information on upright MRI is provided on p37, and differences between weight-bearing and recumbent spinal motion are discussed on p32.

The examination of axial motion from 2D images is currently unreliable and improved 3D methods are available, but some of these methods are complicated. Thus they remain in the research arena and their clinical utility and role in CNSLBP is unknown. The addition of new methods by which to study spinal motion provides us with additional *in vivo* information, although the problems of variation in participants, methodology, and outcomes remain. This limits our interpretation of how such differences observed in populations can be translated through to clinical practice. As observed by Vtovec et al in his review of 2D and 3D methods for quantifying axial rotation

> "It is not possible to draw firm conclusions on which method is the most useful from the practical or clinical point of view". (Vrtovec et al. 2009a).

2.14.6   Initial intervertebral attainment rate and laxity

Recognising that the spine is a dynamic structure, semi static and continuous intervertebral motion data have been examined with some kinematic parameters emerging from these techniques. The initial intervertebral attainment rate, also called laxity, was agreed following an international forum about spinal biomechanics. (Mellor et al. 2009; Breen et al. 2012). It is defined as the ratio of the initial gradient of the segment over the first 10° of passive table rotation and is discussed in further detail in Chapter 7 p129.

Laxity is a suggestion for measuring a proxy of neutral zone *in vivo*, agreed upon by the first international forum on QF (Breen et al. 2012). Laxity is based upon studies by Teyhen et al (Teyhen et al. 2007b) and Wong et al (Wong et al. 2004) who measured the attainment rate of the whole outward motion from fluoroscopic sequences. Limiting this measurement to the initial stages recognises that an increased initial attainment

rate would reflect failure of the passive subsystem to maintain stability (see The Neutral Zone p18) akin to joint laxity (Crawford et al. 1998).

Other attempts to measure and describe the NZ both *in vitro* and *in vivo* include mathematical modelling (Magjarevic et al. 2007) and animal models (Oxland 1992; Thompson et al. 2003). Kumar and Panjabi claim to have measured the NZ from *in vivo* axial rotation in humans by using 20° of the full trunk motion as the demarcation between the NZ and the elastic zone (EZ) (Kumar and Panjabi 1995). Despite this, it is not a measurement in standard clinical use although Evans and Breen proposed a new model for mechanically efficient cavitation production during high velocity spinal manipulation, and stated that cavitation would be more efficiently produced when the target joint was distracted within the NZ region (Evans and Breen 2006).

2.15 Difficulties in measuring intervertebral motion

It was recognised early on that reducing errors from functional radiography requires the accurate identification of bony reference landmarks that are affected by radiographic projection (Smith 1934) and magnification. Additionally the quality of the image is paramount (Shaffer et al. 1990). Aho et al proposed one of the early techniques for direct measurement of IV rotation from functional radiography (Aho et al. 1955) but this technique was not widely adopted

A common method of measurement, still used today, is direct comparison of functional radiographs (Dvorak et al. 1991a) and an early proposal by Begg and Falconer (Begg and Falconer 1949) involved tracing the sacrum from the extension view and super-imposing this onto the flexion view although only Tanz (Tanz 1953) studied the inter observer reliability of this method, which was reported as 2°.

The overall issues associated with functional radiography mean that it is neither sensitive nor specific for back pain (Haughton et al. 2002) which has led to investigation of other methods such as CT (see p36) and MRI (see p37). However these suffer from magnification/distortion and image degradation in the presence of metal implants and so are unsuitable for some post-operative studies. Although coupled motion can be measured from with CT and MRI, these methods also suffer from errors associated with manual identification of bony landmarks.

Computer assisted measurements on digital images have reduced errors (Yeager et al. 2014) and Lee reported these, from superimposition of radiographs, as 1^0 when averaging and scaling were used to reduce errors (Lee 2001). Frobin et al comprehensively described a computed method of measuring sagittal displacement independent of errors due to magnification, distortion and coupled movements (Frobin

et al. 1997). Known as Distortion Compensated Roentgen Analysis (DCRA) it is the basis of some computer assisted measurements of 2D spinal motion (Teyhen et al. 2005; Breen et al. 2006; Mellor et al. 2009), and has been adapted for QF (Breen et al. 2012).

The incorporation of computed measurements from digital images rely upon pixel recognition and include cross correlation methods (Muggleton and Allen 1997; Bifulco et al. 2002), active shape contouring methods (Lee et al. 2002), and splines (Brinckmann et al. 2007). Increasingly sophisticated methods combining modelling are now being proposed, although in some instances the model is based on one participant, errors with this technique are not reported (Zheng et al. 2003) and their complexity preclude their clinical use. DCRA is utilised in the analysis of motion in this thesis (see Image processing p62).

Techniques incorporating computed measurements, DCRA and fluoroscopic imaging is known as quantitative fluoroscopy (QF) and has become increasingly sophisticated, automatically identifying vertebral edges (Teyhen et al. 2005) or locating the positions of vertebrae in subsequent images (automated tracking). This reduces inter observer measurement errors (Breen 2011; van Loon et al. 2012; Yeager et al. 2014), thus studies of mid-range motion from QF are providing more data. (Lee et al. 2002; Wong et al. 2004; Breen et al. 2006; Auerbach et al. 2007; Ahmadi et al. 2009; Mellor et al. 2009). However, many of these techniques have not standardised participant positioning, range or velocity and thus continue to suffer high inter and intra subject variation. Additionally there has been inconsistency in the kinematic parameters reported due, in part, to its novelty, although these were addressed at an international forum (Breen et al. 2012).

2.16 Weight-bearing versus recumbent intervertebral motion

Whether *in vivo* measurements are undertaken weight-bearing or recumbent obviously has implications for interpreting the results given that weight-bearing includes axial gravitational loads. The debate between measuring motion from weight-bearing or recumbent is linked to the physiological state. There is presumed to be no muscular or motor influence with recumbent passive motion thus giving a truer picture of the passive holding elements (see Figure 2-5 p20). Conversely weight-bearing studies incorporate all three subsystems so it is difficult to interpret the results.

By convention, functional radiography is generally undertaken in the erect sagittal position, whereas for logistical reasons CT is always undertaken in a recumbent

position; MRI, bi-planar radiography, and QF can be either. For functional radiographs, patients generally stand in neutral before bending forward to their maximum flexion, and then bending backwards to maximum extension (Knutsson 1944; Pennal et al. 1972; Penning and Blickman 1980). Occasionally a stabiliser around the pelvis may be used (Gianturco 1944; Dvorak et al. 1991a) and some studies have started from a sitting position with a flattened lordosis (Smith 1934; Begg and Falconer 1949; Hasner et al. 1952; Allbrook 1957; Jirout 1957; Morgan and King 1957; Mensor and Duvall 1959; Putto and Tallroth 1990; Taghipour-Darzi et al. 2009).

Fritz et al (Fritz et al. 2005) used seated postures for flexion and standing postures for extension, claiming these postures most challenged the segments based on research from Putto and Tallroth who concluded that maximal stressing would yield maximum movement and thus reveal instability (Putto and Tallroth 1990). Conversely others have used recumbent non weight-bearing positions (Tanz 1953; Hanley et al. 1976; Penning et al. 1984; Dupuis et al. 1985; Wood et al. 1994). An attempt to isolate the active and passive motion subsystems was undertaken by Kulig et al in a recumbent MRI study by comparing a PA mobilisation technique (passive) with recumbent extension push ups (active). They declared that active motion produced greater global rotation at 4/5 segments (Kulig et al. 2007), but conversely, they showed it was passive motion that identified a higher proportion of hyper mobile segments. Clearly there is a need to understand further the contributions of the biomechanical subsystems and their relationship to pain and spinal motion.

Passive recumbent motion in healthy volunteers has been demonstrated with sEMG to invoke very little muscular activity (Mellor et al. 2009) and it is hypothesised that controlling the range and speed of trunk motion would also reduce motor contro variability (Breen et al. 2012). This is because the fear of movement may act as check rein against conscious bending (motor control) of the trunk and prompt muscle 'guarding' resulting in under estimation of motion (Nizard et al. 2001). While it may be argued that recumbent passive motion imaging is less representative of the spine under physiological loading, the counter argument is that such a method helps disaggregate the contribution of the passive subsystem. The cause of abnormal motion could then be attributed to the discs, vertebral bodies (including the facet joints) and/ or ligaments.

The debate between passive and active, or recumbent and weight-bearing, motion has recently moved to the MRI arena (see Magnetic Resonance Imaging p37) with the advent of open upright scanners. Authors state that that static weight-bearing MRI is superior to recumbent imaging for visualising anterior spondylolisthesis, posterior disc

bulges (Ferreiro Perez et al. 2007), degenerative changes (Tarantino et al. 2013) and changes in disc height (Shymon et al. 2014). A recent review by the American Agency for Healthcare Research and Quality (AHRQ) noted that potential subgroups of patients may particularly benefit from loading stress MRI but notes that these, as yet, cannot be identified and calls for further research to improve the diagnostic performance and clinical utility of weight-bearing MRI (Chung et al. 2011). It is expected that the body of knowledge in this arena will enlarge as open upright MRI becomes more accessible. Furthermore a comparison of weight-bearing versus recumbent motion is currently underway using QF and a standardised motion protocol, with early indications suggesting that the inclusion of muscular and motor control increases the variability of intervertebral motion (Breen et al 2013).

2.17 Techniques for measuring intervertebral motion *in vivo*

The change from analogue and mechanical technology to digital and virtual modelling has revolutionised how we use medical imaging to measure intervertebral motion, promising greater information about *in vivo* biomechanics. One could argue that using different imaging techniques increases variability in the methods, however, each technique has added further information about the complexity of spinal biomechanics.

2.17.1   Invasive approaches

Invasive approaches include roentgen stereophotogrammetry (RSA) which involve bi-planar radiographic measurements of metal markers implanted within the vertebrae (Olsson et al. 1977; Egund et al. 1978; Selvik 1978, 1989; Johnsson et al. 1990; Selvik 1990; Axelsson et al. 1992; Johnsson et al. 1992; Leivseth et al. 1998; Axelsson and Karlsson 2004). This is most often used for long term follow up following surgery (Halldin et al. 2005) and claims an accuracy of between 0.15^{O} and 1.5^{O} for rotation (Karrholm 1989), although it cannot be used in pre surgical and non-operative studies. It can measure motion in all three planes by utilising bi-planar radiographs of the lumbar spine in six positions. In terms of radiation dose this is equivalent to 12 oblique lumbar spine radiographs which imparts a radiation dose of approximately 27.6 cGy.cm^2. This is more than four times the radiation dose for passive recumbent QF (6.13 cGy.cm^2 see Figure 10-1 p187) although QF only measures motion in two planes (radiation dose is further discussed in Chapter 10 p177).

Direct measurements include percutaneous intra pedicle screws implanted into vertebral bodies (Dickey 2002), or Steinman pins implanted into the posterior spinous

processes (Gregerson and Lucas 1967; Gunzburg 1991). These methods do not utilise radiation but their invasive nature precludes their acceptability as a clinical tool.

2.17.2   Non-invasive approaches

Non- invasive methods include medical imaging, goniometry, clinical tests (Alqarni et al. 2011) and direct palpation (Cook and Hegedus 2011). For precise measurement of intervertebral motion these have high errors and low reliability (Troke 2007; Schneider et al. 2008), which make them unsuitable thus they are not included in this review.

Within medical imaging, modalities for measuring intervertebral motion include bi-planar radiography, computed tomography (CT), magnetic resonance imaging (MRI) which can be static or dynamic, hybrid imaging (combining two or more modalities), ultrasound and quantitative fluoroscopy (QF). The EOS 2D/3D (EOS Imaging, Paris, France is a new imaging modality that claims to measure motion, but further investigation shows it does not take measurements from bending postures; its clinical application is in measuring static IV angles for scoliosis. Its advantage is its low radiation dose and ability to image the whole spine simultaneously without magnification or distortion. While some of these modalities are used predominantly for research, due in part to their availability and ease of use, others, such as CT and MRI are in general clinical use. They claim to measure motion but require a static posture for up to 45 seconds. Hence of these, only fluoroscopy can truly assess dynamic *in vivo* biomechanics when it is combined with quantitative measurement to avoid the errors associated with radiographic images.

2.17.2.1   *Bi planar imaging*

Prior to CT and MRI, bi-planar radiography (images taken orthogonally) was the only method that allowed the 3D reconstruction of the spine *in vivo* (Pearcy 1984; Pearcy and Whittle 1982; Stokes et al. 1981). Pearcy used this technique to comprehensively explain the motion of the lumbar spine in all three planes (Pearcy 1985). However, the logistics of analysis, plus the correct identification of anatomical landmarks, meant it was prone to measurement errors (Dumas et al. 2004). Tibrewal used bi-planar radiography to study motion following discectomy and reported increased motion in the axial and coronal planes (Tibrewal 1985), whereas Stokes and Frymoyer did not find bi-planar radiography useful for detecting instability (Stokes and Frymoyer 1987), and Farfan noted that axial coupling associated with sagittal translation was not detectable with this technique (Farfan 1970).

RSA (previously mentioned) uses bi-planar radiography, has good accuracy, and obviates the need for bony landmark identification, but is invasive. More recently bi-

planar imaging has come to the fore in the clinical domain with the EOS 2D/3D (EOS Imaging, Paris, France) although EOS has not yet been applied to measuring intervertebral motion at the end of trunk range.

Bi-planar imaging has been essential in the development of computer modelling for treatment of deformities such as scoliosis (Humbert et al. 2009; Moura et al. 2011). Simultaneous bi-planar fluoroscopy has also been combined with MRI in a hybrid approach to model the 3D motion of the spine during every day functional activities (Li et al. 2009), or to model the effects of movement on the facet joints in those with spondylolisthesis (Yao et al. 2012). Zheng et al demonstrated that 3D modelling of spinal motion was possible from one single plane lateral fluoroscopic image, which has obvious implications for reducing the radiation dose (Zheng et al. 2011) (see Chapter 10 p177).

If bi-planar imaging is not simultaneous then correction algorithms are available that claim to adjust for possible changes in patient position between acquisitions (Legaye et al. 2009) although the accuracy for rotation was reported to be 1.5^{o} which, arguably, is too high for intervertebral measurements. Additionally Pomero et al detail 3D reconstruction times of between 2-4 hours for a static spine (Pomero et al. 2004) so the algorithms used to model 3D spinal motion would be time consuming, precluding it from routine clinical use.

2.17.2.2 *Computed Tomography*

Computed tomography (CT) was introduced in the 1970's and revolutionised medical imaging, allowing images in all three planes plus 3D reconstructions. It is excellent at demonstrating bony anatomy allowing detailed visualisation of degenerative conditions such as osteophytes and osteoarthritis. Given that these are thought to affect movement, it was only a matter of time before researchers turned their attention to measuring biomechanics. Unfortunately scans can only be undertaken in the recumbent position, and there is a limited area within which to move (the bore diameter). As such the majority of research has focussed on axial rotation, which Rogers found, was as accurate and reliable as RSA (Rogers et al. 2005), later confirmed by Zuhlke (Zuhlke et al. 2009).

Attempts have been made to use CT with a proxy for weight-bearing such an axial compression device (Garcia-Asensio 2003) and, using this method, Cartolari determined that there were abnormalities present in 21% in patients with suspected instability (Cartolari 1997). Passive flexion extension of the facet joints has also been examined with CT in healthy participants although the author notes limitation of trunk motion (Svedmark et al. 2011). Ohtori et al used the term 'kinematic CT' to describe

their acquisition of axial rotation data, but the patient was static during image acquisition (Ohtori et al. 2010). True kinematic CT, with a scan time of 1 second, is available in research settings for smaller joints such as the knee (Muhle et al. 1999) but it has not been translated to the lumbar spine because the radiation dose is too high [3].

CT is better used to demonstrate increased axial rotation in degenerate discs (Blankenbaker et al. 2006) and has proven to be the most accurate imaging technique for non-invasive investigation of axial rotation (Singer et al. 1989; Ochia et al. 2006). It is better at producing images in the presence of metal implants where MRI is limited, which has obvious implications for post fusion imaging. However, similar to functional views, CT can only acquire static images and suffers from accurate identification of bony landmarks (Vrtovec et al. 2009a). Consequently, it not envisaged that CT will routinely play a role in the clinical measurement of intervertebral motion.

2.17.2.3 *Magnetic Resonance Imaging*

The first commercial MRI scanner in the UK was installed in 1983 at the University of Manchester medical school (Carver and Carver 2006) and it evolved rapidly with advances both in hardware and software. As with CT, MRI scans were, until recently, only able to acquire images from a fixed static position. Similar to CT, the majority of MRI scanners also only acquire images from the recumbent position, and their limited bore diameter means full range flexion extension studies are impossible. Unlike CT there is no radiation dose, so this modality is seen as safe providing the patient meets certain criteria regarding metal objects.

The 3D nature of both MRI and CT make them ideal for studying axial rotation (Haughton et al. 2002; Fujii et al. 2007) (see p29) and because both methods reconstruct images in 3D, it is possible to measure movement that may simultaneously occur in more than one plane. However, most clinical MRI spine examinations are recumbent, and imaging the spine in a relaxed position could misinterpret the positional nature of pathology such as spinal stenosis (Saifuddin et al. 2003).

Attempts have been made to image the spine in a recumbent axially loaded position (Danielson and Willen 2001) but these are not truly physiological. Recently, open coil scanners have enabled functional studies in the weight-bearing positions (McGregor et al. 2002b; Jinkins et al. 2003; Beneck et al. 2005; Alyas et al. 2008; Rodriguez-Soto et al. 2013), thus the debate that has run throughout functional radiography concerning

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[3] The radiation dose for all CT examinations is between 0.4mSv to 1.5mSv per head of population per year. This is in contrast to the UK background dose of 2.7mSV per annum (HPA 2008).

active weight-bearing or passive recumbent motion, has moved into the MRI arena (see p32).

McGregor et al (McGregor et al. 2002b) combined both weight-bearing and recumbent MRI to examine recumbent neutral and weight-bearing flexion-extension postures in isthmic or degenerative spondylolisthesis, and compared these to an existing database of healthy volunteers (no back pain). No significant differences in intervertebral motion were found between the three groups. Conversely, a case study by Hedberg et al reports that a weight-bearing flexion extension MRI confirmed the findings of a mechanical and diagnostic assessment which demonstrated a dynamic spinal stenosis that reduced in flexion and increased in extension (Hedberg et al. 2012). Limitations in the acquisition speed of MRI meant only end of range movements (quantity) were compared in McGregor et al's study (McGregor et al. 2002b) whereas Beneck et al were able to obtain images at a rate of 1 per second in their MRI study of intervertebral pain response and PA mobilisation. However, they concluded there was no relationship between intervertebral pain provocation and motion (Beneck et al. 2005).

MRI, while still a relative newcomer to spinal motion *in vivo*, has been established as a workhorse of spinal imaging. The improved image acquisition time in Beneck et al (Beneck et al. 2005) bodes well for future research into spinal motion, but the terminology has yet to be defined. Some authors refer to weight-bearing in the upright position as 'dynamic MRI' (Gedroyc 2008; Tarantino et al. 2013) while others use dynamic MRI to refer to supine images taken in quick succession (1 frame per minute) (Kulig et al. 2004; Landel et al. 2008). Kinetic MRI is used by some to describe weight-bearing flexion extension from an open upright scanner (Miyazaki et al. 2008; Jang et al. 2009; Kong et al. 2009b), whereas Karadimas et al refers to this as positional MRI (pMRI) (Karadimas et al. 2006). Jinkins et al categorised the different acquisition protocols as recumbent MRI (rMRI), Weight bearing neutral MRI (pMRI), and dynamic-kinetic (upright flexion extension) MRI (kMRI.) (Jinkins et al. 2003). Improved access to upright open upright MRI scanners, evolving imaging algorithms enabling faster scan times, and the extra information from all planes, combined with kinetics and no ionising radiation places kinetic MRI in an ideal position to investigate intervertebral motion in the future.

2.17.2.4 Hybrid imaging

Hybrid imaging is a relatively new term within medical imaging and refers to the combination of two modalities into a single new form of imaging often with the potential to demonstrate function or molecular processes within their larger anatomic context (Hricak et al. 2010). The function is most often demonstrated with nuclear medicine,

and this has been used clinically to diagnose the likely cause of low back pain by using a combination of CT and positron emission tomography (PET). Using this approach Agrawal et al reported increased uptake of a metabolically bridging osteophyte at the sacroiliac joint of a patient versus metabolically inactive degenerative changes and stated that the osteophyte was the likely source of pain (Agrawal et al. 2014). In respect to studying intervertebral motion, hybrid imaging often means combining the results from two imaging modalities such as fluoroscopy and MRI (Li et al. 2009; Yao et al. 2012) (see p35), rather than simultaneous acquisition of data. With this method Yao found that patients with degenerative spondylolisthesis showed reduced facet joint rotation, suggesting that this may be a feature of re-stabilisation of the spine as suggested by Knutsson in 1944 (Knutsson 1944).

2.17.2.5   *Ultrasound*

Ultrasound cannot detect bony anatomy and has high operator dependency. However, it is portable, accessible, and safe with no ionising radiation. Hence some researchers have used ultrasound to quantify mechanical parameters of trunk muscles and determine intervertebral stiffness, but they have not found it useful (Desmoulin et al. 2005). Ultrasound has been adapted for 3D global measurements of cervical spine motion (Zebris Medical. 2013) and found to be as reliable as goniometry (Malmstrom et al. 2003), although like goniometry, this technique can only measure global motion.

2.17.2.6   *Fluoroscopy*

Fluoroscopy, the use of low dose pulsed x-ray exposure to provide an 'x-ray video' was initially termed 'cineradiography' and was first used by Fielding in 1956 (Fielding 1956, 1957) to study movement of the cervical spine in healthy adults. Early fluoroscopes imparted a high radiation dose and image quality was poor but this continued to improve and in 1982 Gonon et al used fluoroscopy to measure motion in the lumbar spine, although measurement was not automated (Gonon et al. 1982). Advances in computer and imaging modalities meant that the use of fluoroscopy to measure continuous motion became more achievable and advanced our understanding of biomechanics in both healthy volunteers (Harada et al. 2000; Wong et al. 2004; Mellor et al. 2009) and in disorders such as spondylolisthesis, where motion patterns were reported to be altered (Okawa et al. 1998; Otani 2005).

Fluoroscopy, combined with advanced computer processing algorithms for image analysis, became known as quantitative fluoroscopy (QF). Various methods of measuring kinematic parameters from QF have been proposed, and their reliability or accuracy reported (Cholewicki et al. 1991; Lee et al. 2002; Breen et al. 2006; Taghipour-Darzi et al. 2009; Zhang et al. 2009). Modern techniques can either

automatically identifiy bony landmarks in the initial image (Teyhen et al. 2005) or in subsequent images (Lee et al. 2002; Breen et al. 2006; Wong et al. 2006; Zhang et al. 2009; Yeager et al. 2014) thus reducing operator error. The improved precision upon functional radiography, the ability to measure the mid-range, and the relative availability of fluoroscopy readily lends its use to the clinical setting with a few adaptations to existing equipment.

Lehman distinguishes between simple end range motion and 'higher order' kinematics for measuring the mid-range, which include displacement, velocity and acceleration (Lehman 2004). Quantitative fluoroscopy standardises velocity and acceleration and Lehman noted that a diagnosis based on function, via tools that can quantify dysfunction, could categorize which patients respond best to different therapies, calling for future research into biomechanical assessment techniques that can address this.

However, a limitation of QF is 2D imaging which cannot measure axial motion. Although bi-planar fluoroscopy would overcome this, (see Bi planar imaging p35) such equipment is not readily available within a clinical setting and the methods of analysis and extracting data are complicated. Another limitation is that most studies have unstandardised initial patient positioning, velocity and range, making comparisons difficult (Breen et al. 2012). Justification for examining unstandardised motion is that this accurately reflects the *in vivo* situation, but the individual elements that contribute to the biomechanical control subsystems (see p20) need first to be disaggregated to understand the part they play in intervertebral motion and mechanical LBP. Breen et al (Breen et al. 2006) are the only group to have developed a standardised patient positioning and motion protocol for measuring passive intervertebral motion with QF. It is claimed that there is no muscle interaction in this protocol (Mellor et al. 2009), thus it can examine the passive subsystem by a specially designed passive motion device (see Figure 1-2 p6) which limits out-of-plane rotation and standardises the acquisition of data.

Quantitative passive recumbent fluoroscopy is reported to be accurate to 0.32^o for coronal, and 0.52^o for sagittal plane intervertebral rotation (Breen et al. 2006) with inter observer errors below 1.5^o for rotation and 1.5mm for translation for weight-bearing QF (Cholewicki et al. 1991; Lee et al. 2002; Auerbach et al. 2007; Ahmadi et al. 2009). The passive motion technique reported by Breen et al (Breen et al. 2006) is updated in this thesis (see Procedure p59), as are inter and intra observer and agreement data for maximum passive intervertebral range in the coronal plane. For the sagittal plane these are reported for the first time (see Chapter 5 p79).

Given the ease of availability of fluoroscopy, and its improved accuracy and reliability when combined with quantitative analysis, it is not unreasonable to recommend that QF be used in place of functional radiography in a clinical setting. Indeed this technology is currently being commercialised in the USA and has recently gained FDA 510K clearance for intervertebral motion measurement in both passive and weight-bearing guided motion protocols (Ortho-Kinematics 2014).

In respect to outcomes and considering the limited clinical utility of functional radiographs, if an improved method such as QF can demonstrate a physical problem with intervertebral biomechanics, it lends credibility to the physical treatments based on these (Sahrmann 2002; Abbott et al. 2009; Karayannis et al. 2012). However, it is first necessary to determine the clinical utility of QF by assessing, among other things, its reproducibility, and ability to detect differences between groups. Additionally, it would be useful to determine the diagnostic accuracy of kinematic parameters created from continuous data, (as outlined on p10).

2.18 Limitations in current knowledge and recommendations for further work

The complexities of the relationship between intervertebral motion and CNSLBP render it obscure, in part due to the variation of the methods used to measure motion, their errors and lack of standardisation. This is evident in Figure 2-7 p43 which shows eight kinematic parameters; obtainable from five different non-invasive imaging techniques; with four different initial participant positions, and two different ways of bending. This variability has been recognised by authors, who have called for standardisation of the position of the participant (Rihn et al. 2007), the method of data acquisition (Quinnell 1983; Breen et al. 2012), and agreement and quantification of the variables being measured (Saraste et al. 1985; Breen et al. 2012). This PhD aims to address these by using the method of passive recumbent QF.

There is a need to disaggregate the biomechanical subsystems to understand the differing contributions of each subsystem and to standardise the technique (as above) to reduce measurement variability, which would increase the detection of subtle differences. Finally there is a need to develop kinematic parameters obtainable from continuous data and assess these for use in a clinical setting. One may argue that the introduction of yet another method (QF) will serve only to add to the confusion. However, QF is the only method that can truly measure *in vivo* continuous motion in a reproducible manner by standardising position, data collection and analyses.

Kinematic parameters

- Axial compression
- Sagittal/ coronal rotation
- ICR's
- Translation (vertebral body depth or mm)
- Normalised motion
- Facet joint rotation
- Axial rotation
- Disc height

In vivo data acquisition

- Computed tomography
- Magnetic resonance imaging
- RSA
- Functional radiography
- Quantitative fluoroscopy

Participant positioning

- Static position acquisition at end range or points throughout the bend
- Flattened lordosis non weight-bearing (i.e. hips and knees flexed)
- Natural lordosis non-weight bearing (supine and straight legs)
- Natural lordosis weight-bearing (i.e. standing)
- Flattened lordosis weight-bearing (i.e. seated)
- Continuous motion acquisition
- Guided/limited trunk bends
- Maximum/free trunk bends

Figure 2-7 The various ways of measuring intervertebral motion *in vivo* and how they relate to each other

Chapter 3   Methodology

3.1 Chapter overview

This section outlines the methodological stance and the procedures used to collect passive recumbent QF data and undertake the analyses. Figure 3-1 (p46) is an algorithm of the study from enrolment to data collection and the analysis, and the development of the method is described earlier (see p4) advancing previous research (Breen et al. 2006; Mellor et al. 2009). Ethical considerations, the health and safety of the participants, the sample size calculation, the statement of informed consent, and the recruitment strategy are in this section.

3.1.1 Methodological stance

Research that aims to differentiate between populations may be said to fit within the positivist paradigm, or scientific study. The data in this thesis are quantitative and analyses include reproducibility testing, statistical tests for differences between patients and healthy volunteers, diagnostic accuracy of kinematic parameters, and regression of patient characteristics to motion abnormalities. Previous biomechanical studies have used the positivist paradigm and experimental method, thus the same is chosen to investigate the hypothesis and overall aims in this thesis (see p10).

3.2 Research design

This is an observational prospective cross-sectional study of two cohorts. This design is the most appropriate to compare differences between groups at one point in time.

Healthy volunteers

Patients

Advert and email to all staff and students at the AECC informing them of the study and inviting them to contact the CI

Email to all clinic tutors and interns at the AECC advising them of the entry criteria for patients. CI assessed clinical notes of all patients attending AECC for LBP and contacted those who were suitable.

Database of volunteers name, age, gender, BMI and contact details established

Interested patients completed RMDQ and CPG and given a week to consider involvement. Those meeting criteria for entry contacted and invited to take part

Consent to particpate. Suitable appointment made for data collection

Decline to participate. All identifying details removed

Written informed consent gained. QF examination undertaken

QF data analysed with bespoke tracking algorythm software by CI. Second observer analyses a subset of n = 10 for reproducability

Tracking algorythm failure at one or more vertebral levels between L2-L5. All data removed from study

Reference limits for mIVR, attainment rate, continous motion patterns created from healthy volunteer data n =40

Motion data analysed. Kinematic variables extracted;

- Maximum inter-vertebral rotation (mIVR)
- Initial segment attainment rate
- Continuous motion patterns
--Continuous proprotional motion patterns

Data analysis:
- Differences in means and diagnostic accuracy of mIVR and attainment rate
- Exploration of continous motion reference intervals
- Analysis of continuous proportional range variance
-Radiation dose

Relationship between pain disability and kinematic variables in patients

Figure 3-1 Algorithm of study outline

3.3   Equipment

The equipment used to undertake this study is listed below

- Patient screening questionnaire (appendix Figure 13-5 p238) and reason for clinic attendance questionnaire (appendix Figure 13-6 p239)
- Chronic pain grade questionnaire (CPG) (Von Korff et al. 1992) and 24 item Roland and Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983)
- Image intensifier (II) (Siemens Arcadis Avantic VC10A). Capable of 15 frames per second and a maximum of 120kVp output
- Lead protection for personnel and participants
- Personal radiation monitoring badge
- Paper-work for informed consent and recording of height/weight and exposure factors (appendix Figure 13-8 p241)
- Scales to record participants weight and height measurement apparatus
- Passive motion table and motor capable of recording angle/time (Atlas Clinical Ltd declared conformity under MDD93/42/EEC) (see Figure 3-4 p61)
- Portable hard drive to transfer images from II to computer for analysis
- Matlab V R2007b (The Mathworks Inc) and bespoke software for tracking the vertebral bodies through the motion
- Microsoft works package (Word and Excel) for interpretation of data
- Image J v 1.47 for Windows OS (freely available from http://rsbweb.nih.gov/ij/download.html)
- Statistical software Stats Direct (V2.7.8) and SPSS (V21 IBM computers)
- 2 persons, one of whom is an authorised operator under the IR(ME)R regulations (in this instance the chief investigator (CI)) (The Department of Health. 2000). The second operator was responsible for passive table motion.

3.4   Variables measured

- Maximum intervertebral rotation (mIVR) measured from continuous data
- Initial intervertebral attainment rate over the corresponding 10° of passive table rotation
- Continuous intervertebral rotation (cIVR) patterns in relation to reference intervals
- The variability of continuous proportional intervertebral motion patterns
- Radiation dose (Dose Area Product (DAP) cGY.cm2
- Pain and disability score of patients (CPG and RMDQ)
- Height and weight of all participants.

3.5 Statistical analysis

Statistical analyses were undertaken on demographics and the kinematic variables using SPSS (V21 IBM computers) and Stats Direct (V2.7.8) and are detailed in Table 3-1 (p50) and Table 3-2 (p52).

The level of statistical significance was set at 0.05% for all statistical tests undertaken in this thesis. Differences between groups for age, gender and BMI were assessed with Student's t tests (see Chapter 4 p73). Reproducibility of the kinematic variables mIVR and attainment rate were assessed with the standard error of measurement (SEM $_{agreement}$) and intra class correlations (ICC 2,1) (see Chapter 5 p79).

For mIVR and attainment rate, differences between groups were assessed with independent 2 tailed student's t tests or Mann Whitney U tests (when data were not normally distributed). Diagnostic accuracy was assessed with sensitivity, specificity and area under the curve (AUC), the gold standard being the clinical diagnosis of mechanical low back pain. Additionally for mIVR, upper and lower reference limits were created from healthy volunteer data by calculating $\overline{X} +/- 2SD$ for each level and direction (see Chapter 6 p95).

For initial intervertebral attainment rate only upper reference limits were created (see Chapter 7 p129). The exploratory analysis of cIVR as a kinematic parameter also utilised the principle of upper and lower reference limits by creating them for every 10th of a degree of passive table rotation, (see Chapter 8 p143). Participants with data that exceeded the reference limits were counted as abnormal and differences in these proportions were compared using a Fishers exact 2 tailed test by summation. For cIVR, diagnostic accuracy was calculated from the same proportions using a 2X2 table.

A statistical criticism of the reference interval derivation is that the cut-off criterion for abnormality has been derived from the same data in which the hypothesis of a difference between groups is being tested. To address this for mIVR and attainment rate, an additional analysis was conducted in which the reference intervals were derived from healthy participants. For mIVR these came from from an ongoing independent passive motion QF study which used a different trunk swing protocol (see Chapter 6 p95) and for attainment rate a previously published study (Mellor et al. 2009).

For continuous proportional motion (CPM), a new kinematic variable to capture the variance of the proportional motion patterns was created and called proportional range variance (PRV). This was calculated for each direction and combined for all directions

(combined proportional range variance CPRV). Differences in PRV and CPRV were examined with a Mann Whitney U test, and diagnostic accuracy was assessed with receiver operator characteristics (RoC) that produced sensitivity specificity and area under the curve (AUC), and positive and negative likelihood ratios.

A multiple regression analysis was used to determine any relationship between CPRV and disability or pain in the patient group (see Chapter 9 p159), and the relationship between participant body habitus (gender, height, weight, body mass index (BMI)) and radiation dose was also assessed with a multiple regression analysis (see Chapter 10 p177).

.		Parametric assumptions		Differences between means	
Demographics	Age	Normality Shapiro Wilkes p=0.05	Equality of variance Levine's test p=0.05	Students' t test 2 tailed p=0.05	Mann Whitney U test 2 tailed p=0.05
	Height				
	Weight				
	BMI				
Patients' pain (CPG) Range from 0 – 4 and patients' disability (RMDQ) out of 24		This data is displayed descriptively			
Radiation dose		This data is descriptively described. Effects of participants' demographics on dose were analysed with a multiple linear regression.			

Table 3-1 Statistical tests undertaken on demographic data

Kinematic Variables	Tests of assumptions		Agreement	Reliability	Differences between means		Reference intervals (upper and lower)	Diagnostic accuracy
mIVR	Normality Shapiro Wilkes p=0.05	Homo-geneity of variance Levene's test p=0.05	Standard error of the measurement (agreement) SEM)	ICC 2 way random effects single measures model with absolute agreement (ICC 2,1)	If assump-tions are met: Students t test 2 tailed p=0.05	If assump-tions are not met: Mann Whitney U test 2 tailed p=0.05	Proportions of patients and healthy volunteers exceeding reference limits: Fishers exact test. 2 tailed by summation. P=0.05	Sensitivity and specificity determined by ROC curves, and area under the curve (AUC)
mIVR data from an independent study			n/a	n/a				
Attainment rate			Standard error of the measurement (agreement) (SEM)	ICC 2 way random effects single measures model with absolute agreement				

				(ICC 2,1)				
cIVR reference intervals		n/a	n/a		n/a			Sensitivity and Specificity from the proportions of participants with values out with reference limits
CPM (PRV per direction and CPRV)	Normality Shapiro Wilkes p=0.05	n/a	n/a		Mann Whitney U test 2 tailed p=0.05		n/a	Sensitivity and Specificity determined by ROC curves, and area under the curve (AUC) Negative and positive predictive values

Table 3-2 Statistical analyses undertaken on kinematic variables

3.6   Sample size calculation

A sensitivity of 80% and a specificity of 90% might be thought of as desirable for identifying biomechanical abnormalities in patients and controls. An observed sensitivity of 80% with a sample size of 40 would have a lower 95% confidence interval of 65% and a specificity of 90% would have a lower 95% confidence interval of 77%. Based on the assumption from previous studies of pre-surgical patients, it was estimated that the prevalence of mechanical abnormality in patients and healthy volunteers might be around 60% and 20% respectively, so 40 per group would give the study over 90% power to detect a difference of this magnitude using a two sided 5% level of significance.

3.7   Study population

The overall number of participants in this study was 80, n = 40 patients with CNSLBP and n = 40 healthy volunteers. There was no pre-determined time interval between patients being diagnosed with mechanical CNSLBP and undergoing QF, but the time interval was less than two weeks and it is likely that patients received treatment in this period. The study was performed between September 2009 and September 2013; recruitment commenced 21st April 2010 and ended 27th July 2012. With the exception of seven participants, all underwent 40 degrees of passive motion in each direction [4].

3.7.1 Study setting

All data were collected at one site, the Anglo-European College of Chiropractic (AECC). Bournemouth UK.

3.7.2 Justification of inclusion/exclusion criteria

Inclusion and exclusion criteria are displayed in Figure 3-2 Inclusion criteria, p55 and Figure 3-3 p56. Previous literature was consulted when determining these. The aim was to select patients with CNSLBP who had a primary clinical diagnosis of mechanical LBP and no influence from psychosocial factors such as depression and litigation which are known to increase perceptions of pain and disability (Waddell 1998). The recruitment strategy is displayed in Table 3-3 p57 and justified below.

3.7.2.1   For all participants

Previous studies have identified changes in intervertebral motion due to age (Iguchi et al. 2003; Wong et al. 2004), consequently participation was restricted to those aged between 21 and 51 years. Excluding scoliosis, hyper mobility, prior lumbar spine

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[4] Four patients and one healthy volunteer achieved 30° extension, and one patient and one healthy volunteer achieved 35°.

surgery and/or recent (within the past 12 months) abdominal/pelvis surgery, were chosen to replicate criteria selected by Teyhen et al (Teyhen et al. 2007a), and excluding those who had received a medical radiation exposure of more than eight mSv in the prior two years was to reduce the cumulative radiation burden on participants.

For reasons of informed consent all participants were required to speak English fluently, and because the procedure involved ionising radiation, females of child-bearing age were asked to sign a consent form declaring they were not pregnant. Body Mass Index (BMI) was limited to 30 to reduce the possibility of image quality degradation upon which the algorithms depend, and also to limit the overall radiation dose (which is higher in those with a larger BMI (Mellor et al. 2014a) (see Chapter 10 p177). Consent for general practitioners (GPs) to be informed of participants' involvement was recommended by the National Research Ethics Service UK. However, GPs were not informed of incidental findings without the permission of the participant. An incidental finding was classified as one that warranted further investigation, whereas an anatomical variant would not. An example of the former includes a suspected neoplasm and the latter includes spina bifida occulta (SBO).

3.7.2.2   For patients

Back pain of more than three months duration is labelled chronic (National Institute for Health and Clinical Excellence (NICE) 2009) but 'chronic' pain may also be episodic hence 'more than half the days of the previous year' was added to the definition (Mason 1994). The definition of 'mechanical' is 'aggravated by movement or position' (European Commission 2006; N.H.S 2010), and a positive prone pressure test (where the participant is tender to pressure on the spinous process) was included because it is a symptom of mechanical LBP (Wadsworth 1988; McGill 2007). A score of four or more on the RMDQ was chosen because this is considered the minimum level of disability suitable for inclusion in a major clinical trial (UK BEAM trial team 2004) and is thought to be the minimum score that could reasonably be considered troublesome in chronic musculoskeletal populations (Parsons et al. 2007). A CPG of two or more indicates chronic pain (Von Korff et al. 1992).

Along with scoliosis for all participants, patients were excluded if the reason for their clinically diagnosed mechanical low back pain was due to stenosis, spondylolisthesis, or pathology such as infection. They were also excluded if they had radicular pain[5].

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[5] This was not an exclusion criterion for healthy volunteers and it subsequently transpired that a healthy volunteer was being treated for leg pain that was likely radicular. This is discussed on p208

Inclusion criteria all participants:

- Male and female. Age 21-51yrs (Wong et al 2006)

- Able to understand written information in English.

- Willing to participate and give informed consent.

- Menstruation within last 28 days, or evidence of contraceptive use, or sterility (for females only).

- Consent to GP being informed of inclusion in study.

Patient inclusion criteria

- Back pain of >3m duration or present for more than half the days in the previous year (Mason 1994)

- Chronic pain grade II or higher (Von Korff et al. 1992)

- Aggravated or relieved by movement or position (European Commission 2006; N.H.S 2010)

- Positive prone lumbar spinous pressure test between L2 to L5 (Wadsworth 1988; McGill 2007)

- Score of 4 or greater on the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983)

Control inclusion criteria

- No history of LBP that ceased normal activity for one day in previous year (Mason 1994)

- Negative prone lumbar spinous pressure test

Figure 3-2 Inclusion criteria

All participant exclusion criteria

- Pregnancy

- Known scoliosis

- Mental illness.

- Depression (Arroll et al. 2003)

- Poor understanding of English.

- Abdominal or pelvic surgery within the last 12 months.

- Previous mid-lumbar spinal surgery.

- Body Mass Index (BMI) > 30.

- Medical radiation exposure in the past two years with a dose of greater than eight mSv (defined as CT scan of chest, abdomen or pelvis or interventional procedures

  under radiological control i.e. angiography).

- Current involvement in any other research study.

- Hyper-mobility syndrome.

Patient exclusion criteria

- Pathology such as fracture, infection, neoplasm.

- Spinal stenosis.

- Spondyolisthesis.

- Radicular pain.

- Litigation or compensation pending

Figure 3-3 Exclusion criteria

3.8   Recruitment strategy

A convenience sample was used for both patients and healthy volunteers, and a summary of the recruitment process is given in Table 3-3 p57.

Recruitment strategy	Number approached	Number declined	Number excluded	Number success-fully imaged (%)
Clinic tutors and interns identifying potential patients	Unknown altogether. Twenty consented for transfer of personal details to be passed to the CI	2	7	11 (55)
Patients referred from outside sources	16	4	7	5 (31)
Hand searching new patient notes who indicated low back pain as their reason for consulting	327 patient notes searched. Of these 71 were approached with Chronic Pain Grade (CPG) questionnaires and Roland and Morris Disability Questionnaires (RMDQ). Eight were suitable. Six declined to take part due to time constraints.	6	63	2 (2.8)
Patients who filled in an initial screening questionnaire when they attended the AECC clinic.	229	6	200	23 (10)
NHS patients	Three patients identified. One met criteria	0	2	1 (33)
Healthy volunteers	146	0	0	40 (27.4)

Table 3-3 Summary of recruitment process for patients and healthy volunteers.

3.8.1 Recruitment strategy for patients

The populations from which CNSLBP patients were recruited were:

- Attending the AECC with LBP

- Referred for QF from an external referrer

- Referred from a local NHS physiotherapy department.

The inclusion of local NHS patients from Poole Hospitals NHS Foundation Trust physiotherapy referrals was added following issues with slow recruitment and rigorously applied inclusion/exclusion criteria. This involved gaining 'patient identification centre' approval from the Trust (appendices Figure 13-2 p222) and yielded one suitable patient.

For new patients attending the AECC with LBP, an amendment to the protocol allowed the CI direct access to patient notes to obtain further information on their complaint. Suitable participants were informed and requested to complete the initial questionnaire (appendix Figure 13-5 p238) which included screening for depression (Arroll et al. 2003), chronic pain grade severity (CPG) (Von Korff et al. 1992) and level of disability (Roland and Morris 1983).

To capture returning patients attending the AECC, a clinic attendance questionnaire was handed to all patients over a three month period (appendix Figure 13-6 p239). The CI accessed the notes of those whose primary complaint was CNSLBP and followed the procedure above. Logistics prevented the screening questionnaires being consecutively distributed, but the population was deemed to have been reached when the majority of patients handed the questionnaires reported already having completed them.

Altogether 42 patients were recruited and two had unusable data due to failed analysis of L5 in the sagittal plane.

3.8.2 Recruitment strategy for healthy volunteers

Healthy volunteers were drawn from a self-selected convenience sample of students, staff and visitors to the AECC who answered email or poster advertisements (appendix Figure 13-7 p240). Lectures to undergraduates were also given, and there was a response to word of mouth. Those who were interested contacted the CI and submitted their name, gender, date of birth, height, weight and contact details (email and phone) which were held on a secure excel database. 149 volunteers submitted their details. When a patient was recruited the database was searched to find the closest match for gender, age and BMI. The initial priority was gender, followed by age, +/- 3 years then BMI +/- 2 points. If more than one suitable match was found with these criteria, weight and height (as a deconstruction of BMI) were considered in that order.

3.9 Procedure

3.9.1 Data collection

Participants changed into a radiolucent gown and removed metal artefacts, such as piercings, which could appear in the field of view. Their height and weight were recorded and the procedure was explained, (supplementary videos 1 and 2 demonstrate left and flexion QF acquisition). Following image acquisition participants were given information on how to keep up-to-date with developments in the study and the imaging factors (kVp/time and Dose Area Product (DAP)) were recorded (appendix Figure 13-8 p241).

3.9.1.1 Coronal plane intervertebral data collection

All participants lay supine on the motion table. L3/4 was positioned over the fulcrum of the table and lead protection was placed over thyroid, breast and gonad tissue (see Figure 3-4 p61). An initial fluoroscopic image confirmed the neutral starting position and adjustments were made if necessary before participant's knees were supported by a cushion to flatten the lumbar lordosis. This reduced coupled motion and allowed better visualisation of the L5 vertebral body in the radiographic images (see p27). Participants practised 40° of passive motion in 10° increments and a fluoroscopic image was taken when the table was at 40° to ensure all vertebrae remained in the field of view with no out-of-plane rotation. The imaging sequence began with a countdown to coordinate fluoroscopy and table motion. Image acquisition was 15 frames per second, and the exposure factors (kVp and mAs) were determined by the ionising chambers of the intensifier, which were locked to maintain the imaging quality. The above procedure was then repeated for movement to the right.

3.9.1.2 Sagittal plane intervertebral data collection

Following left and right data acquisition, patients were positioned as for a lateral lumbar radiographic spine (Stewart Whitley et al. 2005). Lead protection was placed as before, and L3/4 matched to the fulcrum of the table. Additionally, for sagittal data lead screening was attached to the back of the patient's gown to reduce the artefacts caused by radiographic flare. Adjustments were made to patient positioning if out-of-plane rotation occurred. In extension it was noted that seven participants (five patients and two healthy volunteers) rotated out-of-plane at 40°. In these instances the overall table motion was reduced to a point (35° or 30°) where the out-of-plane motion did not occur and all the data were included in the analysis.

3.9.1.3 *Trunk motion data collection*

The proxy for trunk motion was passive table rotation and this was measured using a voltmeter connected the table's motor and calibrated with a protractor to match the range and timing of the 40° motion sequences. The data points were later filtered for each participant to match the intervertebral data. This allowed intervertebral motion and table motion to display graphically, with table motion on the x axis and intervertebral rotation on the y axis (see Figure 3-11 p69). Measurements for maximum intervertebral rotation (mIVR), initial intervertebral attainment rate, continuous intervertebral rotation (cIVR) and continuous proportional motion (CPM) were taken from this. It is acknowledged that the mIVR are not the maximum value attainable due to the standardisation of trunk motion to 40^{0}.
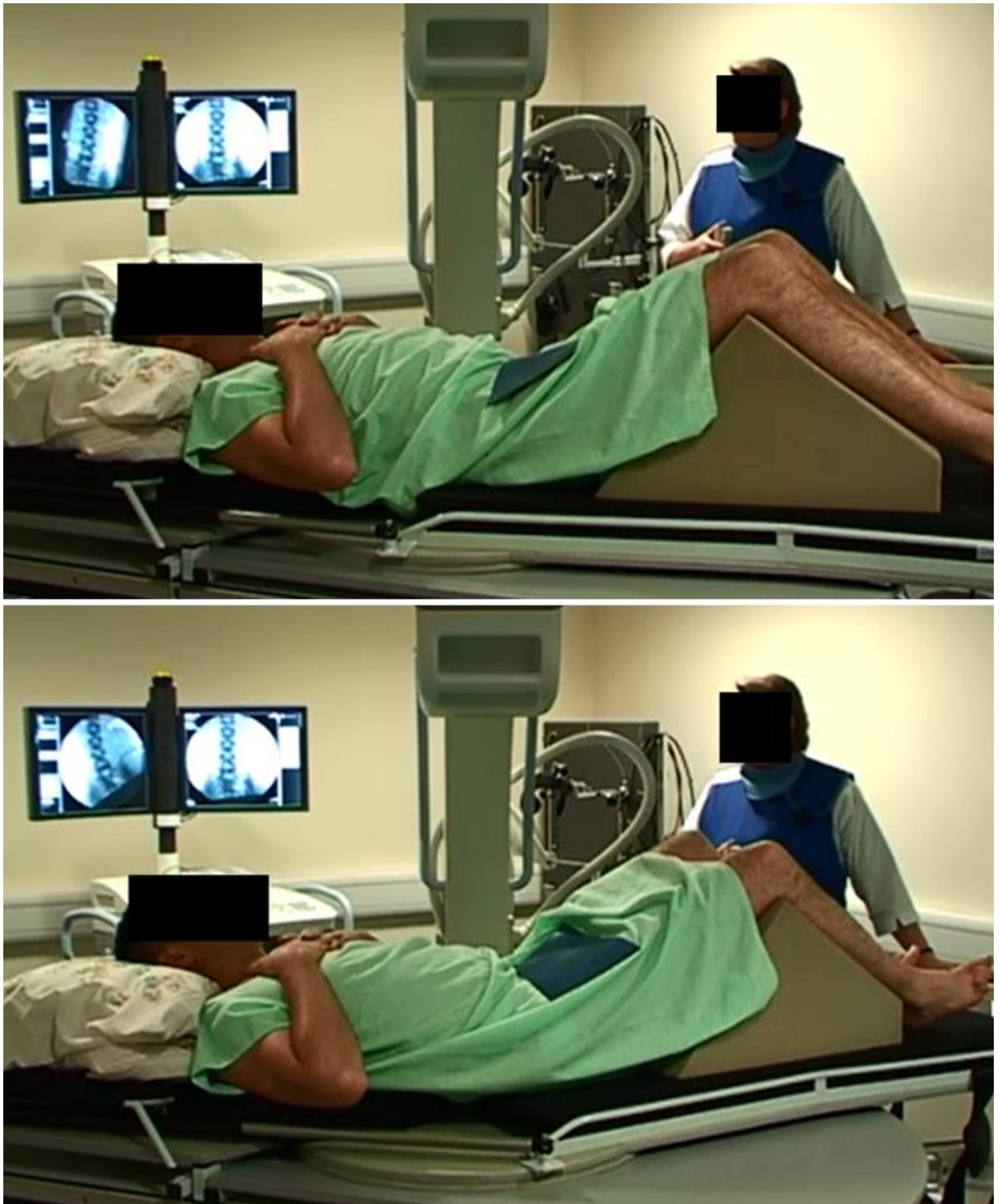
Figure 3-4 Passive motion table at neutral and 40°

3.9.2 Examination of incidental findings/anatomical variants and disc degeneration

Each sequence was examined for the presence of incidental or anatomical variants by a qualified chiropractor trained to interpret medical images, and these are represented in Table 4-2 p75; they were not verified by a second observer. It was beyond the scope of this analysis to examine differences between motion patterns and anatomical variants due to the small numbers of these occurring in the sample.

The exploration of the grading of disc degeneration on fluoroscopic sequences was undertaken by two independent experienced observers (a professor of musculoskeletal health care and a professor of rheumatology), who viewed both the AP and lateral fluoroscopic sequences on a standard personal computer. This was not a formal study of agreement so the conditions were not tightly controlled. Furthermore, each observer was asked to determine any degeneration between L2 to L5 on a scale of 0 to 4 (it was not necessary to specify which level), with 0 representing no degeneration and 4 representing the most severe degeneration (Kellgren and Lawrence 1958). Each observer was double blinded and agreement was analysed with a Cohen's kappa statistic ($p=0.05$).

3.9.3 Image processing

The fluoroscopic sequences were transferred to a desktop computer via an external hard drive. Each fluoroscopy sequence typically contained up to 250 individual DICOM images and was 500 megabytes (MB) in size (see supplementary videos 3 and 4 detailing fluoroscopic sequences in left and flexion bending). Individual images in the sequences were extracted using Image J software, creating individual .tif images that were approximately 1.5MB (Figure 3-5 p63). These images underwent an operator-defined series of edge enhancements using bespoke software written in Matlab (Figure 3-6 p64).
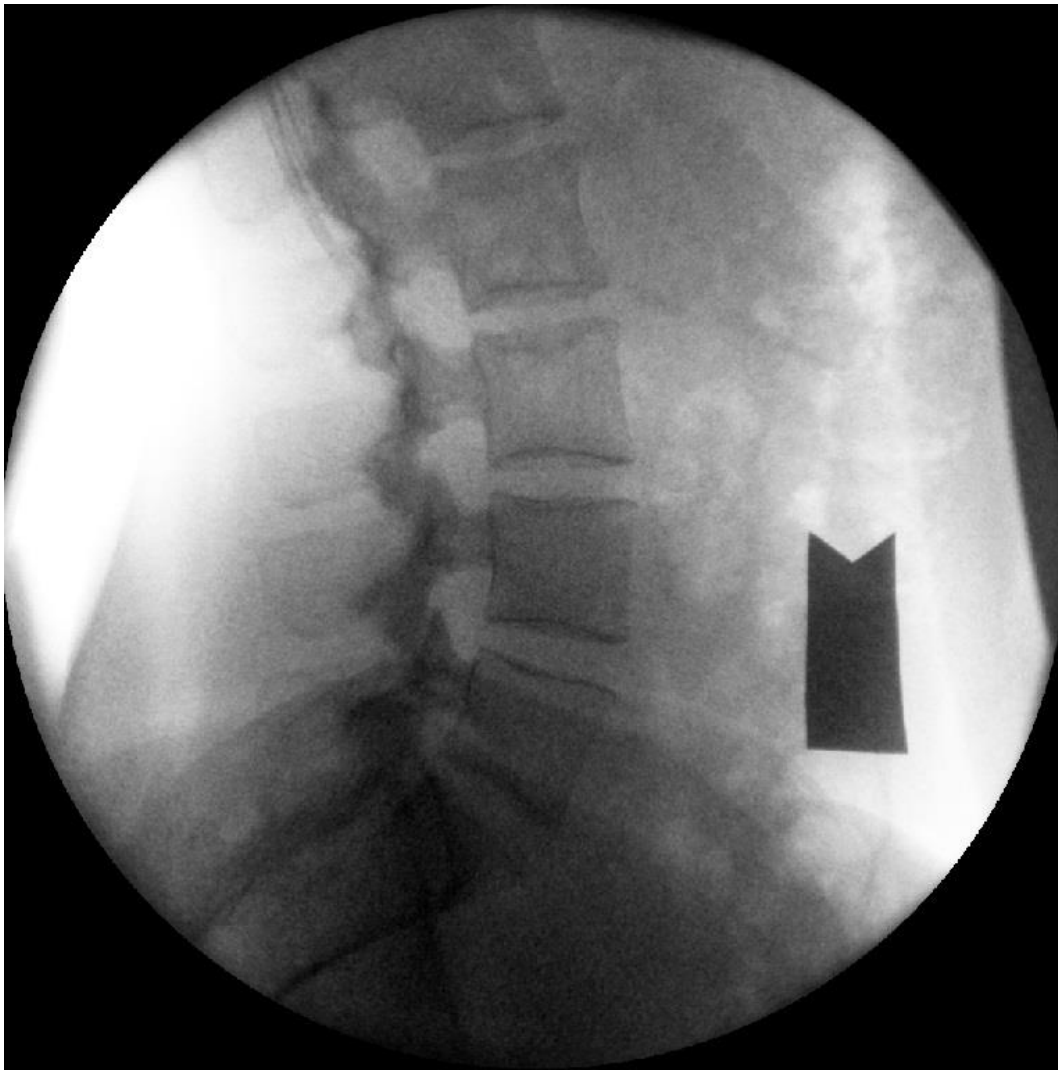
Figure 3-5 Example of the first fluoroscopic image extracted from a sagittal sequence
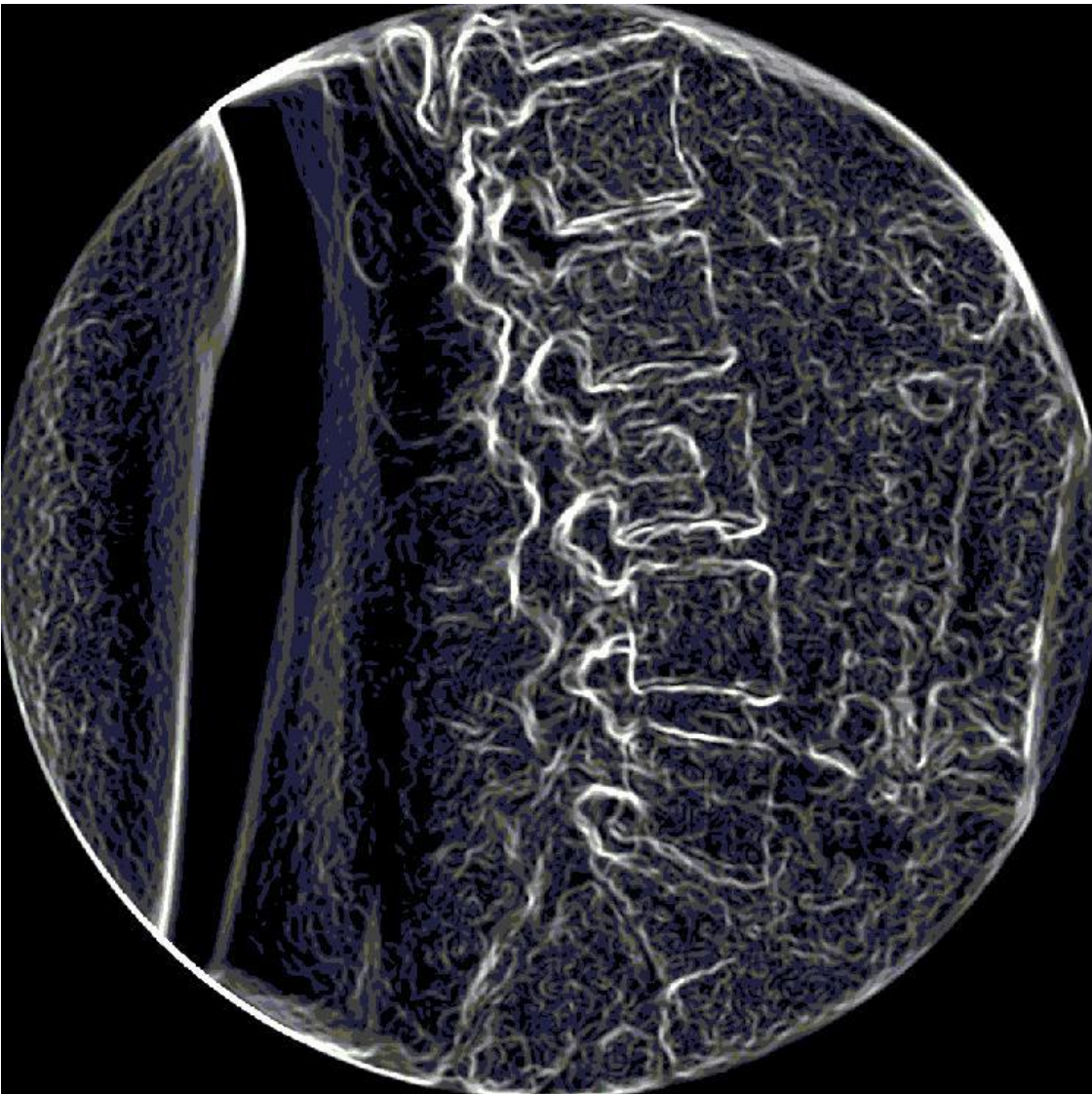
Figure 3-6 Edge enhancement of the first fluoroscopic image from a sagittal sequence

Following separation of the images two templates were placed over each vertebral body. The initial reference template was a four point template (see Figure 3-7 p65) which automatically calculated the x and y vertebral positions in subsequent images. A second tracking template was manually drawn around the cortical margins and these register each vertebral body throughout the sequence using the cross-correlation method described in Muggleton and Allen (Muggleton and Allen 1997), and a rolling average over two images to reduce noise (Breen et al. 2012). The calculations incorporate the DCRA method (Frobin 1996) and the templates were placed five times and averaged to reduce noise.

3.9.4 Quality assurance of image processing

Initial output was a graphical representation of vertebral positions where y = angle and x = frame number. All five trackings were displayed (see Figure 3-8 p66) and instances

where results were not consistent were visually checked by playing back the fluoroscopic sequences with the tracking templates (see supplementary video 5 as an example for left bending). If the templates did not track they were replaced or removed. This was sometimes necessary if the pixels within the tracking templates changed, for instance due to the presence of bowel gas (see Chapter 11 Limitations and recommendations for further work p206).
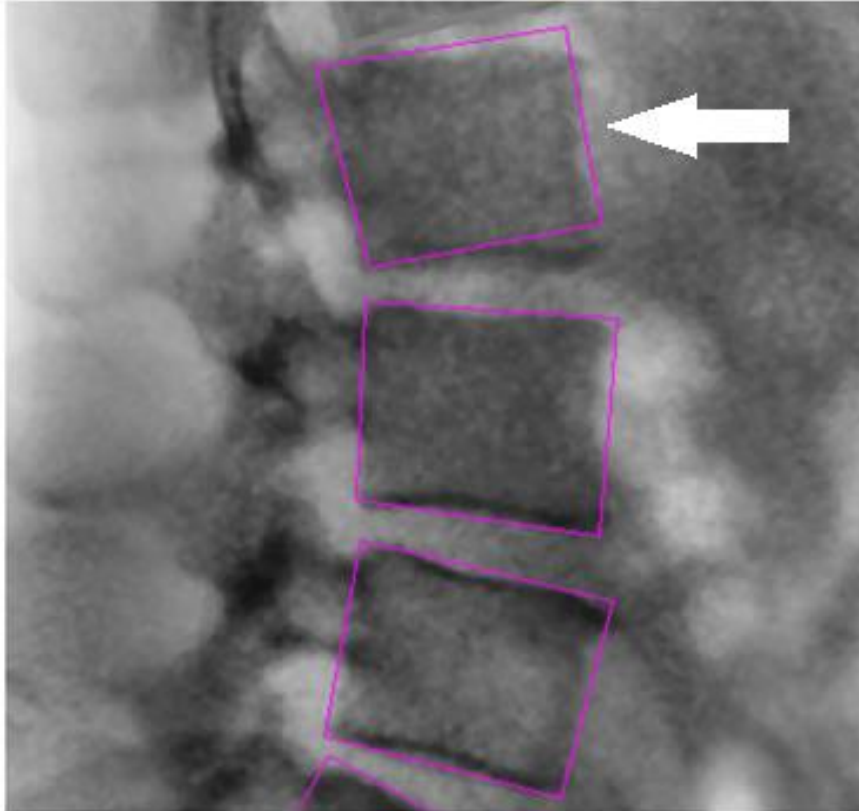
Figure 3-7 Lumbar spine fluoroscopic image with reference templates indicating a template that is no longer tracking the vertebra (white arrow)
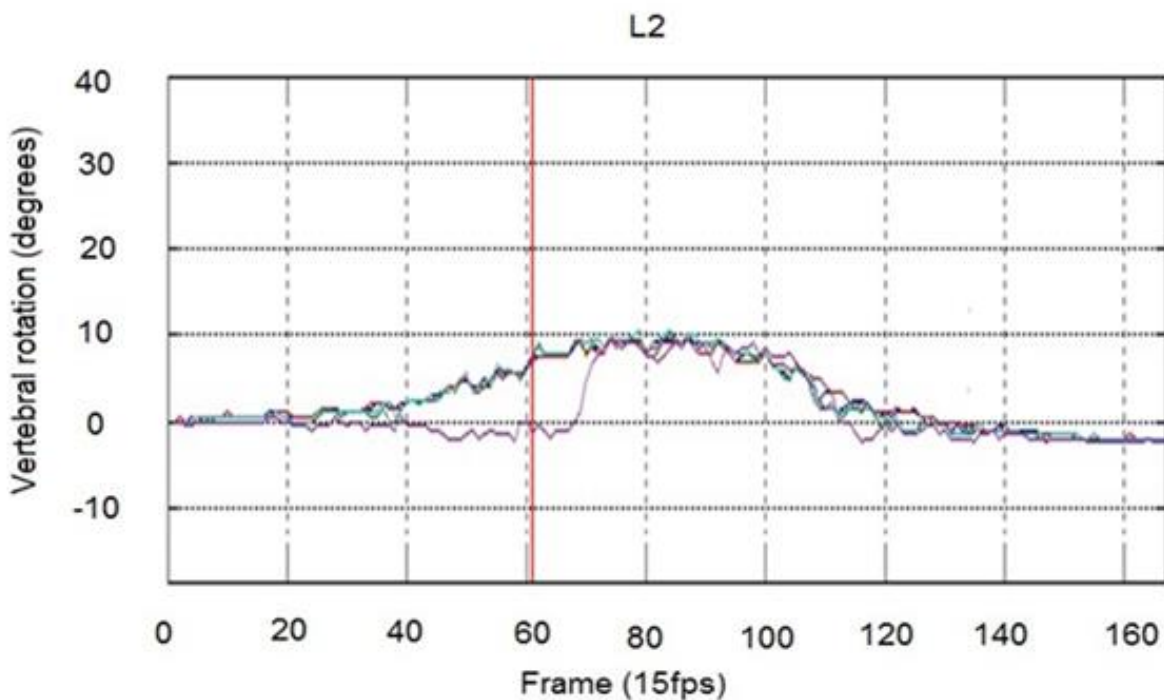
Figure 3-8 Raw unsmoothed vertebral angle output (y) and frame number (x); example of 1/5 tests (purple line) not following L2 vertebral body between frames 40 to 75

3.9.5 Raw data extraction

The average of all five trackings for each vertebrae were displayed (see Figure 3-9 p67) and subtracting these produced intervertebral rotation curves, consisting of the mean and 25 possible combinations per vertebral body (represented as yellow scatter showing the agreement of each template (see Figure 3-10 p68).

Despite the range and rate of trunk motion being controlled with a passive motion table, each sequence did not always contain the same number of images. Consequently the x axis was transformed from the image frame number to passive motion table angle to further standardise data. An example of smoothed intervertebral continuous motion from which calculations for mIVR, cIVR and CPM were undertaken is in Figure 3-11 p69.
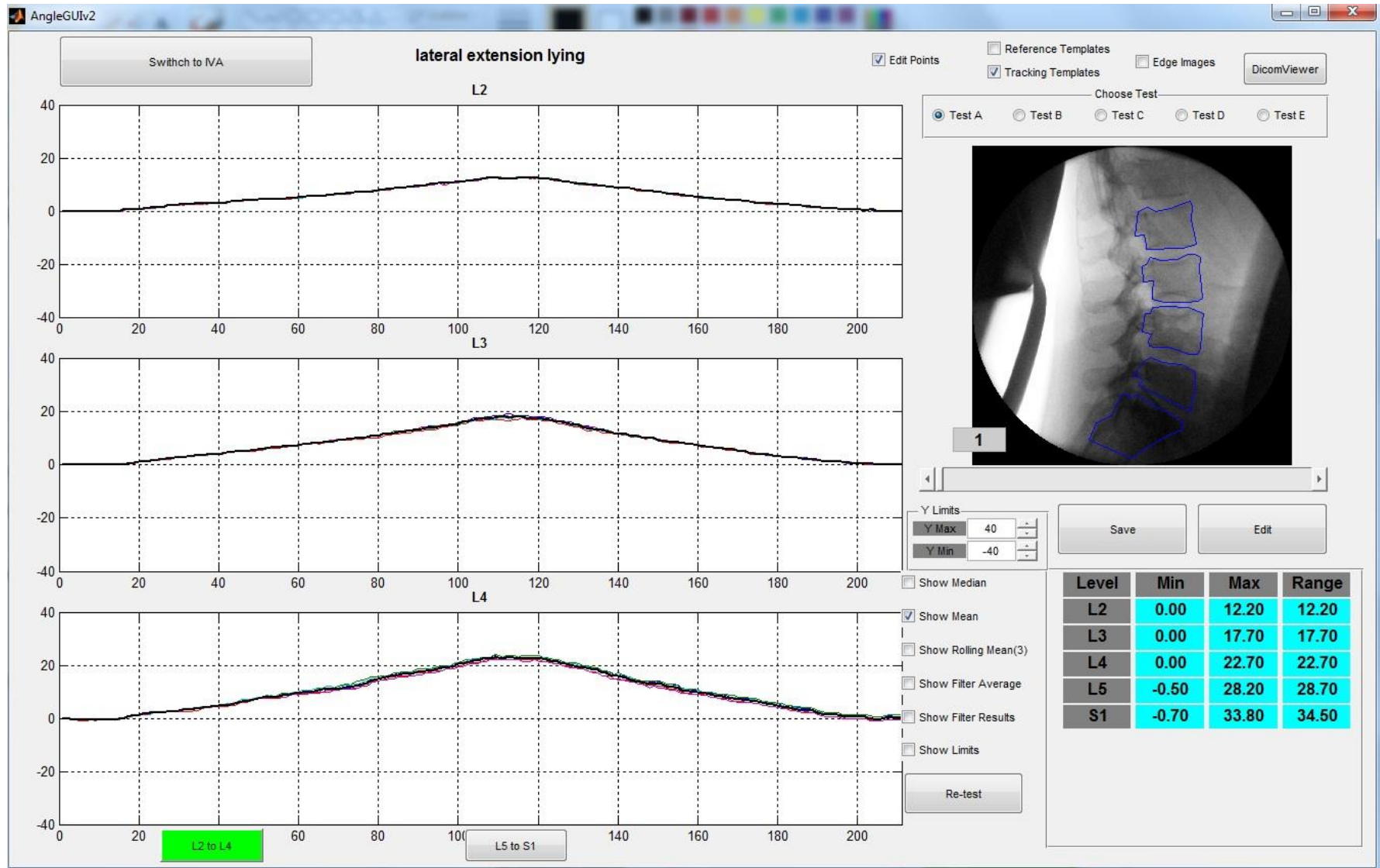
Figure 3-9 Raw output of vertebral angles (y axis) against frame number (x axis)
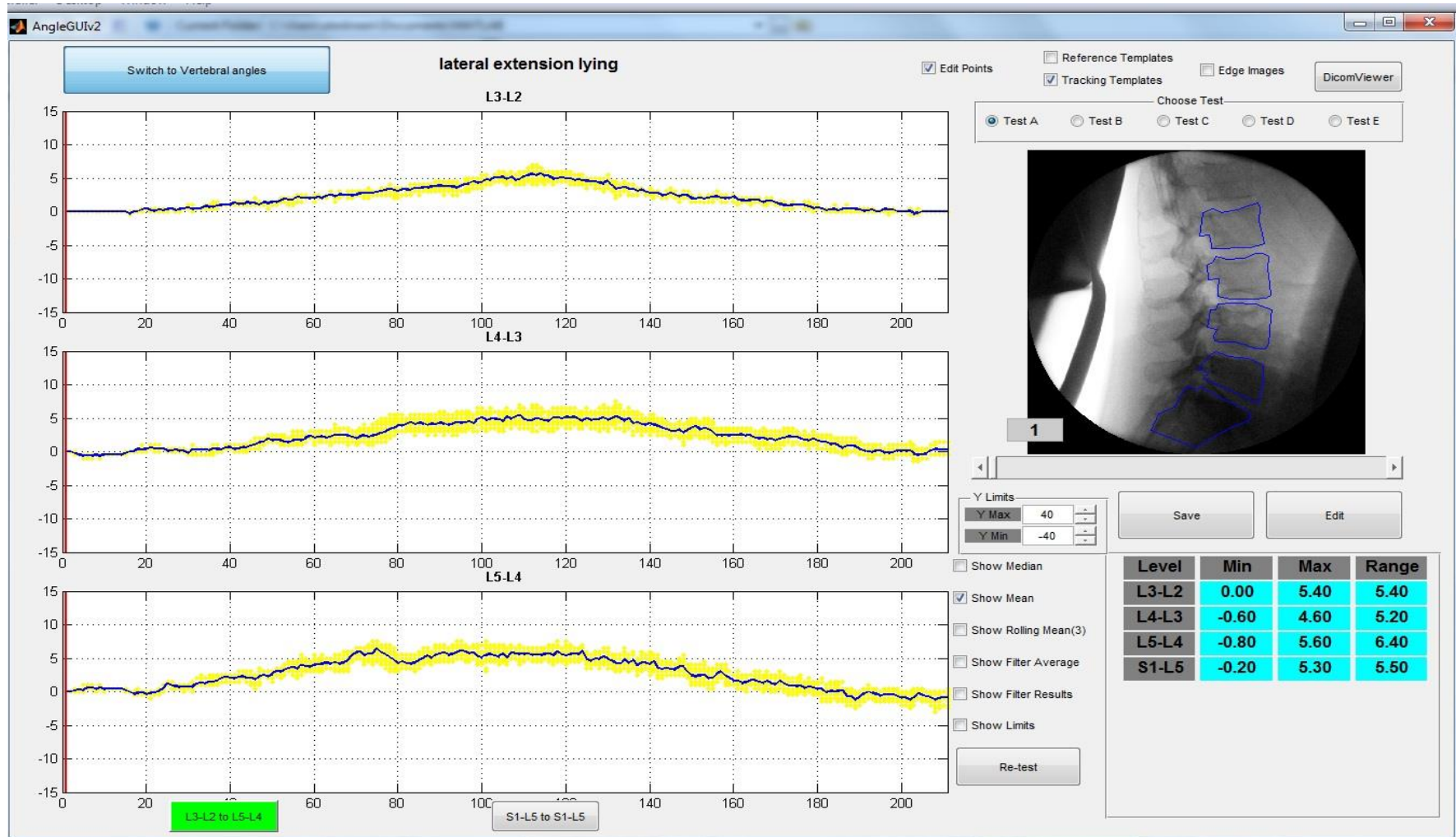
Figure 3-10 The mean intervertebral angle data (y axis) against frame number (x axis) before smoothing [6].

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[6] Note the y axis on Figure 3-9 and Figure 3-10 are different, which is why the raw intervertebral output in the latter appears less smooth.
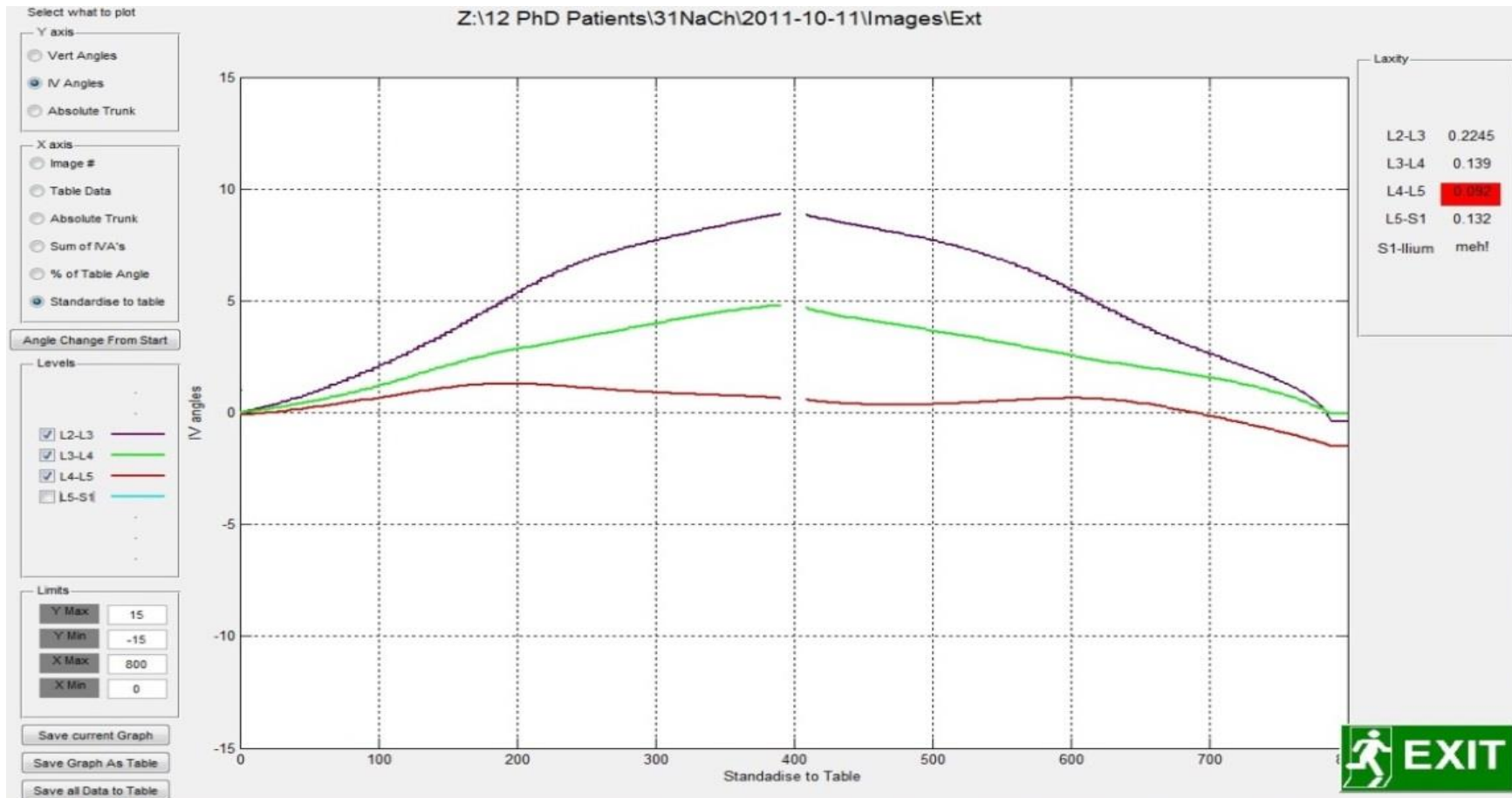
Figure 3-11 Smoothed mean intervertebral rotation L2 to L5 (y axis) against table rotation (y axis) [7]

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[7] There is missing data between 39.8^o and 40° due to unstable transformations of passive table motion data at this point.

3.9.6 Missing data

If any of the five tests appeared to not track the vertebral body at any point during the motion (see Figure 3-7 p65) that portion was removed and replaced with newly drawn templates. In practice this was time consuming; hence if only one or two tests failed to track the vertebral bodies for a small distance, these portions of the results were removed and not replaced (as would be the case for the one test in Figure 3-8 p66 between frames 22 and 70). This part of the analysis was at the discretion of the operator.

The transformation of frame number to table angle on the x axis meant that intervertebral motion at 40° was an unstable measurement. To overcome this, data between +39 and -39° was removed so all values were based on a stable transformation of the data. Graphically this is represented as a missing part of the motion graphs at 40° table motion (Figure 3-11 p69) and represented less than one second of imaging. Additionally, seven participants were unable to reach 40° of motion in extension without rotating out-of-plane. These participants were taken to the maximum range they could achieve without associated out-of-plane rotation and, when displayed with table motion on the x axis, it was displayed as missing data.

Because passive motion QF cannot measure axial rotation, due to errors in measurement, meant this plane was excluded. As previously mentioned, visual inspection of the motion sequences and the standardised procedure limited the amount of out of plane, or coupled rotations. It is acknowledged that the exclusion of the axial plane provides an incomplete picture of in vivo mid lumbar biomechanics.

3.10 Health and safety

The motion table has declared conformity (Atlas Clinical Ltd MDD93/42/EEC) and the fluoroscopy unit (Siemens Arcadis Avantic VC10A) is CE marked (CE0123). The QF procedure did not require specific approval from MHRA. The AECC local rules for radiation exposure were adhered to at all times, as were the policies for COSHH and RIDDOR. The radiation protection advisor at Poole General Hospital was the lead medical physics expert and reviewed the radiation dosage data. All participants received gonad shielding from the primary radiation beam and the CI wore a radiation monitoring badge and personal protective equipment (lead protective gowns or behind a lead screen). Female participants were asked to confirm they were not pregnant. The 28 day last menstrual period (LMP) rule or written confirmation of contraception /sterility was obtained.

3.11 Ethical considerations

The study involved ionising radiation (x-rays) so national research ethics approval was required. The ethics application was completed online using IRAS version 2.2 and submitted to Southampton Ethics Committee A. Approval was gained on 2nd October 2009 (09/HO5O2/99) (appendices Figure 13-1 p221). A major amendment to the study was submitted via IRAS version 3 on 14/09/2010. The amendment changed the recruitment strategy to allow the chief investigator (CI) to personally approach potential patients, and to widen recruitment to local chiropractic clinics and the NHS. Information governance and the Data Protection Act 1998 were adhered to and the treatment of incidental findings was made explicit in the participant information leaflets (appendices Figure 13-3 p227 & Figure 13-4 p235). Incidental findings were defined as either anatomical variants not requiring further treatment (such as spina bifida occulta) and any anomaly that may warrant further investigation. The consideration of incidental findings in this study led to a co-authored editorial on the treatment of such (England and Mellor 2012).

3.12 Sponsorship and statement of informed consent

The sponsor of this study was the AECC, and the funder was the NIHR (see p7). The CI updated Good Clinical Practice Training (GCP) in 2012 and gained informed consent as per guidance issued by the Department of Health (Department of Health. 2001).

3.13 Contribution to new knowledge

In terms of research methodology this thesis includes further development and implementation of a QF passive motion imaging protocol. A previous protocol used digitisation of 8 bit analogue images collected at five frames per second (fps). Sequences were automatically measurable in the coronal plane but limitations precluded automated measurement of sagittal plane data (Breen et al. 2006). In contrast this protocol collects DICOM (digital imaging and communications in medicine) standard digital images on a 1024x1024 pixel matrix at 15 fps. This increased digital information enabled automated analysis of sagittal plane data for the first time. Additionally all participants were positioned with L3/4 centred to the fulcrum of the passive motion table to reduce potential variation from different starting positions, and motion was divided into separate sequences for left, right, flexion, and extension.

Chapter 4   Participant characteristics

4.1   Chapter overview

In this section participant demographics, including the differences between patients and healthy volunteers for gender, age and body mass index (BMI), are presented along with anatomical variations and the exploratory grading of disc degeneration by two experienced observers. Agreement on the grade of disc degeneration was analysed with Cohens Kappa statistic to determine the strength of the agreement (Landis and Koch 1977). This chapter also presents an overview of the patients' scores on the Chronic Pain Grade (CPG) (Von Korff et al. 1992) (including seven sub dimensions of pain that are graded on a numerical rating scale 0- 10), and their disability scores on the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983).

4.2   Method

Demographic data collection is detailed in Data collection p59. Statistical analysis is detailed in Table 3-1 p50. Patients' pain and disability were descriptively analysed and the images assessed for incidental findings and disc degeneration as detailed on p62.

4.3   Results

4.3.1 Participant demographics

Demographic data are presented in Table 4-1 p74. Height, weight and BMI were all normally distributed; age was not. There were no significant differences between groups for age, height, weight or BMI.

The full data set is in the appendices and includes: Normality of patient data Table 13-1 p244; normality of healthy volunteer data Table 13-2 p244; and homogeneity of variance and independent t test results Table 13-3 p244.

	Patients	Healthy volunteers	P =
N	40	40	-
Mean age yrs. (SD)	35.9 (8.6) (range 21 to 50)	35.7 (8.4) (range 21 to 50)	0.59*
Gender (% male)	55% (n=22)	55% (n=22)	-
Mean height cm (SD)	174.3 (9.0) (range 154 to 192)	173.2 (10) (range 151 to 191.5)	0.61
Mean weight Kg (SD)	74.86 (12.05) (range 50 to 97)	74.04 (12.57) (range 51.2 to 97.6)	0.78
Mean Body Mass Index BMI (SD)	24.5 (2.6) (range 19.8 to 29.3)	24.5 (2.8) (range 19.5 to 31.5)	0.98
Mean "6 month intensity" (von Korff/10) (SD)	5.9 (1.7) (range 3 to 10)	-	-
Mean "Worst possible pain in the past 6 months" (von Korff/10) (SD)	8.3 (1.2) (range 5 to 10)	-	-
Mean "Current pain intensity" (von Korff/10) (SD)	4.1 (2.1) (range 0 to 8)	-	-
Mean disability (RMDQ)/24 (SD)	7.8 (4.1) (range 4 to19)	-	-

Table 4-1 Patient demographics (*Mann Whitney U test)

4.3.2 Incidental findings, anatomical variants and disc degeneration

No participant had any incidental finding that warranted further investigation. Noted anatomical variants are presented in Table 4-2 p75. A participant may have had more than one anatomical variant and thus may have been counted more than once. For instance one healthy volunteer had retro-position between L2 to L5 and spina bifida occulta (SBO), and another healthy participant had SBO and a transitional vertebra.

Because this was not a formal study of agreement, and there were low numbers of participants with disc degeneration, it was not appropriate to undertake further statistical analyses and is therefore included here as an introduction to the feasibility of grading disc degeneration from fluoroscopic images.

The frequencies (%) of disc degeneration in patients and controls for each rater are in Table 4-3 p75 and were assessed with Cohen's kappa (unweighted) = 0.41 (95% confidence interval 0.33 to 0.67) p <0.001, which is interpreted as moderate agreement.

	Anatomical variants	
	Patients	Healthy volunteers
Transitional vertebra	3	3
L5 Sacralised	1	3
Spina bifida occulta	1	4
Retroposition of any segment between L2 to L5	2	5
Schmorls nodes	3	2

Table 4-2 Anatomical variants

Grade of disc degeneration (Kellgren and Lawrence 1958)	Observer 1 frequencies (%)		Observer 2 frequencies (%)	
	Patients	Healthy Volunteers	Patients	Healthy Volunteers
0	17 (42.5%)	31 (77.5%)	25 (62.5%)	33 (82.5%)
1	18 (45%)	9 (22.5%)	11 (27.5%)	7 (17.5%)
2	3 (7.5%)	0	3 (7.5%)	0
3	2 (5%)	0	1 (5%)	0
4	0	0	0	0

Table 4-3 Frequency (%) of the grades of disc degeneration in patients and healthy volunteers per observer

4.3.3 Patient characteristics of pain and disability

The minimum entry criteria for patients were an RMDQ score of 4/24 and a CPG grade of two or greater[8]. Patients had a mean RMDQ score of 7.8 (SD 4.1 see Table 4-1 p74). The distribution of the grade of pain amongst patients, and their mean results for seven numerical rating scales (0-10) contained within the CPG are shown in Table 4-4 p76. Copies of the CPG and RMDQ are in the patient questionnaire (see appendix Figure 13-5 p238).

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[8] The CPG is graded from zero to four, with two being the cut off for chronic pain.

Patients		
Chronic Pain Grade frequency (percent)	Grade 2	Grade 3	Grade 4
	27 (67.5%)	8 (20%)	5 (12.5%)

Table 4-4 Distribution of patients' pain grade (CPG)

Seven dimensions of the Chronic Pain Grade scale.	Patients mean score (SD)
1. How would you rate your back pain at the present time, which is right now? 0 is no pain and 10 is pain as bad as it could be	4.1 (2.1)
2. In the past 6 months, how intense was your WORST pain? 0 is no pain and 10 is pain as bad as it could be	8.3 (1.2)
3. In the past 6 months, on average how intense was your pain (that is your usual pain at times you were experiencing pain? 0 is no pain and 10 is pain as bad as it could be	5.9 (1.7)
4. How many days in the last 6 months have you been kept from your usual activities?	7.9 (14.3)
5. In the past 6 months how much has your back pain interfered with your usual daily activities? 0 is no interference and 10 is extreme change	5.8 (2.7)
6. In the past 6 months, how much as your back pain changed your ability to take part in recreational, social and family activities? 0 is no change and 10 is extreme change	4.9 (2.7)
7. In the past 6 months, how much has your back pain changed your ability to work (including housework)? 0 is no change and 10 is extreme change	4.2 (2.8)

Table 4-5 Individual dimensions and patients' mean responses from the CPG questionnaire

4.4 Discussion

It was important to ensure both groups had similar characteristics to limit the influence of variables that may influence biomechanics such as gender, age (Wong et al. 2004) and BMI. These results show that the two groups were similar thus these variables are unlikely to confound subsequent analyses.

The initial assessment of anatomical variants was intended to investigate the effect of these on motion patterns but their incidence in this sample is too low for meaningful conclusions to be drawn. Similarly the grading of disc degeneration from fluoroscopic sequences is difficult due to the low resolution of the images. In clinical practice the

Kellgren and Lawrence scale is designed for use with radiographs that are viewed in optimum conditions (Kellgren and Lawrence 1958) and although there was moderate agreement for disc degeneration in this study, the kappa statistic was less than 0.5 hence it was at the lower end of this classification.

Consequently for both anatomical variants and disc degeneration, this data may only be suitable for case studies, with a recommendation that the feasibility of assessing disc degeneration on fluoroscopic sequences be undertaken in a larger sample size. A further discussion of continuous intervertebral rotation in a participant with grade 3 disc degeneration is in Chapter 8 on p155 (see Figure 8-4).

Descriptive analysis of the RMDQ reported the mean baseline score in patients was 12.1 (Roland and Fairbank 2000). Patients in this study had a low mean RMDQ score that is indicative of a self-referring primary care population from which the patients were selected. For the CPG, a pain grade of 2 was the minimum required to enter the study, and this represented 2/3 of the sample (see Table 4-4 p76). This further delineates in Table 4-5 p76 which, with the exception of item four, are on 10 point numerical rating scales. However, the CPG was administered as recruitment criteria thus the answer to question 1 (how would you rate your back pain at the present time, which is right now? 0 is no pain and 10 is pain as bad as it could be see Table 4-5 p76) was not related to the time of data collection. It would have been an improvement to repeat question 1 immediately prior to the data collection and analyse this with kinematic parameters to determine whether current level of pain has any relationship to passive motion.

4.5   Limitations and recommendations for future work

The limitation of the age range (21-51) meant the sample may not have been representative of the population, given that studies have found the incidence of low back pain is highest in the third decade, and overall prevalence increases with age until the 60-65 year age group and then gradually declines (Hoy et al. 2010) Furthermore, Wong et al (Wong 2004) demonstrated changes in the biomechanics of healthy participants in those over 51years and it was for this reason the age was limited to 51 in this study. These results are only applicable to the age range within this thesis and it is a recommendation to extend this work to the older age group.

The inclusion and exclusion criteria were intended to limit patients to those whose back pain was mechanical. As the study progressed it became clear that the criteria meant some patients were rejected when they were suitable. For instance, Arroll's two item screening tool for depression has a sensitivity of 97% (95% confidence intervals 83%

to 99%) but its specificity is lower at 67% (95% confidence intervals 62% to 72%) (Arroll et al. 2003) which means potential participants may have been incorrectly labelled as depressed and excluded.

Anatomical variants and disc degeneration influence biomechanics and Hasegawa et al reported that the angle of a facet joint was more important than tropism in instability (Hasegawa et al. 2011). However, screening for anatomical variants would require an initial fluoroscopic image as part of the selection criteria and this cannot be justified on grounds of radiation dose. An alternative approach would be to use MRI. Additionally the influence of anatomical variants and different stages of disc degeneration on intervertebral biomechanics is recommended for a future study with a larger sample size, given that the prevalence of transitional vertebra in a healthy population is thought to be up to a third (Apazidis et al. 2011).

Finally the exclusion criteria included leg pain of radicular origin for patients, but did not explicitly state this for healthy volunteers. As the study progressed it came to light that one healthy volunteer had leg pain of radicular origin although he did not have back pain. This is further discussed in the General Discussion Chapter 11 p197. An improvement would be to include 'leg pain' as an exclusion criteria for all participants.

4.6 Conclusion

The two groups were evenly matched for their demographics. This means that differences in intervertebral kinematic parameters can be interpreted with a greater level of confidence. Patients also demonstrated pain scores on the individual numerical rating scales with the Von Korff Chronic pain questionnaire that indicated their pain and disability was moderate, which is typical of a care seeking primary care population.

Chapter 5   Reproducibility of two kinematic parameters; maximum intervertebral rotation and initial intervertebral attainment rate

5.1   Chapter overview

Chapter 5 reports intra and inter observer reproducibility (standard error of the measurement (SEM)) and intra class correlations (ICC's) for the analysis of two kinematic parameters, the maximum intervertebral rotation (mIVR) and initial intervertebral attainment rate. The accuracy of QF when compared to a cadaveric model has been previously reported (Breen et al. 2006). Guidelines for reporting reliability and agreement studies (GRRAS) were proposed in 2011 (Kottner et al. 2011) and have been followed in this chapter (see appendices, Table 13-12 p252). The reproducibility of interest was the user interaction of placing templates and the extraction of mIVR and initial intervertebral attainment rate data. A randomly selected sample of patients and healthy volunteers (n=10) from a sample of 53[9] were assessed by two independent trained observers blind to each other's results

5.2   Rationale for study

Maximum intervertebral rotation (mIVR) from the end of trunk range is a common kinematic parameter to report reproducibility. Therefore the rationale for reporting the reproducibility of mIVR in this thesis is to; update previously reported values for the coronal plane (Breen et al. 2006), report values in the sagittal plane for the first time, and reflect the greater consideration given to reducing variation in the measurement of intervertebral rotation with passive recumbent QF.

Initial intervertebral attainment rate is a new parameter that was postulated as a proxy measurement of the neutral zone (NZ) *in vivo,* in recognition that intervertebral rotation is not linear (Mimura et al. 1994; Wong et al. 2006). It is postulated from cadaveric studies that the neutral zone is different in those with disc degeneration (Kettler et al. 2011). It is therefore reasonable to examine the reproducibility of a method that measures this *in vivo* and to date no other study has reported this.

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[9] The CI did not undertake the sampling.

5.3   Literature review

Measurements are always prone to errors, which mean the true value is different to the measured value. The importance of the error's magnitude depends upon the context of the measurements. For instance, a higher degree of measurement error may be acceptable in a clinical trial but be unacceptably large for individual patient management (Bartlett and Frost 2008). Reproducibility is an umbrella term for the concepts of agreement and reliability (de Vet et al. 2006) and this thesis follows the recommendations of De Vet et al in using the standard error of measurement (SEM $_{agreement}$) to describe agreement, and intra class correlations (ICC $_{agreement}$) to describe reliability. SEM and ICC 'agreement' were chosen over SEM and ICC consistency to reflect the importance of systematic differences between observers.

Potential sources of error include intra and inter observer measurements, intra (test/retest) and inter subject (natural physiologic variation), and intra and inter site (variation in participant position, imaging equipment and processing methods) (Deitz 2010). *In vivo* intervertebral studies claim better agreement than clinical palpation tests due to their objective output (Alqarni et al. 2011) and other *in vivo* QF studies (and computer assisted measurements from functional radiographs) have sought to determine their measurement error (Teyhen et al. 2005; Breen et al. 2006; Pearson et al. 2011; van Loon et al. 2012; Yeager et al. 2014). Comparisons are difficult however, confounded by interchangeable use of terminology; such as agreement, reliability, reproducibility and repeatability (Bartlett and Frost 2008).

The use of statistical analysis is also variable (Haas 1991) and includes Pearson's correlation (Cakir et al. 2006), the root mean square (RMS) (Hindle et al. 1990; Breen et al. 2006; Ahmadi et al. 2009; Williams et al. 2010) SEM (Taghipour-Darzi et al. 2009; Yeager et al. 2014), proportions of agreement (PA) or 95% limits of agreement (LOA) (also known as Bland-Altman plots) (Bland 1996; van Loon et al. 2012; Yeager et al. 2014), intra class correlations(ICC)(Shrout and Fleiss 1979), and coefficients of repeatability (Yeager et al. 2014) (CR) or coefficients of variation (Okawa et al. 1998). Furthermore, inconsistency remains with some authors using LOA to demonstrate agreement of the same method (van Loon et al. 2012; Yeager et al. 2014) whereas others state LOA are for comparison of two different methods (Bland 1996) that share the same scale of measurement (Streiner and Norman 2005).

Selection of an appropriate index to evaluate agreement and reliability is dependent on the methods used (Weir 2005; Kottner et al. 2011) and factors that include the context in which the study is being undertaken, the type of variable under consideration, and the number of observers making assessments (Gisev et al. 2013). The concepts of

reliability and agreement are often confused with correlation (Costa-Santos et al. 2005), but agreement and reliability are two distinct concepts. Agreement measures how well a test performed more than once will return the same value, whereas reliability places this agreement in the context of overall variability (between study subjects) (Streiner and Norman 2005; de Vet et al. 2006; Kottner et al. 2011). Hence agreement (SEM) is reported in the same scale as the test, and reliability (ICC), which is reported on a scale of 0-1, is the ability of the test to differentiate between participants. Situations may arise where agreement is high and reliability is low, such as when there is little variability amongst repeated scores and low variability between different individuals. Kottner and Streiner give the example of all observers rating medical students as 'excellent', which would demonstrate perfect agreement but a reliability of zero because there is no between subject variance (Kottner and Streiner 2011).

Within individual measurement parameters such as the ICC there are sub classifications. For instance Shrout and Fleiss discuss 6 different forms of the ICC and provide guidelines dependent upon the study design (Shrout and Fleiss 1979). This was further elaborated by McGraw and Wong (McGraw and Wong 1996) who introduced the concept of random or fixed effect models and produced an algorithm for ICC selection. The SEM can portray absolute agreement or consistency of measurements (de Vet et al. 2006) where 'SEM agreement' takes into account systematic differences between observers and 'SEM consistency' does not, although few studies declare which SEM they calculated.

Some studies attribute a Likert scale from poor to excellent to interpret ICCs (Costa-Santos et al. 2011). One scale states that less than 0.40 is poor, 0.40 to 0.75 is fair to good, and a value of greater than 0.75 shows excellent reproducibility (Rosner 2005) but other studies caution against the use of such a scale stating that the ICCs need to be interpreted within the context of the measurement (Sampat et al. 2006) and Shrout notes that there is no consensus for a good ICC (Shrout 1998).

5.4 Methods

A subset of 10 participants (comprising 5 patients and 5 healthy volunteers) were randomly selected from a database of 53 participants by observer B. This was a pragmatic approach to suit observer B's MSc project (Breen 2011), which took place during the course of this thesis. Segments L2/3, L3/4 and L4/5 for each direction (left, right, flexion extension) were examined.

Intra observer variability was calculated from observer A (the CI) who undertook the analyses twice. Inter observer variability was calculated from observer A's first analysis, and observer B's first analysis. Both observers independently placed the templates on the vertebral bodies (as described in Image processing p62) on two separate occasions within a period of 2 months, and each observer had a minimum of 4 years' experience with QF analysis.

5.4.1 Data extraction

Maximum intervertebral rotation (mIVR) was calculated as the difference between the minimum and maximum rotation achieved at any point throughout the bend (see Figure 5-1 p83). Attainment rate was calculated as the initial gradient of the intervertebral angle over the gradient of the passive table rotation, over 10° of table rotation. The graphic user interface returned a number called 'Laxity'.

5.5   Calculation of SEM and ICC

Statistical analysis is detailed in Table 3-2 p52 and justified below.

SEM agreement (de Vet et al. 2006) was used for both intra and inter observer agreement and was chosen over consistency because it included systematic differences between and within observers. For both inter and intra observer reliability a 2 way random effects single measures model with absolute agreement was selected (ICC 2,1). A 2 way random effects model is relevant when both selection of patients and selection of observers is considered random, and includes an interaction term where differences between observers may differ according to the patient being observed. A single measures model is suitable for individual item scores, and looking at absolute agreement accounts for systematic differences between observers.

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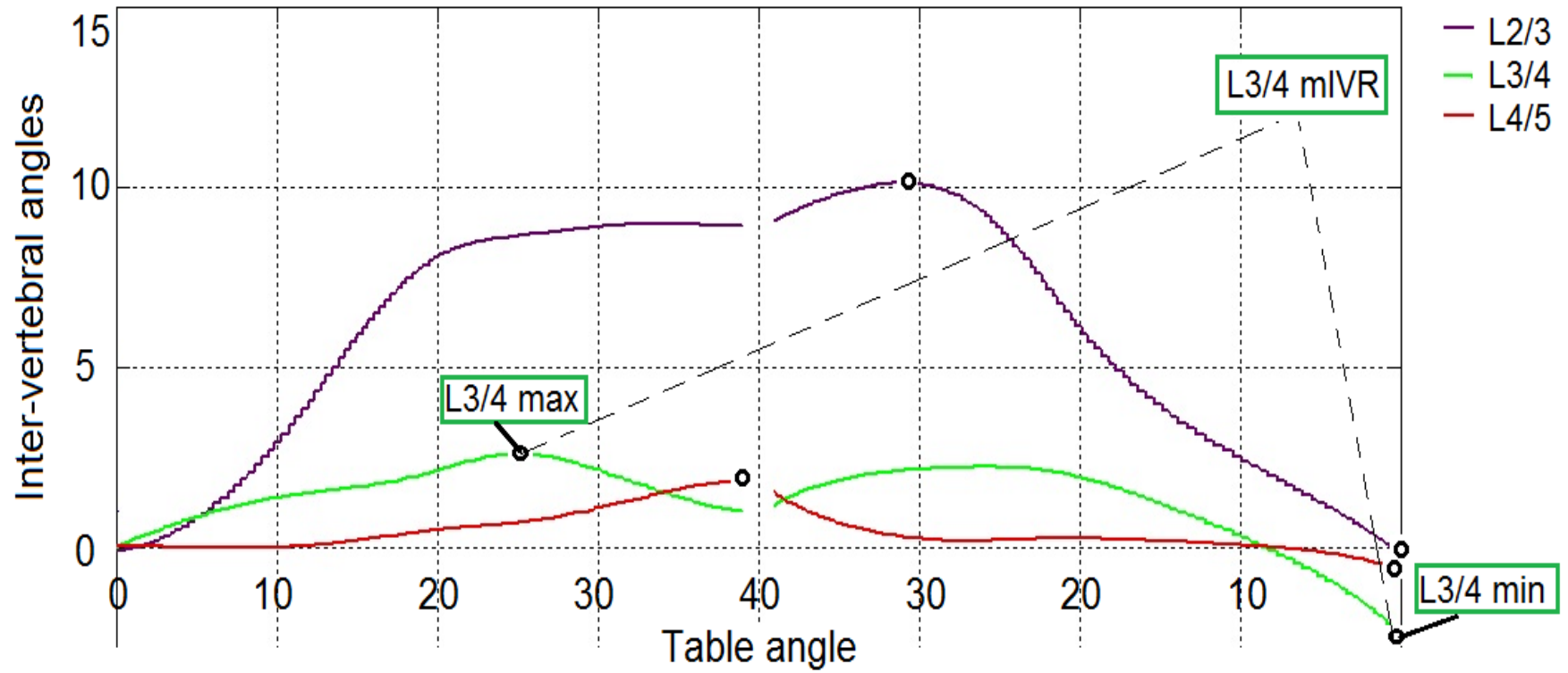
Figure 5-1 Measurement of mIVR for L3/4

5.6 Results

5.6.1 Demographics

The sample consisted of four males and one female from the patient group and the same from the healthy volunteer group. The mean age was 37.9 (SD =7.8) and their mean BMI 25.2 (SD2.2). Descriptive data of the mean and SD for mIVR and attainment rate values are in Table 13-16 p257 and Table 13-25 p268 respectively.

5.6.2 Agreement and reliability of maximum intervertebral rotation

Per level and direction the lowest SEM (the highest agreement) was 0.08^{o} (intra observer L2/3 right) and the highest SEM (the lowest agreement) was 0.77^{o} (inter observer L2/3 in extension).

Intra-vertebral level	Intra observer SEM agreement (degrees)			
	Left	Right	Flexion	Extension
L2/3	0.17	0.08	0.13	0.35
L3/4	0.16	0.11	0.13	0.24
L4/5	0.15	0.12	0.10	0.19

Table 5-1 Maximum IVR; Intra observer SEM

Intervertebral level	Inter observer SEM agreement (degrees)			
	Left	Right	Flexion	Extension
L2/3	0.46	0.55	0.31	0.77
L3/4	0.28	0.18	0.17	0.41
L4/5	0.26	0.20	0.31	0.27

Table 5-2 Maximum IVR; Inter observer SEM

The greatest reliability for an individual level was intra observer reliability for L4/5 extension (0.990 95% confidence interval 0.962 to 0.998). Conversely the same level and direction had the lowest inter observer reliability (0.610 95% confidence limits 0.03 to 0.889). On reflection it was noted that one participant had a transitional vertebrae and the segment had been incorrectly labelled on one of the analyses. This was not repeated because this is designed to reflect a 'real life' situation where such errors may happen. Caution is certainly advised for future analyses of the sagittal plane with a recommendation to document the labelling of vertebral bodies and correlating these to the coronal images.

Inter-vertebral level	Intra observer ICC (95% confidence intervals)			
	Left	Right	Flexion	Extension
L2/3	0.884 (0.539 to 0.971)	0.924 (0.728 to 0.981)	0.968 (0.870 to 0.992)	0.905 (0.682 to 0.975)
L3/4	0.833 (0.469 to 0.956)	0.962 (0.863 to 0.990)	0.932 (0.766 to 0.982)	0.962 (0.857 to 0.990)
L4/5	0.987 (0.949 to 0.997)	0.972 (0.890 to 0.993)	0.985 (0.831 to 0.997)	0.990 (0.962 to 0.998)

Table 5-3 Maximum IVR; Intra observer reliability (ICC 2, 1)

Inter-vertebral level	Inter observer ICC (95% confidence intervals)			
	Left	Right	Flexion	Extension
L2/3	0.888 (0.562 to 0.972)	0.869 (0.578 to 0.965)	0.624 (0.037 to 0.891)	0.761 (0.273 to 0.935)
L3/4	0.890 (0.640 to 0.971)	0.943 (0.787 to 0.985)	0.853 (0.527 to 0.961)	0.763 (0.310 to 0.935
L4/5	0.950 (0.812 to 0.987)	0.941 (0.788 to 0.985)	0.803 (0.410 to 0.947)	0.610 (0.03 to 0.889)

Table 5-4 Maximum IVR; Inter observer reliability (ICC 2, 1)

5.6.3 Agreement and reliability of attainment rate

Results for all levels and directions are in Table 5-5 p86, Table 5-6 p86, Table 5-7 p87 and Table 5-8 p87.

The lowest SEM (the highest agreement) was 0.007 (intra observer L2/3 and L4/5 flexion) and the highest SEM (the lowest agreement) was 0.060 (inter observer L4/5 extension).

Intervertebral level	Intra observer SEM agreement			
	Left	Right	Flexion	Extension
L2/3	0.016	0.013	0.007	0.019
L3/4	0.028	0.014	0.009	0.010
L4/5	0.012	0.015	0.007	0.009

Table 5-5 Initial intervertebral attainment rate; Intra observer SEM

Intervertebral level	Inter observer SEM agreement			
	Left	Right	Flexion	Extension
L2/3	0.017	0.019	0.033	0.017
L3/4	0.024	0.017	0.012	0.025
L4/5	0.024	0.020	0.039	0.060

Table 5-6 Initial intervertebral attainment rate; Inter observer SEM

The greatest reliability for segments was intra observer left L4/5, which returned an ICC of 0.993 (95% confidence interval 0.964 to 0.998). The level with the lowest reliability was for inter observer extension L4/5, with an ICC of 0.610 (95% confidence interval -0.30 to 0.889)[10].

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[10] The ICC may in some instances also be negative if the statistical package allows this calculation, as is the case with the lower 95% confidence interval for attainment rate L4/5 extension. In such instances the value should be interpreted as 0 and no reliability be inferred.

Inter-vertebral level	Intra observer ICC (95% confidence intervals)			
	Left	Right	Flexion	Extension
L2/3	0.942 (0.762 to 0.986)	0.989 (0.958 to 0.997)	0.977 (0.900 to 0.994)	0.868 (0.550 to 0.966)
L3/4	0.956 (0.807 to 0.989)	0.976 (0.887 to 0.994)	0.932 (0.766 to 0.982)	0.962 (0.857 to 0.990)
L4/5	0.993 (0.964 to 0.998)	0.989 (0.960 to 0.997)	0.985 (0.831 to 0.997)	0.990 (0.962 to 0.998)

Table 5-7 Initial intervertebral attainment rate; Intra observer reliability (ICC 2, 1)

Inter-vertebral level	Inter observer ICC (95% confidence intervals)			
	Left	Right	Flexion	Extension
L2/3	0.924 (0.730 to 0.981)	0.944 (0.804 to 0.986)	0.621 (0.037 to 0.890)	0.905 (0.682 to 0.975)
L3/4	0.905 (0.666 to 0.976)	0.953 (0.831 to 0.988)	0.854 (0.532 to 0.961)	0.763 (0.310 to 0.935)
L4/5	0.972 (0.898 to 0.993)	0.968 (0.863 to 0.992)	0.803 (0.401 to 0.947)	0.610 (-0.30 to 0.889)

Table 5-8 Initial intervertebral attainment rate; Inter observer reliability (ICC 2, 1)

5.7 Discussion

Values of reliability are estimates of true reliability and should therefore be reported with confidence intervals to indicate the uncertainty of the estimation. It is acknowledged that confidence intervals are a function of sample size and would be smaller in this study if n was greater than ten. However, a sample size of ten has been used in other studies (McGregor et al. 1995) and was chosen as a manageable sample.

Additionally, reliability depends on the population in who the measurements are made, not just the measurement errors of the method itself (Bartlett and Frost 2008). Many researchers maintain demonstration of good intra and inter observer reliability is a

minimum requirement of a good test, however Streiner and Norman state that both are unnecessary because inter observer reliability contains all the sources of error from intra observer plus errors arising from between observers, thus inter observer reliability is sufficient (Streiner and Norman 1995). If this were the case however then one would expect inter observer reliability to be equal or less than intra observer reliability. This was not the case in this thesis for every segment, and this demonstrates that intra and inter observer reliability are demonstrating different aspects of reproducibility, or it may be a reflection of sampling error, in which case it is important to demonstrate both. Consequently both sets of results were provided for completeness and as an introduction to a recommendation that further work should include inter and intra rater reliability studies of other kinematic parameters derived from QF, in order to assess its usefulness as a clinical tool.

In this thesis, reproducibility was undertaken to determine the feasibility of measuring mIVR and attainment rate in QF studies. Of interest is that the highest agreement and reliability for mIVR is in the coronal plane (L2/3 right and L3/4 left respectively) as is the highest reliability for attainment rate. It is likely that this is due to more pixel information available within the templates' borders for AP images allowing for better tracking. This is demonstrated in Figure 5-2 p89 that shows the edge enhanced vertebral bodies with an AP image on the left and a lateral image on the right. Note that there are more contrasting pixels in the AP vertebral body.
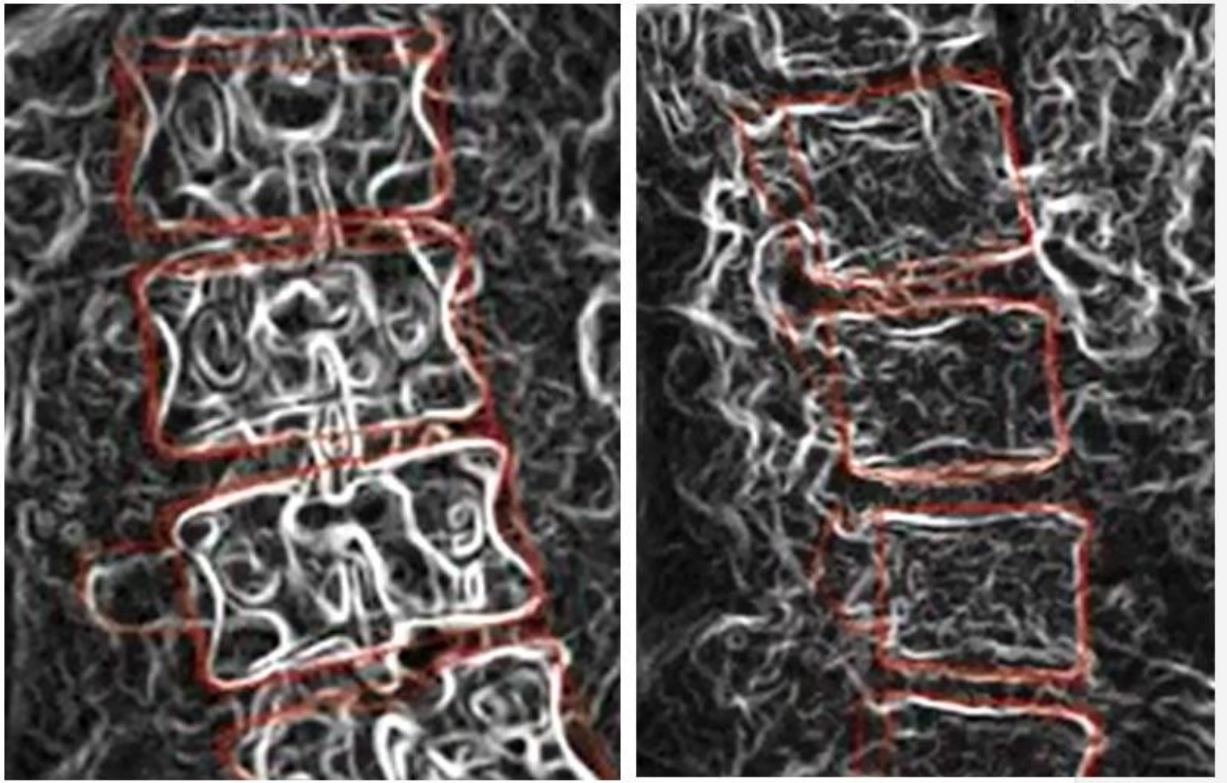
Figure 5-2 Difference in AP and lateral edge enhanced tracking

The plane of motion with the lowest agreement and reliability for both mIVR and attainment rate is extension. This is likely to be due to out-of-plane rotation, which is more evident in extension, particularly as seven participants overall could not achieve 40° passive extension rotation, and four of these were within this sample for reproducibility.

Researchers often quote an overall measure of reproducibility as a summary statistic, such as an average across all levels and directions (Teyhen et al. 2005; Ahmadi et al. 2009; Yeager et al. 2014). However, this has led to some authors such as Yeager et al (Yeager et al. 2014) inflating their sample size by reporting the reproducibility for the overall number of segments rather than participants and this is likely to increase the risk of a type one error if conducting hypotheses tests, or incorrect calculation of confidence intervals. Other authors state a summary value, but not how it was calculated (Ahmadi et al. 2009). The summary statistic reported by Yeager pertains to both recumbent and weight-bearing motion in both the coronal and sagittal plane, whereas Ahmadi et al only examined weight bearing motion in the sagittal plane. Hence, while it may initially appear useful to have an overall summary statistic, it may be erroneous to compare these. Clinical practice of observing and assessing movement patterns consider each direction individually (McKenzie and May 2003). Additionally combining data for different planes does not take into account that template tracking fails more often in the sagittal plane due to the reduced number of

contrasting pixels in this plane. For these reasons, a summary statistic for agreement and reliability is not reported in this thesis.

Calculation of reproducibility parameters determines how a test may be used, considering that higher reproducibility is needed for individual scores versus population screening or determining the smallest detectable change (SDC) in longitudinal studies. De Vet et al proposed that SEM * 2 is a suitable calculation for the SDC (de Vet et al. 2006) and if this is applied to rotation it would mean that the greatest SDC would be 1.47^o for L2/3 extension (The lowest agreement multiplied by 2). Thus, if a study of passive motion QF were to measure two values that were within 1.47^o the change in values could be due to error rather than any intervention. For attainment rate the lowest agreement is for L4/5 extension, (SEM = 0.060), of which the SDC would be 0.120. As this is not a familiar unit of measurement, it is useful to place it in context of the mean and SD attainment rate measurements from both populations that are depicted in Chapter 7 (p129).

5.7.1 Comparison of these results with other studies

5.7.1.1 Maximum intervertebral rotation (mIVR)

Yeager et al (2014) reported summary SEMs in their comparison of QF and computer assisted digital measurements from functional radiographs (Yeager et al. 2014). Although they combined segments for analysis, their SEMs for QF ranged from 0.1^o for intra observer rotation to 0.22^o for inter observer rotation. Similarly Ahmadi et el reported summary SEMs as 1.19^o for both intra and inter observer studies (range 0.62^o to 1.45^o) (Ahmadi et al. 2009). Both these are of a similar order to the SEMs in this study (ranging from 0.081^o intra observer right L2/3 to 0.772^o inter observer extension L2/3) indicating that the image analysis for passive recumbent QF is a method with high reproducibility.

Interestingly, Yeager et al also provides a summary statistic for computer assisted digital measurements that ranged from 2.59^o and 3.38^o for intra and inter observer respectively. This is in contrast to Pearson et al who compared manual assessments from radiographic film to computer assisted digital measurements and reported a summary SEM of 0.5^o for computer assisted methods and 2.5^o for manual methods (Pearson et al. 2011). Both studies demonstrate the improved reproducibility when computer assisted measurements are employed that appears to improve even further when this is translated to a fully automated measurement of motion.

Teyhen et al also undertook studies using QF (weight-bearing with unstandardised trunk range) and reported the SEM of an automated landmark algorithm on the initial

fluoroscopic image that ranged from 0.7° to 1.4° for intra image reliability (the lowest ICC was 0.91 (range 0.82 -0.94)) (Teyhen et al. 2005). This method was not translated to automatic measurement of subsequent images in the sequence.

Previous studies of passive QF have reported reproducibility based on data analysis of QF (Breen et al. 2006; van Loon et al. 2012), but SEM for mIVR has not been reported. Breen et al reported a summary RMS of 1.86° for coronal rotation that was a repeated measures analysis including intra-subject variation, and Van Loon et al only reported ICCs for translation. It is theorised that an algorithm that could both identify vertebrae in initial images and track them through the sequence would further reduce intra and inter observer errors.

For reliability, reported as ICCs, Yeager et al reported a summary statistic of 0.983 (95% confidence interval 0.980 to 0.985) and 0.958 (95% confidence interval 0.948 to 0.967) (Yeager et al. 2014). Ahmadi et al reported 0.95 (95% confidence interval 0.890 to 0.980) and 0.92 (95% confidence interval 0.84 to 0.96) for intra and inter observer QF respectively (Ahmadi et al. 2009). These are both similar to the ICCs in this study, which ranged from 0.737 (95% confidence interval 0.228 to 0.928) to 0.998 (confidence interval 0.992 to 0.999) for extension L2/3 inter observer and left L4/5 intra observer reliability respectively. It is notable that Yaeger et al and Ahmadi et al demonstrate narrower confidence intervals than in this study, which is reflective of their larger sample size (n=61 and n=30 respectively).

It would be an improvement to this study to repeat the analyses with a larger sample size and include all participants (n=80). In this thesis the sample size of 10 was selected for pragmatic reasons and to suit an MSc project completed during the data collection phase of this thesis (Breen 2011). At this stage the full sample size had not yet been recruited. It is acknowledged that undertaking reproducibility studies on a population that may not vary (such as would be expected in healthy volunteers) could skew the results, as discussed in Limitations and recommendations for future work p92.

5.7.1.2   Initial intervertebral attainment rate

A previous study by the CI presented two potential methods for measuring the NZ *in vivo* (Mellor et al. 2009). The first method was based upon Mimura et al (Mimura et al. 1994) and compared the proportion of motion achieved at 10° of trunk bend relative to overall motion. However, this method was untenable with low discriminating properties and reliability (the ICC was 0.612, 95% confidence interval 0.575 to 0.650). The second method, of measuring the initial gradient of the outward intervertebral motion, was an

advancement upon Crawford et al (Crawford et al. 1998) who used a 'nth percent slope technique" for *in vitro* measurements, and Lee et al (Lee et al. 2002) who measured the whole outward IV gradient. Lee et al reported the reproducibility of their method, but they did not specifically test the reproducibility of data analyses and reported RMS values. For the measurement of the gradient of intervertebral motion over the first 10° of trunk rotation, Mellor et al (2009) previously reported a summary ICC of 0.429 (95% confidence interval 0.399 to 0.460), which has been improved upon in this thesis.

5.7.2 Limitations and recommendations for future work

ICCs may return a lower value if there is low variability within the sample (Weir 2005), it is a therefore recommended that the reproducibility of kinematic parameters are undertaken with a larger sample size. These results also need replication at other sites to include inter site variation, and it recommended that intra and inter subject variability are also considered[11].

Finally other kinematic parameters, such as continuous intervertebral rotation (cIVR) (see Chapter 8 p143) and continuous proportional motion (CPM see Chapter 9 p159), need to be assessed for reproducibility before they can be advanced as suitable measurements. It would be feasible to assess CPM with SEM and ICC's, but for cIVR a numerical output would need to be developed such as polynomial fitting to the curve. Williams et al used a similar technique for assessing the reliability of continuous motion curves for global lumbar motion (Williams et al. 2013).

5.7.3 Clinical implications

The acceptable reproducibility of mIVRs means that they are useful in determining amount of rotation in the coronal and sagittal plane and could be used in clinical practice. However, the reproducibility of the whole examination, which includes different operators undertaking the QF and positioning the patient, needs to be considered.

Knowing whether a passive motion protocol can be used to determine hyper mobility depends upon the segment being adequately stressed. The stressing of a segment is also pertinent to the measurement of attainment rate because an *in vivo* proxy measurement for the neutral zone would be meaningless for a stiff segment. Thus it is recommended that attainment rate is further developed, including selection of a suitable cut off value for hypo mobility. This is further discussed in Chapter 7 p129.

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[11] Research is currently underway at the CI's host institution The Institute for Musculoskeletal Research and Clinical Implementation (IMRCI) to determine intra and inter subject variation.

5.8 Conclusion

This study has conformed to the GRRAS guidelines (Kottner et al. 2011) summarised in the appendix Table 13-12 p252. Compared to other studies the results for reproducibility for mIVRs in this study are within acceptable limits. They are more reliable than manual methods and, on the basis of this the diagnostic utility of mIVRs and differences between patients and healthy volunteers are reported in the following chapter (see Chapter 6 p95).

By contrast, reproducibility for initial intervertebral attainment rate is not as high. The SDC for attainment rate is 0.120 (2 + SEM of L4/5 extension) and this needs to be considered if this parameter was to be used as an outcome measure. It is advised that further refinement of this method is undertaken and the analysis repeated with a larger sample size. The reader is referred to Chapter 7 p129 for an assessment of attainment rate as a kinematic parameter.

5.9 Contribution to new knowledge

There is little standardisation amongst terms used to report reproducibility of QF studies. Breen et al (2006) used an older acquisition method based on the digitisation of analogue images for automated analysis in the coronal plane. Breen (2011) measured passive motion translation and ICR's, and Van Loon et al only measured translation in the sagittal plane (van Loon et al. 2012), whereas Yeager et al measured sagittal rotation and translation with a different image acquisition protocol incorporating both weight-bearing and passive configurations from several centres, thus including inter-site variation (Yeager et al. 2014).

This is the first time that inter and intra observer agreement and reliability for passive intervertebral rotation in the sagittal and coronal planes have been reported for mIVR and attainment rate. Specifically the reproducibility pertains to inter and intra observer errors for data analysis, which incorporates placing of the templates, defining start and end points for data analysis, and data output extraction. This is a strength that enumerates one aspect of the reproducibility of this technique; although inter and intra subject, and site variability need to be considered in the context of QF in a clinical setting

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Chapter 6 Maximum intervertebral rotation

6.1 Chapter overview

The first kinematic variable to be developed was the maximum intervertebral rotation (mIVR). Data acquisition and raw outputs are described earlier (Chapter 3 p45) and differences in means, diagnostic accuracy, and reference intervals are examined.

6.2 Introduction

Current methods for measuring intervertebral range of motion measure from the point of maximum trunk bend, which is highly variable (discussed in Chapter 2 p9). Here, an alternative method of measuring this, which considers the entire bend, is proposed.

The sample size was based on estimated diagnostic accuracy (sensitivity and specificity) for kinematic parameters developed from QF to discriminate between patients with CNSLPB and healthy controls (see p53). The results were initially examined for reproducibility (see Chapter 5 p79) before further statistical testing (see Table 3-1 p50). These analyses were undertaken for each level and direction (n=12) and the STARD criteria[12] were followed for the reporting of the results in this chapter (Bossuyt et al. 2003) (see appendices Table 13-13 p256).

The protocol stated that reference limits would be developed from healthy volunteer data in this study and used as exploratory cut off values for hyper and hypo mobility. Although this is an *a priori* analysis using a composite reference standard (Rutjes et al. 2007) it is acknowledged that using this data as both reference and comparator is problematical. However, this technique has been employed in other studies of intervertebral motion (Schneider et al. 2005; Abbott et al. 2006; Kulig et al. 2007), which increases the possibility of a type one error but in this thesis avoids irradiating a third cohort.

6.2.1.1 Independent passive recumbent QF study

The problem of having no independent data for reference intervals was addressed when, during the course of this study, healthy volunteer data from a separate but similar passive recumbent QF study became available. This data had a different passive motion protocol that moved the upper spine (torso) instead of the lower spine (pelvis) (see Figure 6-4 p113), a smaller sample size, and an updated version of the image processing code. Despite these differences it provided continuous passive

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[12] **STA**ndards for the **R**eporting of **D**iagnostic accuracy studies

motion data that was used to create independent reference limits for completeness, and avoid the increased risk of a type one error. The groups in this study were tested against the independent reference intervals with the following two aims:

i)   To determine whether mean mIVRs from two groups of healthy volunteers were significantly different when a 'hip' or 'torso' passive motion protocol was used (see Independent study hypotheses: p112).

ii)   To determine whether more patients than healthy volunteers exceeded mIVR reference intervals developed from independent data.

6.3   Rationale for study

The rationale for this study is to determine the usefulness of mIVRs as a kinematic parameter by assessing differences in mean values between groups, and diagnostic accuracy. Because there are 12 individual segments/directions to compare, it is not expected that every segment and direction will demonstrate a significant difference or have high sensitivity and specificity.

To determine whether hypo and hyper mobility may be measurable from mIVRs and passive recumbent QF, and because differences between mean values and diagnostic accuracy do not indicate whether a segment may be hyper or hypo mobile, reference intervals were created from two cohorts of healthy volunteers, (the group from this thesis and the second cohort introduced halfway through the thesis from an independent separate, but similar, QF study). The patient and healthy volunteer groups from this thesis were compared with reference intervals and data were counted as abnormal if they were outside these reference intervals (further delineated into hyper mobility if above the upper reference interval and hypo mobility if below the lower limit).

6.4   Literature review

6.5   Summary of literature

The main literature review (see Chapter 2 p9) demonstrates that intervertebral motion is unreliable when measured at the end of trunk range. The literature review in this chapter demonstrates the difficulties in creating cut off values for abnormal intervertebral rotation, which is confounded by variation and errors.

6.5.1 Defining abnormal intervertebral motion *in vivo.*

Cadaveric studies have taught us that intervertebral motion is not linear, and it has previously been difficult to measure the mid-range motion *in vivo*. Consequently clinical and research studies have focussed on end range measurements. For this, functional radiography remains the most common method, (due mainly to its accessibility) but it's a method prone to many sources of error (Deitz 2010) and, despite many normative values for intervertebral motion in the literature (Allbrook 1957; Gonon et al. 1982; Pearcy 1984; Pearcy et al. 1984; Hayes et al. 1989; Yamamoto et al. 1989; White and Panjabi 1990; Dvorak et al. 1991b), there are still no fixed cut off values for normal or abnormal motion. Additionally, studies reporting intervertebral motion from pathological states often fail to agree on their definition of pathology, leading to confusion in much the same way the debate over the meaning of instability prevails (see p21).

Digitisations of medical images and computer aided measurement have helped to reduce errors from image quality in functional radiography although it is still a relatively crude method. The varying definitions of 'abnormal' have primarily focussed on flexion-extension motion, such as translation greater than 3mm (Boden and Wiesel 1990; Boden 1996; Bram et al. 1998; Iguchi et al. 2004; Jang et al. 2009) but the origin of this cut off value is unclear. Hayes (Hayes et al. 1989) references both Dupuis (Dupuis et al. 1985) and Frymoyer and Selby (Frymoyer and Selby 1985) in discussion of a 3mm cut off value, although neither author mention this value in their original studies. Hayes disagreed with 3mm being the distinction between 'normal' and 'abnormal' by demonstrating more than 20% of asymptomatic individuals have more than 4mm translation (Hayes et al. 1989). Boden and Wiesel showed 42% of the healthy population had static measurements greater than 3mm on sagittal radiographs whereas only 5% showed movement greater than this on functional views (Boden and Wiesel 1990), and Morgan and King state instability is present if translation is between 3mm to 1.7cm (Morgan and King 1957) whereas Aho demonstrated translation increased in proportion to intervertebral rotation and was as high as 9mm in a healthy participant who also had 13° at L4/5 (Aho et al. 1955).

Further definitions of abnormal motion include translation greater than 3mm translation combined with rotation greater than 10° (Kong et al. 2009a). Iguchi used these to examine translation and rotation with age (Iguchi et al. 2003) and clinical instability (Iguchi et al. 2004), as did Kanemura (Kanemura 2009). Leone (Leone et al. 2009) states more than 4mm translation and 10° infers radiographic instability and credits Dupuis (Dupuis et al. 1985) Posner (Posner et al. 1982) and Morgan and King (Morgan and King 1957) as support for these values although these authors do not mention such cut offs. Nevertheless, these values are frequently used to discern

between abnormal and normal (Hanley 1995; Sonntag and Marciano 1995; Weinstein et al. 2006). White and Panjabi suggest even greater values of 4.5mm, or 15% of the vertebral body width as indicative of instability (White and Panjabi 1990) although for this to be clinically significant they acknowledge this needs to be combined with other signs and symptoms including excessive angular rotation. More recent studies involving flexion-extension MRI have adopted this approach (Rihn et al. 2007) and do not use previously defined cut off values.

The problem of direct measurement and scale has led some authors to use a definition based on adjacent segments. While such scaling can account for radiographic magnification (Lee 2005) it does not help define normal or abnormal. Some authors claim that flexion extension rotation greater than 10° of the adjacent segment is abnormal (Pitkanen and Manninen 1994) while others have used percentage vertebral body width. Posner et al (Posner et al. 1982) defined abnormal, which they call instability, as A-P translation in flexion greater than 8%, or extension greater than 9% of adjacent vertebral body width but their results are from cadaveric studies. However, Boden and Wiesel agreed that more than 8% of vertebral body width for flexion/extension combined is abnormal (Boden and Wiesel 1990).

Using different values as a cut off makes it impossible to combine or compare results. Furthermore labelling excessive motion as instability may lead to a tendency to equate it with hyper mobility, which may not be pathological or symptomatic (Muggleton et al. 2000). Celestini et al (Celestini et al. 2005) states there does not appear to be any systematic relationship between hyper mobility and instability and Dvorak et al (Dvorak et al. 1991a) noted angular values could be greater than 20° in a healthy population. Despite this confusion, the American Medical Association's (AMA) Evaluation of Permanent Impairment (American Medical Association 2008)[13] recognises a condition called 'Alteration of Motion Segment Integrity' (AOMSI) that is defined in the lumbar spine as translation greater than 4.5mm and rotation greater than 15° at segments L1/2, L2/3 and L3/4. 20° at L4/5 and 25° at L5/S1 measured from weight-bearing functional radiographs.

6.5.2 Reference intervals for hyper and hypo mobility

A way of defining normal, as in where the majority of the values are expected to lie, is to create a reference interval from a healthy population. A reference interval describes the variations of measurements within a healthy population and it is generally defined as observed values that are within the 95% of all values, providing the data has a Gaussian distribution. Bland notes that the term 'reference interval' avoids the

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[13] The AMA is used to determine worker's compensation in the USA

confusion between 'normal' as used in medicine and 'normal distribution' as used in statistics, despite the common method of calculation depending upon a statistically normal (Gaussian) distribution (Bland 1996). The Clinical Standard Laboratory Institute (CLSI) further delineate the terms used in connection with reference intervals (Figure 6-1 p100), adhered to in this thesis.

There are other ways to calculate reference intervals, although the CSLI guidelines emphasize that the method of calculation is less important than selecting appropriate reference subjects, an adequate sample size, and avoiding pre-analytical errors (CLSI 2008). They recommend of a minimum of 120 observations, although they recognise that a reference interval can be created from smaller groups if the measurement technique has increased precision. Thus, from a Gaussian population, the reference interval is defined as the values that fall between $\overline{X} +/-1.96SD$ although this is often rounded up to $\overline{X} +/-2SD$ (Bland 1996). In a population that is not normally distributed, if the data cannot be transformed then it is recommended that the reference interval may be estimated by the 2.5[th] and 97.5[th] centiles (Bland 1996; CLSI 2008).

For *in vivo* intervertebral motion, the $\overline{X} +/-2SD$ has previously been used for cut off values to identify hyper and hypo mobile segments with both MRI (Kulig et al. 2007) and functional radiographs (Schneider et al. 2005; Abbott et al. 2006). These were not referred to as 'reference intervals' and confidence limits were not displayed, possibly because the sample sizes in these studies were small (Kulig et al, n=20, Abbott et al n=30 and Schneider et al n = 20). Interestingly, Kulig et al and Abbot et al reported conflicting results; Kulig et al found significant associations between hyper mobility and LBP (and no significant associations with hypo mobility) whereas Abbott et al discovered the opposite (associations between hypo mobility and LBP, but not hyper mobility). However, Kulig et al studied recumbent extension (both passive and active) and Abbot et al studied weight-bearing flexion. If such results were replicated in other studies it would point to a need to examine flexion and extension independently.

Reference individuals – a person selected for testing based on well-defined criteria. It is usually important to define the person's state of health

Comprise a

Reference population – a group consisting of all the reference individuals

From which is selected a

Reference sample group – an adequate number of persons selected from the reference population

On which are determined

Reference values – The observed value obtained from a reference individual which may be compared to a reference value, reference distribution, reference limit or reference interval

That characterise

Reference distribution – the distribution of the reference values

From which are calculated

Reference limits – A value derived from the reference distribution and used for descriptive purposes. It is common to define a reference limit so the stated fraction of reference values are 'greater than or equal' and 'less than or equal' to the respective upper or lower reference limit.

That may define

Reference intervals – The values between and including two reference limits

Figure 6-1 Definitions of terms used in connection with reference intervals (CLSO 2008)

Deitz et al (Deitz 2010) reviewed fifteen datasets of maximum IV rotation in the sagittal plane from healthy participants, but claimed that only three of the datasets (Pearcy et al. 1984; Boden and Wiesel 1990; Frobin 1996) could be combined because they

published mean values and standard deviations, and adequately described their methods. Deitz combined these to create values based on the aggregated $\overline{X} +/- 2SD$ from the combined sample size of 112 males (see Table 6-1 p101), however, given the variability in technique and errors (discussed in the main literature review Chapter 2 p9) it may be erroneous to combine such data. This is further illustrated by Zuberbier et al who reviewed lumbar RoM tests, (both global and intervertebral) and reported that mean scores and standard deviations for lumbar range of motion measurements showed a high degree of overlap between the scores of healthy volunteers and those with LBP (Zuberbier et al. 2001).

	Aggregated Mean across 3 sites (º)	Aggregated SD across 3 sites	Lower reference limit (º)	Upper reference limit (º)
L1/2	10.6	3.8	3	18.3
L2/3	11.6	4.4	2.8	20.4
L3/4	11.8	5.1	1.6	22
L4/5	13.8	6	1.7	25.8
L5/S1	11.9	6.4	-1	24.8

Table 6-1 Average sagittal RoM and reference limits combined from 3 comparable studies; taken from Deitz et al (Deitz 2010)

Attention is brought to the negative lower cut off value for L5/S1 in Table 6-1 p101, which initially suggests that for a segment to be labelled as hypo mobile it has to display paradoxical motion although it could also be a statistical issue.

Paradoxical motion was previously thought to be a feature of instability (Knutsson 1944; Schneider et al. 2005) . The lower cut off values derived from Abbot et al are even greater (-2.44º for L4/5 and -5.71º for L5/S1), which has interesting implications for their results as they conclude that hypo mobility is associated with CNSLBP, when it may in fact be paradoxical motion. The negative value may also be associated with sampling error or indicate that the assumption of normal distribution is not true.

The wide range of reference intervals and negative lower reference limits makes them difficult to use in clinical practice, but if such variability could be reduced, reference intervals for intervertebral rotation could provide useful insights into hyper and hypo mobility in the spine and its relationship to pain. It is important to distinguish between these two sub groups as the underlying biology and treatment options are different (i.e. mobilisation such as spinal manipulative therapy for hyper mobility, and stabilisation such as fusion for hyper mobility).

6.6   Research question

Can maximum intervertebral rotation (mIVR) measured from continuous data distinguish between patients and healthy volunteers?

6.7   Aim

The aim of this study was to examine mIVR in both CNSLBP and healthy volunteers when variability in positioning, range and rate of trunk motion, and errors in analysis were reduced.

6.8   Hypothesis

1. Using ROC analysis, maximum intervertebral rotation measured from passive recumbent motion can distinguish between patients with mechanical low back pain and healthy volunteers

Secondary hypotheses were:

2. There will be significant differences in the mean mIVR in patients compared to healthy volunteers.
3. There will be significant differences in the proportion of patients with mIVR values outside the reference intervals.

6.9   Methods

The demographics of the patients and healthy volunteers are detailed in Chapter 4 p73. No adverse effects were noted from QF, and the handling of missing values is detailed on p70. The study setting and population, including exclusion and inclusion criteria are defined on p53. The index test was mIVR values (in degrees, per level and direction) that are derived from interval (continuous) variables. The materials and methods are detailed in Chapter 3 (p45) and the procedure is described from p59. Statistical analysis is detailed in Table 3-2 p52, and reproducibility of mIVR values are detailed in Chapter 5 p79.

6.9.1.1   Maximum intervertebral rotation measurements

To obtain maximum intervertebral rotation (mIVR), the range between maximum and minimum in the motion pattern was calculated (see Figure 5-1 p83). Initial graphical output represents left and flexion data as negative, and right and extension as positive on the y axis. For the purpose of mIVR the data were made positive for all directions.

6.9.1.2   Diagnostic accuracy

Maximum IVR values for each participant per level and direction were subject to a ROC analysis in order to calculate sensitivity and specificity with 95% confidence limits, and the area under the curve (AUC). The interpretation of the AUC is given below in Table 6-2 p103.

AUC	Interpretation
1.0	Perfect
0.9 to 0.99	Excellent
0.8 to 0.89	Good
0.7 to 0.79	Fair
0.51 to 0.69	Poor
0.5	Worthless

Table 6-2 Interpretation of the area under the ROC curve (Institute for Evidence-Based Health Professions Education 2010)

Given that the sample size was small and that the frequency of mechanical disruption as the cause of back pain in the population was unknown, likelihood ratios and positive and negative predictive values were not calculated.

6.9.1.3   Reference limits created from healthy volunteers in this study

Upper and lower reference limits ($\overline{X} +/- 2SD$) were created from healthy volunteer data (n=40) in this study to compare to patient data (see p98). Observed values for each participant (n=80) per level and direction (n=12) were compared to the reference limits to determine those that had values

 i) Greater than or equal to the upper reference limit (hyper mobility).
    Or
 ii) Less than or equal to the lower reference limit (hypo mobility)

Data were also combined for overall direction. No weighting was attributed to the counts, hence, in theory one participant may have 12 counts (out with the reference intervals for each level and direction) which, for the purpose of combined analysis, was counted as one.

6.10 Results

6.10.1 Parametric assumptions

Data were normally distributed with the exception of extension L3/4 for healthy volunteers and left L3/4 for patients (see appendix Table 13-14 p256). Right and flexion L4/5 and right L3/4 did not have homogeneity of variance between the two groups (see appendix Table 13-15 p256).

6.10.2 Differences in mean values

Values are descriptively displayed in a box and whisker plot Figure 6-2 p105 [14] and the full data set is in the appendix (Table 13-16 p257) along with the statistical significance of each level and direction Table 13-16 p257. Only left L4/5 showed significant differences (p=0.03), with patients tending to have lower mIVRs than healthy volunteers. Right L3/4 returned a p value of 0.06 and patients tended to have higher mIVRs. This is interesting because they are both in the coronal plane and suggests L3/4 may be compensating for L4/5 to maintain global RoM, although it could also be a chance finding due to 12 individual significance tests being undertaken.

6.10.3 Variation in values

Of note is the larger variation of measurements in patients versus healthy volunteers for all levels, even though the trunk motion and participant positioning was standardised and homogeneity of variance tests were mostly not significant. Also of note is that for flexion, the lower segments (L4/5) have a larger mean value that the upper segments (L2/3), which may be due to the hip swing nature of passive motion, although this was not observed in other directions. For healthy volunteers, the mean percentage of 40° table motion absorbed by L2 to L5 ranged from 11.8% in extension to 64% in left bending. For patients the range of means was greater, from 9.3% in extension to 71.8% in right bending (see Table 6-3 p104).

Direction	Patients	Healthy volunteers
Left % (SD)	48.7 (10.2)	51.3 (8.7)
Right % (SD)	46.1 (10.7)	45.3 (8.6)
Flexion % (SD)	43.1 (10.1)	40 (8.9)
Extension % (SD)	34.9 (11.7)	35.2 (10.7)

Table 6-3 Mean percentage motion taken up between L2 to L5 in patients and healthy volunteers

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[14] This shows mean and median values for each level and direction (minimum and maximum values are represented by the tails).
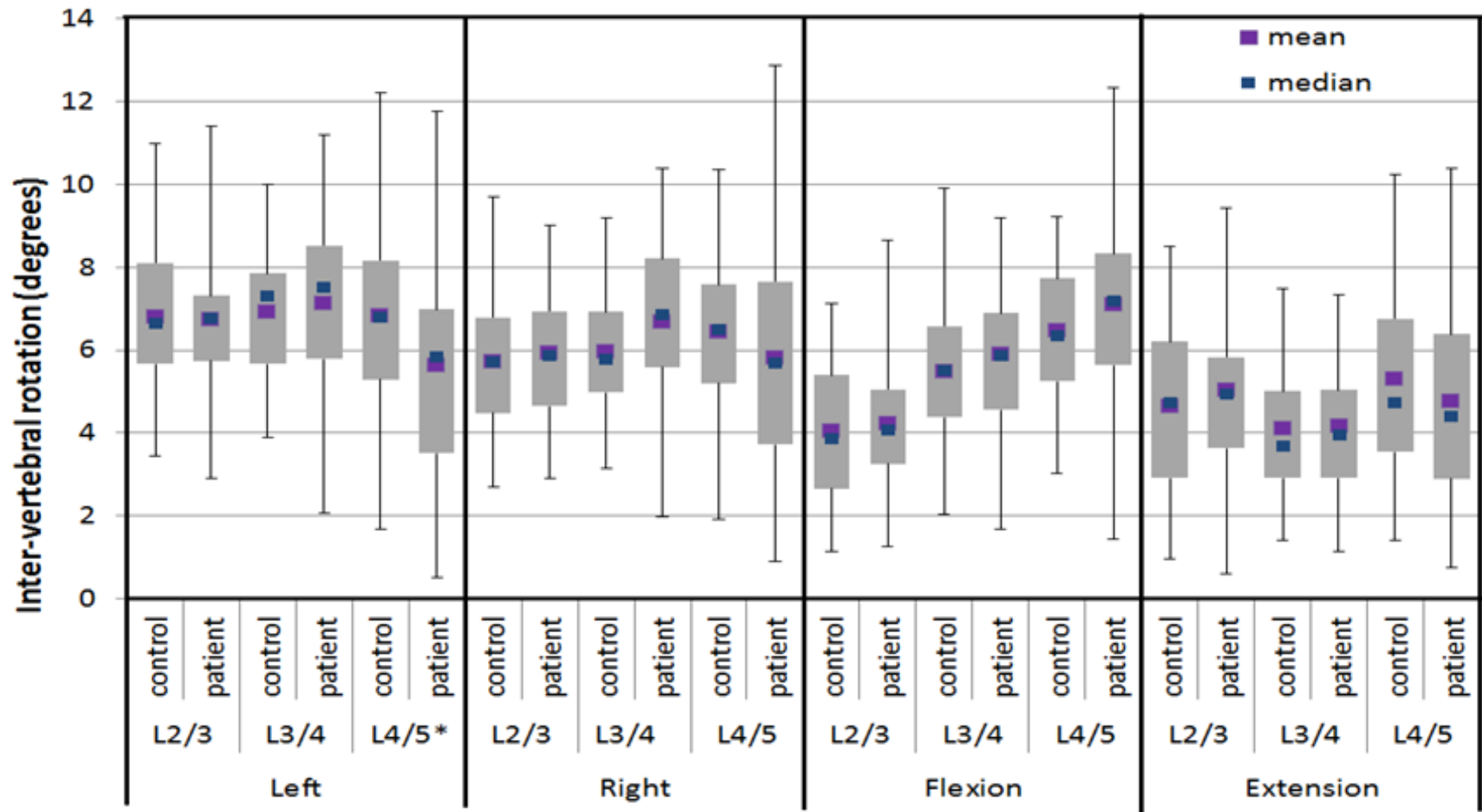
Figure 6-2 Box and whisker plot for mIVR in patients and healthy volunteers

(* statistically significant, p<0.05)

6.10.4   Diagnostic accuracy

Each level and direction was assessed for sensitivity and specificity and area under the curve (AUC) using all possible cut off points, with no consideration for co-dependency. The optimum cut off points were determined by the ROC curves (see Figure 6-3 p106). The greatest AUC was 0.642 for right L3/4 indicating that mIVR's alone cannot distinguish between patients and healthy volunteers, and at this level it is a poor test for discrimination. The fact there is low diagnostic accuracy for intervertebral mIVR values may be a feature of the clinical diagnosis of mechanical LBP that suffers from a diversity of approaches and a lack of uniform interpretation and adequate subgroups so is essentially a flawed gold standard.
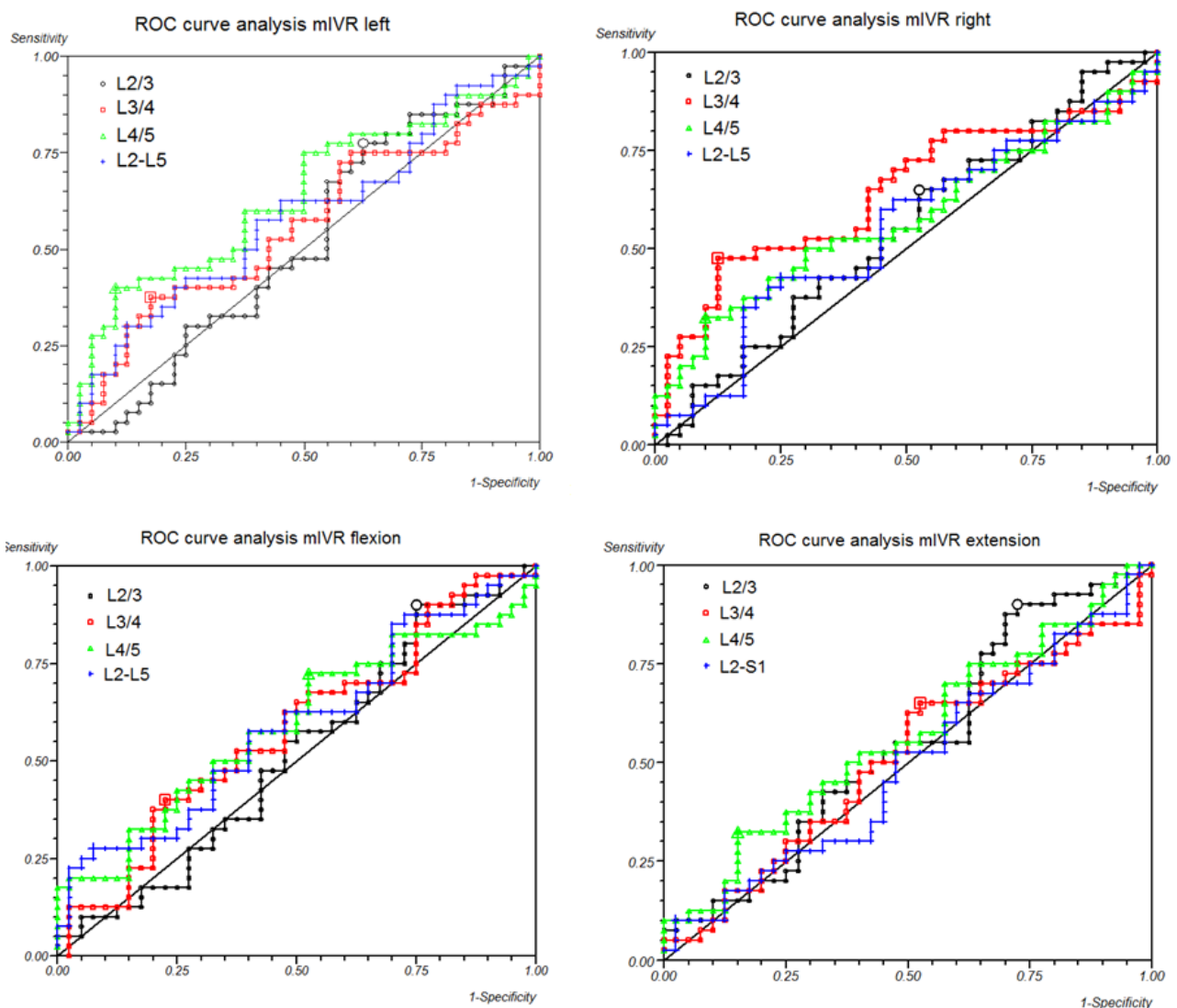
Figure 6-3 ROC curve analysis for mIVRs in each direction

Despite some levels demonstrating specificity greater than 0.8 (flexion L2/3 and extension L2/3), and some levels demonstrating sensitivity greater than 0.9 (left L4/5 right L4/5, flexion combined L2 to L5 and extension combined L2 to L5), no levels had

both high sensitivity and specificity. The highest AUC was 0.642 for right L3/4, with a sensitivity of 0.48 and a specificity of 0.89, which indicates that at this level mIVR is better at ruling out a mechanical derangement than ruling one in, but it is a poor test (see Table 6-2 p103). It is also of note that this level had a p value of 0.06 with patients having higher mean mIVR's than healthy volunteers. (see Table 6-4 p107).

Direction	Level	Sensitivity (95% C.I.)	Specificity (95% C.I.)	AUC (Wilcoxon estimate)
Left	L2/3	0.775 (0.615 to 0.892)	0.375 (0.227 to 0.542)	0.514
	L3/4	0.375 (0.227 to 0.542)	0.825 (0.671 to 0.927)	0.560
	L4/5	0.4 (0.249 to 0.567)	0.9 (0.763 to 0.975)	0.638
	L2-5	0.3 (0.166 to 0.465)	0.875 (0.731 to 0.958)	0.581
Right	L2/3	0.65 (0.483 to 0.793)	0.475 (0.315 to 0.639)	0.546
	L3/4	0.475 (0.315 to 0.638)	0.875 (0.732 to 0.958)	0.642
	L4/5	0.325 (0.186 to 0.491)	0.9 (0.763 to 0.972)	0.579
	L2-5	0.425 (0.27 to 0.591)	0.75 (0.588 to 0.873)	0.548
Flexion	L2/3	0.9 (0.763 to 0.972)	0.25 (0.123 to 0.412)	0.516
	L3/4	0.4 (0.249 to 0.567)	0.775 (0.615 to 0.891)	0.577
	L4/5	0.725 (0.561 to 0.854)	0.475 (0.315 to 0.639)	0.591
	L2-5	0.275 (0.146 to 0.439)	0.925 (0.796 to 0.984)	0.589
Extension	L2/3	0.9 (0.763 to 0.972)	0.275 (0.146 to 0.439)	0.545
	L3/4	0.65 (0.483 to 0.794)	0.475 (0.315 to 0.639)	0.510
	L4/5	0.325 (0.186 to 0.491)	0.85 (0.702 to 0.943)	0.566
	L2-5	0.1 (0.028 to 0.237)	0.975 (0.864 to 0.999)	0.508

Table 6-4 Sensitivity, specificity and AUC for mIVR

6.10.5   Reference intervals

The '*a priori*' reference intervals ($\overline{X} +/-2SD$) created from healthy volunteer data in this study are shown in Table 6-5 p108.

6.10.5.1   Reference intervals for each segment

The numbers of segments exceeding the upper or lower reference limit are presented in Table 6-6 p109. No segment demonstrated a significant proportion of patients falling below the lower reference limit. Only flexion L4/5 showed a significant difference in proportions exceeding the upper reference limit (p = 0.03) where 15% of the patient group exceeded the reference intervals compared to no volunteers. Right L3/4 was

almost significant (p=0.06) with 17.5% of patients returning values greater than the upper reference limit[15].

		Upper reference limit ° (95% C.I)	Lower reference limit ° (95% C.I)
Left	L2/3	10.28 (9.96 to 10.59)	3.32 (3.01 to 3.63)
	L3/4	9.94 (9.62 to 10.25)	3.90 (3.58 to 4.22)
	L4/5	11.20 (10.89 to 11.51)	2.44 2.13 to 2.76)
Right	L2/3	8.90 (8.61 to 9.19)	2.53 (2.24 to 2.82)
	L3/4	8.61 (8.32 to 8.91)	3.32 (3.02 to 3.61)
	L4/5	10.27 (9.96 to 10.57)	2.61 (2.30 to 2.91)
Flexion	L2/3	7.13 (6.89 to 7.37)	0.97 (0.73 to 1.21)
	L3/4	8.99 (8.71 to 9.27)	2.00 (1.72 to 2.28)
	L4/5	9.49 (9.18 to 9.79)	3.43 (3.13 to 3.74)
Ext	L2/3	8.44 (8.18 to 8.70)	0.84 (0.58 to 1.10)
	L3/4	7.16 (6.92 to 7.41)	1.06 (0.082 to 1.30)
	L4/5	10.06 (9.78 to 10.33)	0.57 (0.29 to 0.85)

Table 6-5 Upper and lower reference intervals for mIVR for each level and direction derived from healthy volunteers (95% C.I)

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[15] 2.5% of healthy volunteers exceeded right L3/4, which is the expected observation

		Above the upper reference limit			Below the lower limit		
		patients	healthy volunteers	Fisher's Exact p=	patients	healthy volunteers	Fisher's Exact p=
left	L2/3	1	2	>0.99	1	0	>0.99
	L3/4	1	1	-	4	0	0.12
	L4/5	1	1	-	5	1	0.20
right	L2/3	1	1	-	0	0	-
	L3/4	7	1	0.06	3	1	0.62
	L4/5	2	1	>0.99	6	1	0.11
flex	L2/3	2	0	0.49	0	0	-
	L3/4	1	1	-	1	0	>0.99
	L4/5	6	0	0.03	4	1	0.36
ext	L2/3	3	1	0.65	1	0	>0.99
	L3/4	2	2	-	0	0	-
	L4/5	0	2	0.49	0	0	-

Table 6-6 Number of participants with mIVR values outside reference intervals per segment and significant differences in proportions (Fishers two tailed exact test)

It would be erroneous to conclude that there is an association between flexion L4/5 hyper mobility and being a patient based on these results due to nature of the reference interval derivation, the small sample size and the multiple significance tests. They are reported here as a possible solution to objectively measuring hyper and hypo mobility from passive QF motion data.

6.10.5.2   *Reference limits for direction, plane of motion, and combined*

Intervertebral data were combined to enable each direction, plane and overall motion to be examined (see Table 6-7 p110).

	Above the upper reference interval			Below the lower reference interval		
	patients	healthy volunteers	Fisher's Exact p=	patients	healthy volunteers	Fisher's Exact p=
left	3	4	>0.99	10	1	0.01
right	8	2	0.09	9	2	0.05
flex	9	1	0.01	5	1	0.2
ext	5	5	-	1	0	>0.99
Coronal	9	5	0.38	9	2	0.05
Sagittal	11	6	0.27	4	1	0.359
All combined	16	10	0.23	11	3	0.04

Table 6-7 Counts for patients and healthy volunteers who have mIVR values outside the reference interval for direction, plane of motion and overall.

Four instances demonstrated patients had proportionally more values below the lower reference limit than healthy volunteers. These were; Left p= 0.01, Right p = 0.05, Coronal p = 0.05, and all directions and levels combined p = 0.04. For left and right motion, the numbers of patients and healthy volunteers below the lower limit was 10 (25%) and 1(2.5%), and 9 (22.5%) and 2 (5%) respectively. For exceeding the upper limit, flexion (p=0.01) had 9 (22.5%) patients and only one healthy volunteer (2.5%). When combined the proportions were not statistically significant.

It is interesting to note that the coronal plane demonstrates statistical significance for hypo mobility, and flexion shows statistical significance for hyper mobility. This suggests that within this group there is a subgroup of both hyper and hypo mobility, which also explains the greater variation in overall mIVR values, and has important implications for treatment options.

6.10.6   Summary of results for mIVR:

1. No levels demonstrated high sensitivity and specificity suitable for a diagnostic test, the greatest AUC was just 0.642 for right L3/4. Consequently the primary hypothesis that passive recumbent motion can distinguish between patients with mechanical low back pain and healthy volunteers was rejected.
2. The secondary hypothesis was that there will be significant differences in mean mIVR values between patients and healthy volunteers. This was also rejected because only one out of twelve segments demonstrated statistical significance.
3. The third hypothesis was that patients will have a higher proportion of mIVR values outside the reference interval. This was partially accepted because when

segments were combined, three out of four directions demonstrated a statistical significance between groups.

Deriving reference interval from the same population to be tested (in this case the healthy volunteers) increases the risk of a type one error. For this reason no firm conclusions can be drawn from these mIVR reference limits although, when combined with the differences in mean values and diagnostic accuracy, there appears to be more biomechanical differences between patients and healthy volunteers in the coronal plane, and this warrants further investigation.

6.11 Independent passive recumbent QF study:

6.11.1   Introducing independent healthy volunteer data

The increased risk of making a type one error was addressed when, during the course of this thesis, new data from a similar QF study were made available. The other study used passive QF but crucially had a different motion protocol where the trunk moved to 40° and the hips were stationary (the opposite to this study) See Figure 6-4 p113. The concern was that the passive hip swing protocol would influence the lower levels to rotate further than the upper levels, and the opposite would be true with the trunk swing protocol. This could introduce some unknown and systematic confounders, consequently statistically significant differences in mIVR means of the two healthy volunteer groups were first assessed, and only those segments with no significant differences were used to develop independent reference limits $(\overline{X} +/- 2SD)$.

6.11.2   Independent study hypotheses:

1. There will be no differences in mIVR mean values of the two groups of healthy volunteers
2. Patients will have a greater proportion of mIVR values outside the independent reference intervals compared to healthy volunteers.

6.11.3   Independent study methods

Maximum IVR values and standard deviations from healthy volunteers (n = 17 for sagittal data and 20 for coronal data), aged from 36 -52yrs, were obtained. The analyses of the independent data were undertaken by 4 other trained observers using a slightly different version of the analysis software, of which, the ICCs/SEMs are unknown. However, image acquisition was performed with the same equipment using the same passive range and velocity. Statistical analysis is detailed in Table 3-2 p52.
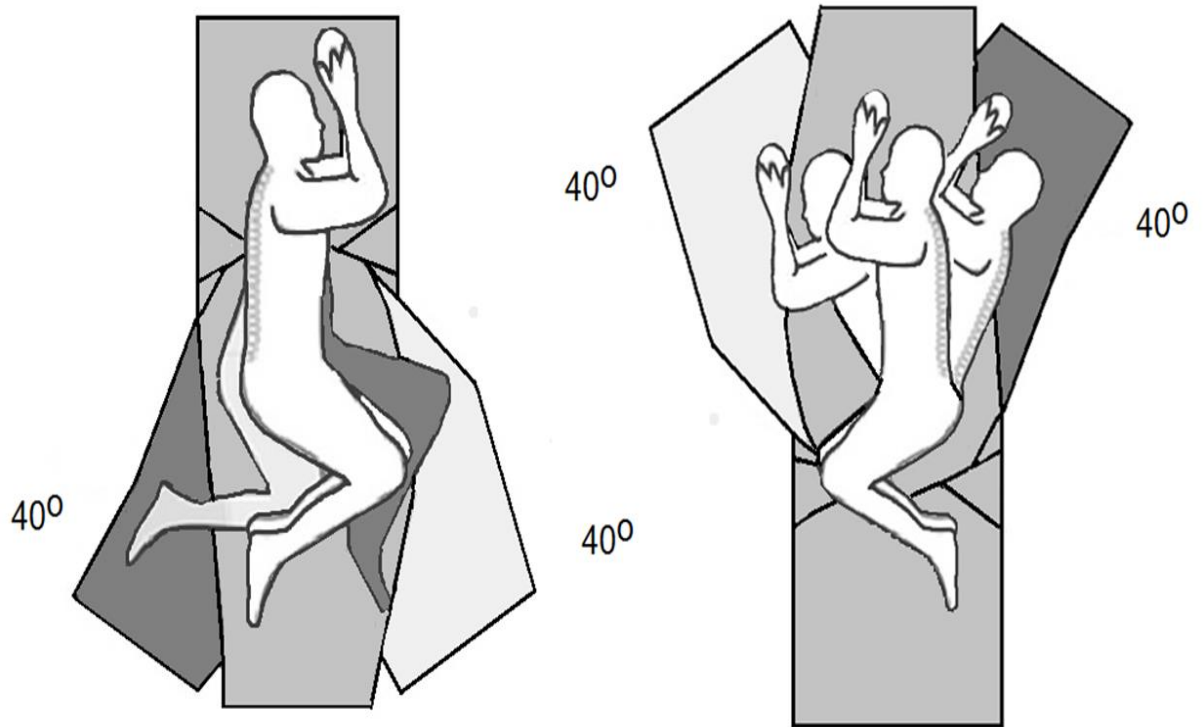
Figure 6-4 Left: Hip swing (this study). Right; trunk swing (independent study)

6.11.4   Independent study results:

The author examined the data for parametric assumptions and not all data met these (see Table 13-17 p258 and Table 13-18 p258 in the appendix). The statistical test for examining differences between means of the two healthy volunteer groups was selected accordingly, and only three segments showed significance, right L3/4 p =0.01, extension L3/4 p = 0.01 and extension L4/5 p = 0.01 (see Table 13-19 p259 in the appendix). Figure 6-5 p115 depicts the minimum, maximum, means and reference intervals from the healthy volunteer data in this study and the independent study (the shaded segments are those levels with significant differences and are not used in the reference interval analysis). The values for the upper and lower reference intervals from the independent data are in Table 6-8 p114.

	Left °		Right °		Flexion °		Extension °	
	Lower ref limit	Upper ref limit	Lower ref limit	Upper ref limit	Lower ref limit	Upper ref limit	Lower ref limit	Upper ref limit
L2/3	3.12	10.32	2.75	9.37	0.96	6.75	2.05	6.61
L3/4	4.07	10.16	4.44	9.55	2.12	9.92	1.99	8.62
L4/5	2.26	10.13	2.90	9.97	2.07	10.81	-2.66	8.76

Table 6-8 Upper and lower reference intervals for mIVR derived from healthy volunteers in a similar study[16]

6.11.4.1.1 a) Reference limits from independent data

Once again, counts were divided into: i) Exceeding the upper reference limit and ii) Falling below the lower reference limit. Table 6-9 p116 shows no significant differences in the proportions of patients or healthy volunteers from this thesis, demonstrating no differences for hyper or hypo mobility when independent reference intervals were used. It was not possible to combine data for right and extension, nor sagittal coronal and overall motion because some segments in these directions (the shaded areas in Table 6-8 p114) demonstrated significant differences to the healthy volunteer data in this study. Data were combined for left and flexion but again there were no significant associations for hyper or hypo mobility (see the appendix, Table 13-21 p261).

6.11.5   Independent study: summary

The primary hypothesis was that there were no statistically significant differences in mean mIVRs from two groups of healthy volunteers. This was partially supported because there were no differences for five out of twelve segments. The secondary hypothesis was that patients will have a greater proportion of mIVR values outside the reference interval than healthy volunteers (n=40) was also rejected. However, these data were introduced for exploratory reasons and has a small sample size (n=17 to 20), thus caution is advised when interpreting the results.

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[16] The shaded are in Table 6-7 depicts mean mIVR data that were significantly different to the healthy volunteer group in this study.
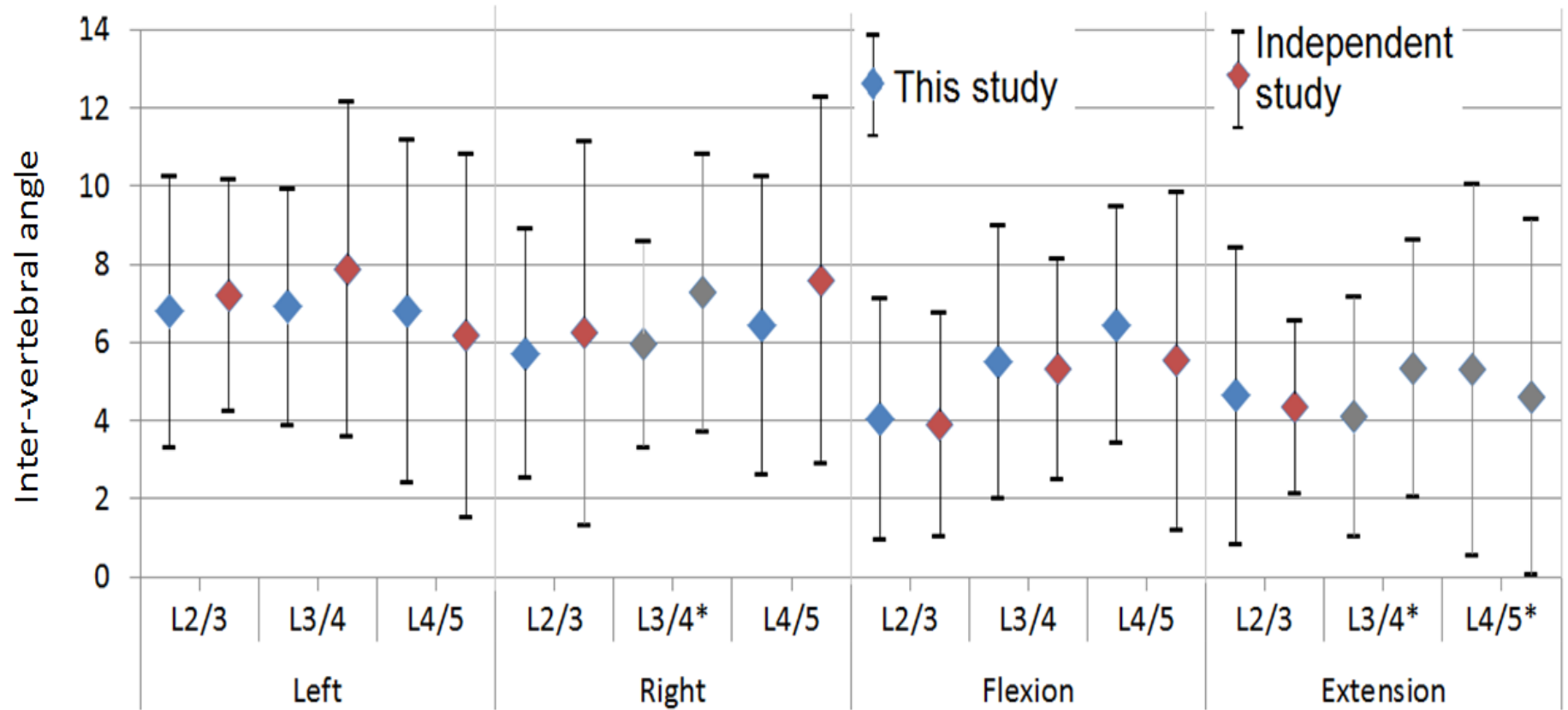
Figure 6-5 Healthy volunteers mean mIVR reference intervals from this study (n=40) and the independent QF study (n=17 to 20) (error bars are upper and lower reference limits)

NB: the grey bars/starred segments are not included in the analysis of reference intervals because there were significant differences in the mean values between groups

		Above upper reference limit			Below lower reference limit		
		patients	healthy volunteers	Fisher's Exact p=	patients	healthy volunteers	Fisher's Exact p=
left	L2/3	1	2	>0.99	1	0	>0.99
	L3/4	1	0	>0.99	4	1	0.36
	L4/5	2	1	>0.99	5	1	0.20
right	L2/3	0	1	>0.99	0	1	>0.99
	L3/4	2	0	0.24	6	0	0.03
	L4/5	2	2	-	6	2	0.26
flex	L2/3	3	0	0.24	0	0	-
	L3/4	0	1	>0.99	1	1	-
	L4/5	3	0	0.24	1	0	>0.99
ext	L2/3	6	7	>0.99	2	4	0.66
	L3/4	0	0	-	5	1	0.20
	L4/5	2	4	0.68	0	0	-

Table 6-9 Statistically significant proportions of participants with mIVR values outside independent reference intervals

6.12 Discussion of mIVR as a kinematic parameter

The definition of mIVR in this thesis is different to the maximum achievable range, but standardisation of range and velocity was necessary to compare patients with healthy volunteers, as noted by Vitzum et al (Vitzthum 2000).

Maximum intervertebral rotation was examined for differences in mean values and diagnostic accuracy, and reference intervals were created as suggested cut offs for hyper and hypo mobility, additionally independent data were introduced as a comparator. Individual intervertebral levels were examined, and data were combined for direction and plane of motion. It is acknowledged that looking at individual levels may be flawed if no account is made for co-dependency, although other studies do not address this (Wong et al. 2004; Abbott et al. 2006; Kulig et al. 2007; Teyhen et al. 2007b). However, it appears that co-dependency may be a factor, because patients have significantly higher mIVR values for right L3/4 and lower values for left L4/5 than healthy volunteers. This could be explained by L3/4 compensating for L4/5 in the coronal plane, as noted by Passias et al also in the coronal plane (Passias et al. 2011).

Maximum IVR values had very low diagnostic accuracy for distinguishing patients from healthy volunteers, and there was no particular trend, unlike for clinical tests, which were found to have a trend of high specificity and low sensitivity (Alqarni et al. 2011). Consequently mIVRs are not recommended as a stand-alone kinematic parameter; rather it is recommended that they be investigated for use in conjunction with other kinematic parameters. This approach has been undertaken in other studies that used sets of kinematic or clinical factors to distinguish between patients and healthy controls.(Childs et al. 2004; Fritz et al. 2005; Teyhen et al. 2007a; Teyhen et al. 2007b).

With respect to reference intervals, data in this thesis demonstrated no hyper or hypo mobility when compared to independent reference limits, and only L4/5 flexion in patients' demonstrated hyper mobility compared to left, right and flexion for hypo mobility when data was combined. The lack of statistical significance may point to a lack of statistical power in this study, and the issue of multiplicity of statistical testing needs to be considered. Furthermore it is still unknown whether passive recumbent motion with controlled trunk range is suitable for detecting hyper mobility because it is not known whether the segments have been sufficiently stressed by a standardised trunk bend. Conversely, if it is presumed that weight-bearing maximum trunk range protocols sufficiently stress segments (as used in functional radiography and some QF studies) then a comparison of passive recumbent results with these studies may help clarify this; however the intra subject variation may make the comparisons untenable.

It is possible to compare passive recumbent results with a weight-bearing study that removes the confounder of unknown trunk range because Wong et al measured intervertebral flexion at 40° of trunk rotation in weight-bearing postures in 100 healthy individuals (Wong et al. 2006). Wong et al's results are compared to these in Table 6-10 p118. And interestingly results from this study are less than those reported for weight-bearing at the same trunk range in two out of three segments. Additionally, a study in progress (Breen et al. 2013) reports greater ranges in weight-bearing than passive motion for flexion and left bending when the trunk is moved to 40°. Consequently it may be that segments are not adequately stressed in the passive hip swing protocol to detect hyper mobility.

This is in contrast to Dvorak et al, who found greater RoM in passive motion (Dvorak et al. 1991a). Indeed they called for further studies into passive recumbent motion hypothesising that a patient in pain would not bend as far as possible in active (weight-bearing) motion and as such would be less likely to reveal a hyper mobile segment. Fear avoidance of movement is well known in the literature (Pfingsten et al. 2001). To

avoid this, the participants in Breen et al's study (2013) undergo guided trunk rotation that is practised, and this could be why their results contradicted Dvorak et al.

Intervertebral level	mIVR passive flexion from healthy volunteers n = 40. Mean $^{\circ}$ (SD)	Wong et al (2006) Weight-bearing flexion at 40° trunk motion in healthy volunteers n=100. Mean $^{\circ}$ (SD)
L2/3	4.05 (1.54)	9.64 (0.99)
L3/4	5.5 (1.75)	8.18 (0.81)
L4/5	6.46 (1.5)	5.94 (1)

Table 6-10 Comparison of healthy volunteer flexion intervertebral rotation at 40° trunk rotation with Wong et al (2006)

Inadequately stressing each segment had important implications in the diagnosis of hyper mobility. Conversely 40° of trunk rotation was found to provide enough force to test hypo mobility because the highest SEM was 0.77° (inter observer L2/3 in extension see Table 5-2 p84) so any movement above this value is unlikely to be due to errors in agreement. This lends credibility to the detection of hypo mobility with QF passive motion, and it is suggested that this is studied further.

Additionally it is interesting to note that that the mean mIVR increases through inferior segments in flexion in this study (See Figure 6-2 p105); the opposite is true for Wong et al (Wong et al. 2004). This may be a reflection of both the nature of movement and the forces acting upon the spine. Additionally, Wong et al's results may be a feature of the phase lag effect that was noted by Kanayama et al in weight-bearing postures (Kanayama et al. 1996) and later confirmed by Breen (Breen 2014), although not subjectively noted in passive recumbent motion.

Ultimately the question of whether a segment is stressed sufficiently to determine rotational hyper mobility with the passive motion QF protocol cannot be answered in this thesis and this has implications in the use of the independent reference intervals developed from the independent QF study. This is because each segment may move to a different mIVR dependent upon whether the upper or lower torso is passively moved, however they add evidence that QF reduces variation when compared to functional radiographs.

6.12.1   Variation within patients

Variation of the percentage of motion taken up by L2 to L5 was subjectively larger in patients than healthy volunteers (see Table 6-3 p104) and this was also observed by Abbott et al (Abbott et al. 2006). Abbott et al proceeded to develop a novel way of addressing this by creating 'normalised within subjects approach' that essentially

calculated the percentage contribution of each segment to the total overall motion. This approach has also been undertaken by Wu et al in the cervical spine (Wu et al. 2010).

The reference intervals and SD's for controlled recumbent passive motion are much smaller than those for weight-bearing functional radiographs (see Figure 6-6 p123) demonstrating QF is a method that reduces variation and sources of measurement error. The passive protocol reduces; the influences of motor and muscular control (see Figure 2-5 p20), intra and inter subject variation in global trunk range, and measurement error. Additionally it reduces the influence of initial lumbar lordosis and the resultant variations in loading that is currently being observed in weight-bearing postures (Breen et al. 2013).

6.12.2   Differences between patients and healthy volunteers

Only one segment demonstrated a statistically significant difference (left L3/4 p=0.03 see Figure 6-2 p105) although a second segment was almost significant (right L4/5 p=0.06). Both of these were in the coronal plane thus on the basis of these results it is recommended that the coronal plane should be included in the radiological assessment of intervertebral motion. Symmetry of motion was previously studied and there was no significant variation in left –right motion (Mellor et al 2009), thus it was not investigated in this thesis.

There were no statistical differences for any levels in the sagittal plane, agreeing with Ahmadi et al (Ahmadi et al. 2009) who used QF, and Okawa et al (Okawa et al. 1998) who used functional radiographs. Both used uncontrolled weight-bearing motion and found no differences between patients and healthy volunteers. Conversely this study contradicts findings by Abbott et al and Kulig et al who found differences in flexion and extension respectively (Abbott et al. 2006; Kulig et al. 2007). The apparent contradictions could be explained by the fact that these studies all use different methods for acquiring and analysing data, they may also be due to multiple significance testing and a small sample size.

Coronal motion has been understudied, in part due to associated coupled rotation. This study reduced that by using a passive recumbent protocol with knees bent to flatten the lumbar lordosis and standardised patient positioning. The quality assurance procedure ensured that coupled rotation, if present, was minimal. Anatomical variations such as facet joint orientation were not considered (Cholewicki et al. 1996) because they would have been difficult to quantify from QF sequences. There is little recent research on coronal intervertebral motion but compared to global coronal motion these findings contrast with McGregor et al (McGregor 1995) who found no differences in the global motion of LBP compared to healthy volunteers. An older study found differences in the

coronal plane (Pitkanen and Manninen 1994) but despite this, Pitkanen and Manninen declared coronal functional radiographs to be of lesser value than sagittal plane functional radiographs, even though they based their conclusions on subjective evaluation of pathological axial rotation.

6.12.3 Diagnostic accuracy of mIVR

The diagnostic accuracy of mIVR's was assessed with sensitivity, specificity and the area under the curve (AUC) for each segment and direction. v

It is not intended that mIVR's from QF would ever be used as a screening tool to determine whether CNSLBP is mechanical, for this both sensitivity and specificity need to be high, although Alqarni et al note that most clinical tests for instability have high specificity and low sensitivity (Alqarni et al. 2011). Fritz et al (Fritz et al. 2005) used functional radiography as the gold standard to report the sensitivity and specificity of clinical variables commonly used in assessing instability. They used cut off values for intervertebral motion derived from White and Panjabi (White and Panjabi 1990) and concluded that various clinical factors, including increased global flexion and extension predicted radiographic instability, but no discussion of the errors associated with radiographic measurement was included.

Teyhen et al (Teyhen et al. 2007b) studied the diagnostic accuracy of eight kinematic parameters derived from QF and concluded that when four or more were present, 95% of patients could be accurately identified with a sensitivity of 1 (confidence interval 0.74 to 1.00) and specificity greater than 0.93 (confidence interval 0.68 to 0.99). The kinematic parameters included mid-range slope and linear displacement (translation), which are measurements unique to QF and not easily transferable to a clinical environment. Additionally Teyhen et al's method included a prior subjective assessment of the QF sequences for abnormal motion and only those that qualified progressed onto the final analysis. This biased selection of patients would serve to inflate sensitivity and specificity.

Advancement upon this study would be to reassess sensitivity and specificity of a number of kinematic parameters (including mIVR) to determine whether, in combination, they are able to distinguish between patients and healthy volunteers to assess underlying mechanics, and thus help direct treatment.

6.12.4 Reference intervals

Differences between, and the sensitivity and specificity of mIVRs do not distinguish between hyper and hypo mobility, but in clinical practice these are seen as distinct sub groups that inform choices between stabilisation and mobilisation treatments

(Liebenson 1996; Peterson and Bergmann 2002). Hyper and hypo mobility are features of differing stages of disc degeneration (Fujiwara et al. 2000; Kong et al. 2009b) and it is important to accurately match the sub category to the right treatment to improve both short and long term outcomes (Brennan et al. 2006), thus mIVR's could not distinguish the stages of disc degeneration unless cut off values for hyper and hypo mobility were created.

Previous cut off values for functional radiographs have been somewhat arbitrary (as discussed in Defining abnormal intervertebral motion *in vivo*. p97), although the method of providing cut off values based on the Gaussian distribution ($\overline{X} +/-2SD$) avoids this. Abbot et al (Abbott et al. 2006) undertook such an approach and labelled motion in patients that exceeded the upper reference limit as 'lumbar intervertebral instability (LSI) and that which fell below the lower limit as 'lumbar intervertebral rigidity' (LSR), the only statistically significant associations were for LSR.

It is recognised that using the values from healthy volunteers to establish reference intervals created from their own data to compare could generate bias. By virtue of the Gaussian distribution, approximately 2.5% of healthy volunteer data should fall above the reference intervals and 2.5% should fall below. However, this was not always the case and in some instances no healthy volunteers had values beyond the reference interval, which is typical of a small sample size (see Table 6-6 p109). Despite this, it is interesting to note that flexion L4/5 was statistically significant for hyper mobility, and that L4/5 (along with L5/S1) is the most commonly fused segment in the spine (Radcliff et al. 2013). In contrast, a previous study found significantly reduced ranges of global motion in flexion for patients with LBP (McGregor 1995).

Hyper mobility has been equated with instability (Muggleton et al. 2000) and although it may be asymptomatic, it has been shown that young males with proven joint hyper mobility have excessive intervertebral motion that is associated with pain (Kim et al. 2014). Spinal instability, defined as a loss of spinal stiffness such that normally tolerated external loads result in pain, has been proposed as a unique subgroup (Frymoyer and Selby 1985; Delitto et al. 1995) and McGregor et al (McGregor 1997) attributed specific aetiologies to hyper and hypo mobility, declaring that those with a spondylolisthesis tended to be hyper mobile while those with stenosis or disc prolapse tended to be hypo mobile. This has since been supported by Passias et al who combined MRI and fluoroscopy noting hypo mobility at segments with discogenic pain (L5/S1) (Passias et al. 2011) and also reported hyper mobility at supra adjacent segments.

In this study when data were combined to examine direction, plane, and overall motion there were no significant differences in the proportions of patients or healthy volunteer's out-with the reference limit in the sagittal plane, but both left and right bending were statistically associated with hypo mobility. As no other studies have examined coronal motion and reference limits, no direct comparisons can be made. However, Abbott et al found significant associations between hypo mobility and LBP using QF and sagittal plane rotation (Abbott et al. 2006) and Teyhen et al (Teyhen et al. 2007a) included mid-range hypo mobility as one for the four kinematic features used to distinguish those with LBP.

The lack of any significant difference with independent reference interval contrasts with the significant associations found when only data from this study was used. This may be a feature of the different participant positioning protocols (see Figure 6-4 p113) or an illustration of how using circular data can increase the risk of a type one error.

To compare sagittal plane data with existing studies (see Table 6-1 p101) the reference intervals were created by summing values for flexion and extension and this introduces further error because, in some instances, the participant was re-positioned between the flexion and extension sequences (for instance if they were slightly out-of-plane after the flexion sequence). Nevertheless, the range of sagittal plane reference limits are less than those from functional radiographs (see Figure 6-6 p123) thus passive recumbent QF reduces variation to the extent that subtle differences between groups may be better examined.

As previously noted it is feasible that 40° of passive trunk rotation may not adequately stress the segments although it is interesting that the reference ranges from this study and the independent group are similar despite small sample sizes (see Figure 6-6 p123). It may be possible to repeat this comparison in the future using increased numbers from the independent study, which is an ongoing study of healthy volunteers in passive and weight-bearing postures (Breen et al. 2013). The results may give us insights into whether there are differences in the mean mIVR's in a passive trunk or hip swing protocol and if the upper or lower segments are stressed further in either protocol. An improved study would be a repeated measures design although this would require irradiating further cohorts.

Overall, it is suggested that mIVRs from continuous data are pursued for passive recumbent motion. This is because it is evident that this method reduces variation between groups, and it is possible that mIVR may just be one kinematic parameter of note in mechanical LBP.
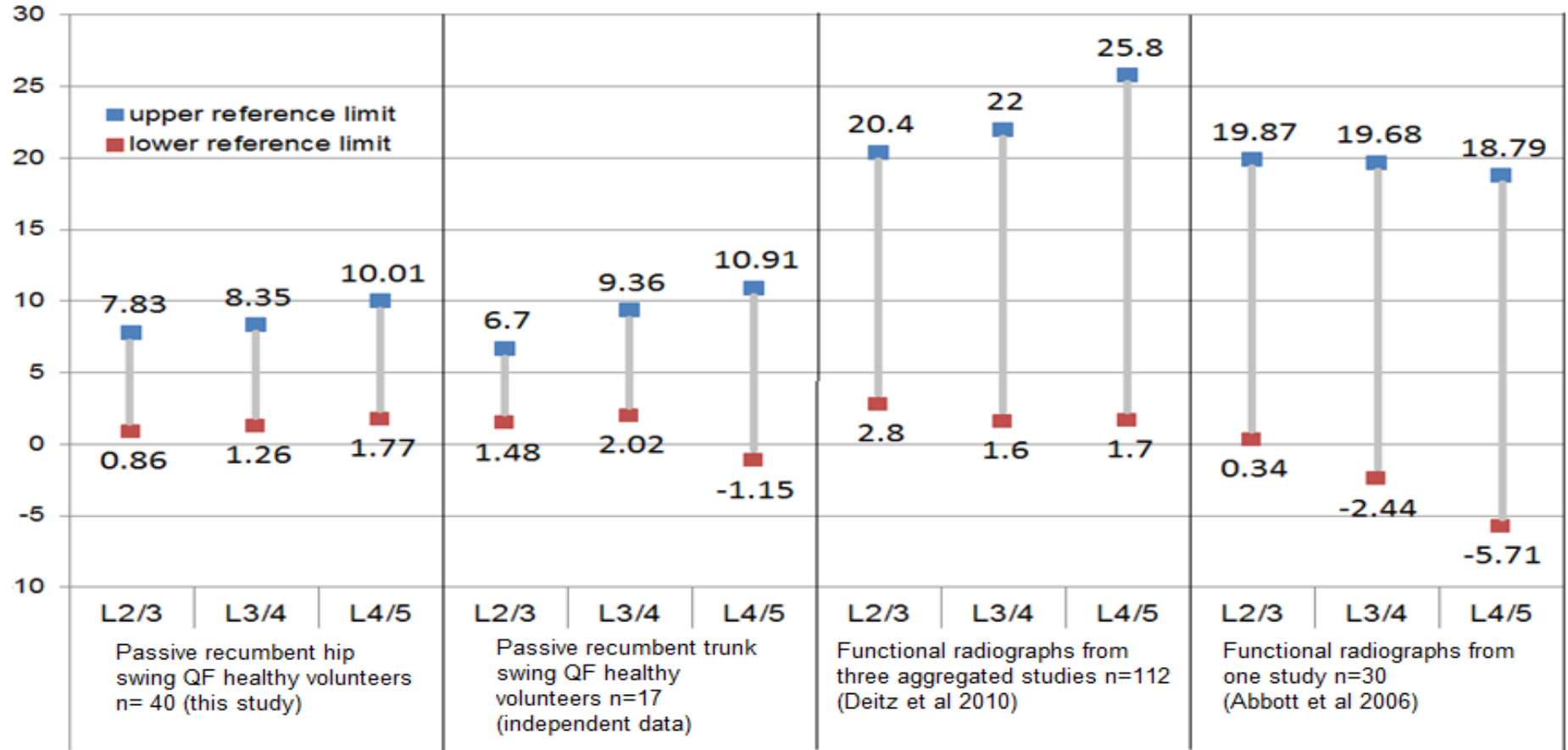
Figure 6-6 Comparison of reference intervals between studies for flexion + extension sagittal motion [17]

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[17]For the two passive recumbent QF studies, sagittal data were created by summing extension and flexion results although this increases the error, which has not been calculated

6.12.5   Discussion of the independent passive recumbent trunk swing study

It is acknowledged that the independent study had a small sample size (n=17 for sagittal and 20 for coronal data) and the movement protocol was different with the hips remaining stationary and the upper trunk moving (see Figure 6-4 p113). However, it was a QF passive recumbent motion procedure and the equipment and motion range and speed were identical.

The pre conception was that a trunk swing protocol would result in greater rotation at the upper segments than the lower segments. If this were true then as well as greater mIVR's for the upper segments in a trunk swing protocol (and the opposite for hip swing) it would also be reasonable to expect a phase lag effect (Kanayama et al. 1996; Ahmadi et al. 2009) as force is transferred up or down the spine. In both passive motion protocols this was not evident and the statistically significant differences between the healthy volunteer groups were not limited to the upper versus lower segments. The 'delayed sequence' pattern of phase lag is controversial in continuous weight-bearing studies. Ahmadi et al (Ahmadi et al. 2009) reported no phase lag in their 20 healthy volunteers although it was present in 9/15 of their LBP sample. Wong et al (Wong et al. 2004; Wong et al. 2006) and Lee et al (Lee et al. 2002) also reported no phase lag in their QF weight-bearing studies and Okawa et al (Okawa et al. 1998) reported mixed results in his mixed sample of patients and controls. Ahmadi et al (Ahmadi et al. 2009) suggested that the phase lag may be related to fixed hip flexion in weight-bearing studies, and an ongoing study comparing weight-bearing with passive motion notes that phase lag seems to happen mainly with weight-bearing, and appears to have a relationship with initial lordotic angle (Breen et al. 2013). This suggests phase lag is influenced more by active and motor control subsystems.

Ultimately no firm conclusion can be drawn on whether trunk swing stresses segments in a different order to hip swing because they were statistically significant differences in 3/12 of the healthy segments. However, the reference intervals created from the independent study were viewed as the closest measurement available for independent analysis. The fact that there were no significant differences in proportions out with the reference intervals and being a patient may mean that the Gaussian reference limits are too wide to identify differences in overall mIVR and a more suitable approach may be to consider differences as a proportion of overall motion (a within subjects approach). Such an approach has previously been undertaken by Teyhen et al and Abbott et al who normalised their results (Abbott et al. 2006; Teyhen et al. 2007a;

Teyhen et al. 2007b) and is further elaborated in Chapter 9 p159, which investigates normalised (percentage) continuous motion patterns.

6.13 Limitations and recommendations for future work

Weight-bearing global trunk RoM is influenced by gender and age (McGregor 1995), whereas intervertebral rotation in the sagittal plane is only affected by age (Wong et al. 2004). Advancement upon this study would be to determine any differences in gender and age for passive recumbent motion to understand the role passive structures play in aging, for which, a larger sample size would be needed.

A limitation of mIVR's are that the segments were considered individually and co-dependency was not accounted for. Although other studies have followed this model (Abbott et al. 2006; Taghipour-Darzi et al. 2012), it is logical to presume that there is co-dependency between intervertebral motion because of the phenomenon of adjacent segment disease (ASD), which can cause early deterioration following spinal fusion (Radcliff et al. 2013). Therefore an improvement to this study would be to analyse mIVR's with a model that accounts for co-variance. A further limitation of mIVR's is that they are unable to describe the motion pattern. Symmetry of motion was not investigated in this thesis because a previous study (Mellor et al 2009) indicated there was no significant variation in left and right motion. However it is a recommendation to re-visit symmetry because Mellor et al (2009) undertook left-right bending as one fluoroscopic sequence whereas the procedure in this thesis separated the sequences.

Measuring mIVR (the range between the maximum and minimum point) does not in itself give an indication of the direction of the differences, thus paradoxical motion may be missed if this method is not used alongside visual inspection of the motion graphs. Although no participants in this study showed evidence of paradoxical motion. A further limitation of mIVR is that, despite using a continuous data set, it is a single numerical output and cannot provide information on the mid-range motion.

The method employed in this study limits trunk rotation to 40°. While this is designed to reduce intra and inter subject variability, not all segments between L2 to L5 absorbed the same amount of motion (see Table 6-3 p104). Thus, as expected, some segments absorbed more motion than others. Thus a major current limitation of the current method is it is not known whether hyper mobility can be detected with controlled motion. To answer this requires output from a study that is currently underway comparing the mIVR's from controlled motion to maximum voluntary trunk bends (Breen et al. 2013).

Another limitation was the patient population and the definition of mechanical low back pain as the gold standard (this is discussed in Chapter 4 Limitations and recommendations for future work p77). A recommendation for future studies would be to ascertain the usefulness of both upper and lower mIVR reference limits against particular derangements in the passive structures of the spine that are thought to influence movement, such as facet joint arthritis and disc degeneration. This would require triangulation with another method that accurately and reliability identifies the derangement such as MRI and the Pfirmann scale (Pfirrmann et al. 2001) to grade disc degeneration

6.13.1   Clinical implications

The current standard of care is weight-bearing sagittal functional radiographs taken at the end of uncontrolled trunk range, which the AMA use to discern alteration of motion segment integrity (AOMSI) in the assessment of workers compensation (American Medical Association 2008), but QF reduces variation and errors so could be used as an advancement. Furthermore the AMA defines a failed fusion as movement in the sagittal plane > 5°, and other studies define it as > 3-5° of motion (Burkus et al. 2001). If mIVR's from passive QF were adopted for this measurement then the assessment would be more reliable. They could also be used to assess failed fusion in the coronal plane, and a passive recumbent motion protocol would reduce or remove the influence of the motor and muscle control, thus truly testing the fused segment.

Given the significant difference in mean mIVR in the coronal plane it may be prudent to suggest the radiological evaluation of intervertebral motion also includes coronal measurements. This is in direct contrast to Pitkanen and Manninen (Pitkanen and Manninen 1994) who declared side bending radiographs to be less helpful than sagittal radiographs for detecting instability, but they cited asynchronicity as a sign of instability and did not measure maximum intervertebral motion.

White and Panjabi (White and Panjabi 1990) assert that the spine is more flexible in flexion than extension by up to 60% but it is not clear if this true for passive recumbent motion. In healthy volunteers, L2 to L5 flexion absorbed 40% of the trunk motion (SD=8.9%) whereas in extension this was reduced to 35.2 % (SD 10.7%) (see Table 6-3 p104) although this included two healthy participants who could not achieve 40^0 of extension trunk rotation. However, because it is the posterior elements, which include the facet joints (see Figure 2-2 p14) that contribute to limiting overall extension, if a participant had an abnormally large mIVR in extension it could point to possible issues in the posterior elements of the spine. This was suggested by Najarian et al (Najarian et al. 2005) who demonstrated posterior elements in a computer modelled segment

increased stability at L4/5 in extension. Thus keeping each direction as a separate examination is recommended and future studies could link movement in the direction that clinically elicits a pain response.

Finally, to implement QF in place of functional views would require a change of practice and the wider economic implications of this would need to be assessed.

6.14 Conclusion

The overall research question for this chapter queried the use of mIVR's as a kinematic parameter. The answer is that they may be useful for the coronal plane, or if combined with other kinematic parameters, but alone they do not have good diagnostic accuracy. Reference intervals show initial promise particularly because they distinguish between hyper and hypo mobility and thus will help better direct treatment, although further studies with independent data are required, along with additional research to determine whether controlled motion adequately stresses segments to their maximum capacity.

Although a single quantitative measurement of mIVR is not sufficient to describe differences in the biomechanics of the spine between patients and healthy volunteers, inclusion of this parameter in a model that includes other kinematic parameters could be useful in determining whether groups of mechanical disruptions exist in those with clinically diagnosed mechanical CNSLBP.

6.15 Contribution to new knowledge

Because QF provides continuous data, mIVR's were calculated as the range between the maximum and minimum rotation[18], regardless of where in the trunk motion these occurred (see Figure 5-1 p83). By contrast, previous imaging studies examining mIVR's have taken the measurement from the same point as the maximum trunk bend, although this does not always correspond with the maximum intervertebral range.

An alternative way of measuring mIVR's is presented from a method where there is no axial loading of the spine, overall trunk rotation is controlled, and there is access to continuous data. It tests these measurements for differences between groups and diagnostic accuracy. Additionally it provides reference intervals as an initial suggestion for cut off values, although the small sample sizes are duly noted. Finally mIVRs may be a useful kinematic parameter if combined with other parameters, for which, further study is recommended.

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[18] NB: In Chapter 9 these are described as the maximum outward value only. Chapter 9 is a published journal paper and there was a need for simplicity in describing the background to continuous proportional intervertebral motion as a kinematic parameter

Chapter 7   Investigation of initial intervertebral attainment rate over 10 degrees of corresponding global rotation

7.1 Chapter overview

This chapter reports on the kinematic parameter called 'initial intervertebral attainment rate', which is the ratio of the gradient of initial intervertebral rotation (IVR) over the corresponding 10° of passive table motion, and advances upon a previous study in the coronal plane by the CI. (Mellor et al. 2009). In previous work the gradients were initially termed 'laxity' and this was further discussed in an international forum on the use of QF (Breen et al. 2012). However, this may be confused with ligamentous laxity and, because mid-range passive motion can also be influenced by the intervertebral disc and bone morphology, the terminology used in this thesis is "attainment rate". Similar studies have utilised gradients (also called slopes) to measure the mid-range but there is limited information on these as a proxy for the neutral zone *in vivo*.

7.2 Introduction

Attainment rates were found to have good reproducibility (see Chapter 5 p79), so were assessed for differences between groups, diagnostic accuracy, and proportions exceeding upper reference intervals ($\overline{X} + 2SD$).

7.3 Rationale for study

The rationale for this study is to determine the diagnostic accuracy of the attainment rate to distinguish between patients with CNSLBP and healthy volunteers. Where possible, the STARD checklist was followed (see Table 13-22 p266). Mellor et al (Mellor et al. 2009) determined that the initial gradient of IVR over the corresponding 10° of global rotation in the coronal plane was a useful measurement when compared to three selected patient case studies. This thesis advanced this by determining differences in the initial attainment rate of patients and healthy volunteers in the coronal and sagittal planes, and the diagnostic accuracy to these to discriminate between groups. Building upon previous work (Mellor et al. 2009), upper reference limits were explored and tested in patients.

7.4 Literature review

End of range measurements cannot measure mid-range kinematics, but in QF studies the mid-range has shown differences in patients with CNSLBP (Teyhen et al. 2007a; Teyhen et al. 2007b) and in those older than 51 years (Wong et al. 2004). Intervertebral rotation (IVR), according to Panjabi's neutral zone theory (see The Neutral Zone p18) consists of two elements, a) the Neutral Zone (NZ) and b) the Elastic Zone (EZ). Although strictly speaking it is an *in vitro* measurement, it is claimed that muscular and motor control of initial motion near to the neutral position (the NZ) can prevent recurrent LBP (Suni et al. 2006), and that this is better suited to quantifying issues related to the function of the spine (Mahato 2013), and that it is a more sensitive indicator of spinal instability than RoM or EZ (Oxland 1992; O'Sullivan 2000).

Reeves et al (Reeves et al. 2007) noted that the definition of stability varies for professions. Reeves et al reviewed the various terms employed and described the interaction of different concepts for the static and dynamic stability of the spine. Specifically they described three concepts:

 a) Stability, which is the path of the object (vertebra) along its intended trajectory

 b) Robustness, the ability of a system to change its parameters (i.e. stiffness) to maintain its stability

c) Performance, which is how rapidly the object returns to its initial position.

The size of the perturbation required to upset the system must be acknowledged (Farfan and Graceovetsky 1984) and using a novel inter-operative system Hasegewa et al demonstrated that flexion stiffness was significantly lower in segments with degenerative spondylolisthesis but the initial motion was significantly larger when compared to a control group (Hasegewa et al. 2009). Additionally cadaveric studies have shown that the initial motion, which demonstrates the segments willingness to move increases with disc degeneration and decreases with increased stiffening (Panjabi et al. 1989; Mimura et al. 1994; Kaigle et al. 1995; Wilke 1995; Zhao et al. 2005) and muscle contraction (Suni et al. 2006). Therefore tis aspect of the motion is considered to be an important measure of spinal stability (O'Sullivan 2000).

Other ways of quantifying initial motion, or the segments willingness to move, exist both *in vivo* and *in vitro*. The NZ ratio (NZR) is suggested as the NZ/RoM * 100 (Mimura et al. 1994; Mahato 2013) and has been shown to increase in all directions with disc degeneration in cadavers (Mimura et al. 1994; Kettler et al. 2011). *In vivo* this

has been compared to a ratio of IVR at 10° trunk rotation/IVR at 40° trunk rotation but it was not found to be a responsive measure when compared to three patient case studies in previous work, plus it was limited to recumbent passive motion in the coronal plane (Mellor et al. 2009). Kanayama et al reported IVR values at 10^0 and 40^0 in the weight-bearing sagittal plane (Kanayama et al. 1996), and both Wong et a and Auerbach et al measured the slopes of continuous motion divided into 10° increments from -10^0 - $+ 50^0$ (Wong et al. 2004; Auerbach et al. 2007). It is noted that 10° is an arbitrary value however.

Other researchers have fitted polynomials to the dynamic curves both *in vitro* and *in vivo*. Thompson et al used sheep specimens and measured dynamic motion with a 4th order polynomial (Thompson et al. 2003). They found the region that most correlated with the NZ concept was confined by a slope of + or -0.05 Nm/degree. Dickey and Gillespie fitted 6th order polynomials to flexion extension curves of porcine segments and measured laxity in flexion with this method (Dickey and Gillespie 2003), and Smit et al created a new definition of the neutral zone *in vitro*, demonstrating that they could objectively measure dynamic motion with sigmoidal curves and mathematical modelling (Smit et al. 2011).

To date there has been no comparison of all methods on the same data so it is difficult to draw comparisons of whether it is possible to measure the *in vivo* equivalent of the NZ, or what aspect of initial motion, reflecting the segments willingness to move when force is applied. Clinically applying the transition between NZ and EZ is difficult because force and loading are unknown. Additionally Brownhill (Brownhill 2010) claims that because the NZ is measured under static loads it may not be suitable for measurement in dynamic motion *in vivo*. Thompson et al (Thompson et al. 2003) criticised the quasi static method and suggested the NZ may be an artefact of this.

It also remains unclear which planes of motion are important in the initial motion. The majority of studies have involved the sagittal plane but Thompson et al also tested segments in lateral and axial rotation and concluded that the NZ was not present in either (Thompson et al. 2003). This was in contrast to Mimura et al (Mimura et al. 1994) and Kettler et al (2011), both of whom found increased NZ's in all planes of motion in cadaveric segments with degenerate discs. While the NZ and EZ are *in vitro* measurements, researchers have studied mid plane motion with quasi static and dynamic imaging methods by dividing continuous motion and measuring the slope of each percentage of total global RoM (Wong et al. 2004; Auerbach et al. 2007; Teyhen et al. 2007b), although the majority of these studies have been in the sagittal plane and weight-bearing.

Teyhen et al (Teyhen et al. 2007a; Teyhen et al. 2007b) measured the slope of motion at 10^0 increments throughout weight-bearing sagittal rotation (reported as percentage motion normalised to L3/S1 angle). They found high sensitivity and specificity for back pain and alterations in the attainment rate for L3/4 and L4/5 at the onset of flexion that was different in healthy volunteers. Consequently, the measurement of initial intervertebral mid-range motion is undertaken in this thesis based on previous studies (Wong et al. 2004; Auerbach et al. 2007; Teyhen et al. 2007b; Mellor et al. 2009), and an international forum that recommended laxity, as a measurement of movement in the initial phases, should be pursued in both passive and weight bearing studies *in vivo* (Breen et al. 2012).

7.5   Research question

Can the initial intervertebral attainment rate of initial intervertebral rotation over the corresponding 10° of passive table motion distinguish between patients and healthy volunteers?

7.6   Aim

The aim of this study was to examine initial attainment rate in both CNSLBP and healthy volunteers to determine whether this would be a useful kinematic parameter.

7.7   Hypothesis

1. Using ROC analysis, Initial attainment rate measured from passive recumbent motion can distinguish between patients with mechanical low back pain and healthy volunteers

Two secondary hypotheses were:

2. There will be significant differences in the mean attainment rates of patients compared to healthy volunteers.
3. There will be significant differences in the proportion of patients with attainment rate values outside the upper reference limit.

7.8   Methods

The methods, including sample size, sample selection and data acquisition are described in Chapter 3 p45 . Data analysis is described in Chapter 5 p79. Statistical analysis is displayed in Table 3-2 p52. STARD guidelines were followed in the reporting of the diagnostic accuracy (see appendix Table 13-22 p266). The index tests

are initial attainment rate values per segment and direction (n=12), which are interval (continuous) variables. Attainment rate was found to have good reproducibility (see

Agreement and reliability of attainment rate p85). No data were excluded from the analysis and there were no missing values

For reference intervals, only the upper reference limit was used because attainment rate is dependent upon movement. Thus the interest is in those participants who exceed the upper reference interval because this would indicate excess movement in the NZ. For proportions exceeding the upper reference limit, the caveats previously discussed, regarding an increased possibility of a type one error also apply to these analyses. To overcome this results from this study are compared to independent published values for the coronal plane (Mellor et al. 2009). All segments were tested per level and direction with no consideration for co-dependency. Data were not combined per direction or plane of motion as it is not clinically meaningful to do so for this kinematic parameter.

7.9   Results

7.9.1 Parametric assumptions of attainment rate

Eighteen out of 24 data sets were normally distributed (see Appendix Table 13-23 p266) and ten out of 12 met the assumption of homogeneity of variance between the two groups (see Appendix Table 13-24 p267). Because not all data were parametric both means and medians are displayed in Figure 7-1 p134.

7.9.2 Differences in mean values

The only significant difference was for left L4/5 (p=0.003) where the means and SDs for patients and healthy volunteers were 0.176 (0.115) and 0.249 (0.097) respectively. (See Appendix Table 13-25 p268). For this level, the inter observer SEM is 0.024 and the inter observer ICC is 0.972 (95% confidence interval 0.898 to 0.993, see Table 5-7 p87 and Table 5-8 p87). If this parameter was used in other studies the SDC would be 0.480 (2*SEM) (de Vet et al. 2006), which means this would be the minimum amount of change not attributable to inter observer agreement.

It is interesting to note that healthy volunteers had a significantly higher mean attainment rate for this level, which is opposite to what was expected (although the hypothesis was two tailed). The reason for this is that five patients had an attainment rate of zero (i.e. the segment was stiff) whereas no healthy volunteers had an attainment rate of zero. It is therefore suggested that this analysis is repeated, excluding participants whose attainment rate is zero.
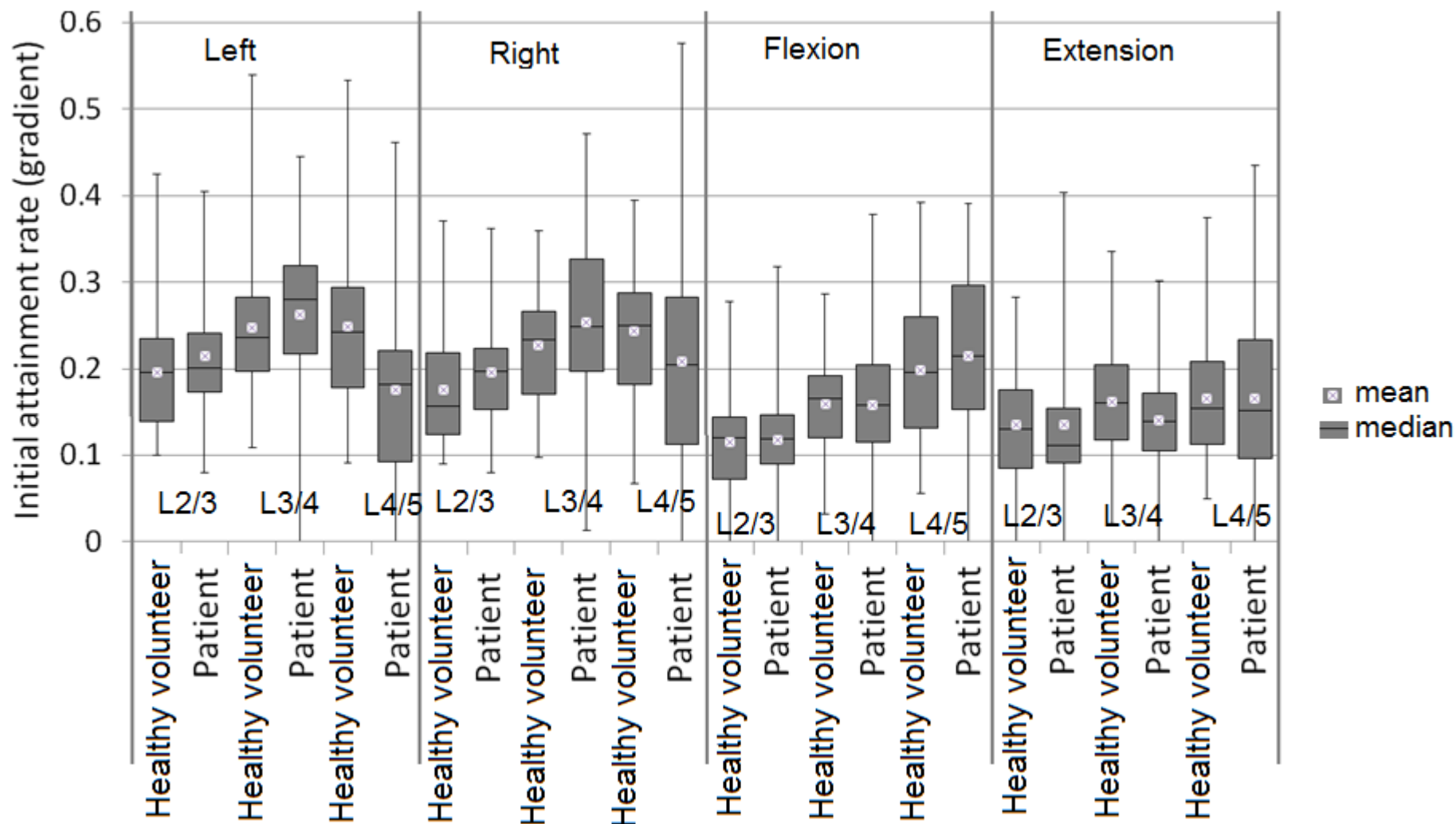
Figure 7-1 Initial intervertebral attainment rate; box and whisker plot for all segments

7.9.3 Diagnostic accuracy of attainment rate

Each level and direction was individually assessed. All results are in the appendix (Table 13-26 p269 and Figure 13-10 p270). The cut off values were selected by the statistical software. Left L4/5 demonstrated the highest sensitivity (0.725, 95% confidence intervals 0.588 to 0.873) and specificity of 0.6 (95% confidence intervals 0.433 to 0.751) but the AUC was 0.683, which means it is a poor test for discriminating between those with and without clinically diagnosed mechanical CNSLBP. Two other segments demonstrated sensitivity and specificity > 0.58 but their AUC was less than 0.7 indicating poor discrimination (see Table 6-2 103). The remaining levels demonstrated both high sensitivity and low specificity, or vice versa, and AUC's less than 0.6. Thus the hypothesis, which was that initial attainment rate can distinguish between patients and healthy volunteers, was rejected for all levels and directions.

7.9.4 Reference intervals for attainment rate

Upper reference limits $(\overline{X} + 2SD)$ were created from healthy volunteer data for each level and direction and are shown in Table 7-1 p136 with a comparison to upper reference limits for the coronal plane from a previous study.

	This study n=40				Mellor et al (2009) (n=7 to 20)	
	Left Upper ref limit ° (95% confidence intervals)	Right Upper ref limit ° (95% confidence intervals)	Flexion Upper ref limit ° (95% confidence intervals)	Extension Upper ref limit ° (95% confidence intervals)	Left Upper ref limit ° (95% confidence intervals)	Right Upper ref limit ° (95% confidence intervals)
L2/3	0.342 (0.326 to 0.359)	0.302 (0.287 to 0.318)	0.240 (0.224 to 0.255)	0.260 (0.245 to 0.276)	0.290 (0.279 to 0.302)	0.429 (0.399 to 0.460)
L3/4	0.401 (0.384 to 0.418)	0.539 (0.343 to 0.374)	0.286 (0.270 to 0.301)	0.300 (0.284 to 0.316)	0.298 (0.267 to 0.309)	0.372 (0.356 to 0.388)
L4/5	0.444 (0.425 to 0.463)	0.396 (0.379 to 0.413)	0.360 (0.342 to 0.376)	0.315 (0.298 to 0.332)	0.359 (0.345 to 0.373)	0.392 (0.377 to 0.407)

Table 7-1 Initial intervertebral attainment rate; upper reference intervals derived from healthy volunteers (95% C.I.) for this study and Mellor et al 2009

Proportions of patients and healthy volunteers who exceeded the upper limit were compared (all results are in the appendix see Table 13-27 p270). Five out of twelve segments were suitable for analysis. Of these, none showed significant associations with being in the patient group and exceeding the upper reference interval for attainment rate. Because this analysis compared healthy volunteer data to cut off values derived from the same, (which increases the risk of a type one error), a separate count was undertaken using independent upper reference limits for left and right attainment rates published in Mellor et al (Mellor et al. 2009) (see Table 7-1 p136). More patients than healthy volunteers exceeded the upper limit from Mellor et al but this was not statistically significant for any segment. The full data set is in the appendix Table 13-28 p271.

7.10 Discussion

The ability to measure continuous mid-range *in vivo* intervertebral motion with good reproducibility is now possible (Chapter 5 p79) and cadaveric studies have pointed towards motion near to the neutral position as being different in spines with degenerate discs However, the cadaveric neutral zone is tested under weight-bearing conditions with a pre load (Panjabi 1992b) that increases intervertebral joint stiffness (Stokes et

al. 2002). Additionally, the ends of the NZ are defined by the positions of the segment prior to the 3rd cycle in each direction, thus it is a quasi-static measurement of residual deformation (Gay et al. 2005), which was criticised by Brownhill (Brownhill 2010). Conversely, this study used *in vivo* dynamic motion graphs and a passive motion protocol to test whether there were differences in patients and healthy volunteers, thus the segments were not axially loaded and only completed one cycle of motion.

It is believed the NZ is a better indicator of the biomechanical integrity of the spine than maximum range (White and Panjabi 1990; Oxland 1992; Panjabi 1992b; Kaigle et al. 1995; Crawford et al. 1998; Kettler et al. 2011), because as the structures that contribute to passive spinal stability in the neutral position (disc, vertebrae and ligaments) begin to fail, other structures further from the neutral position are loaded (e.g. bony articulations). Measuring motion at the beginning of the cycle is a potential indication of the segments resistance, and following injury or degeneration this section may increase as those structures no longer limit movement, and the EZ (maximum range) remains unchanged as other more rigid structures take over to limit motion (Crawford et al. 1998; Kettler et al. 2011). However, it is important to note that these studies have not addressed the influence of muscles and motor control although it is theorised that they play a role (O'Sullivan 2000; Evans and Breen 2006).

Multiple tests of significance were undertaken on this data, however only one was significant at the 5% level (differences in mean values, left L4/5). Accepting this could increase the chance of a type one error, thus they hypotheses for initial intervertebral attainment rate are rejected.

7.10.1   Differences between groups

The only segment with a significant difference in attainment rate was left L4/5 (p=0.003) and this may be a result of multiple statistical testing rather than a true difference, consequently the hypothesis that there were significant differences in the mean values between groups was rejected. The same segment to the right returned a p value of 0.09 although symmetry of left right RoM was not deemed to be important in continuous intervertebral motion (Mellor et al. 2009). Smit et al noted that the neutral position of the spine *in vitro* may not be the segments' neutral position, shifting the zero load condition towards one end of the RoM (Smit et al. 2011). If this is applicable *in vivo* then this strengthens the argument for starting each sequence from a neutral position, as opposed to a previous QF passive motion study that measured one plane as a complete sequence (Breen et al. 2006).

7.10.2   Diagnostic accuracy of attainment rate

No segments demonstrated both high sensitivity and specificity, and no segment had an AUC greater than 0.71, so attainment rate alone is not a suitable kinematic parameter to distinguish between groups. These results contradict Teyhen et al who reported that flexion weight-bearing attainment rates had a sensitivity and specificity of 0.75 (95% confidence intervals 0.53–0.89) and 0.55 (95% confidence intervals 0.34–0.74) for L3/4 between 0-5% of the global rotation, and sensitivity and specificity greater than 0.7 for attainment rates between 5 and 15% of the global motion for L3/5 and L4/5 (Teyhen et al. 2007a; Teyhen et al. 2007b) although patients who had been clinically diagnosed with aberrant movement were pre-selected and undertook weight-bearing unconstrained motion, hence results are not directly comparable to this study.

7.10.3   Upper reference limit

Of interest is that mean attainment rates for healthy volunteers are greater than for patients in L4/5 coronal bending, yet more patients (n=5) than healthy volunteers (n=2) exceeded the upper reference limit (see Table 13-27 p270). This is due to wider variation in attainment rates in patients, which positively skewed the distribution of values (see Figure 7-2 p138).
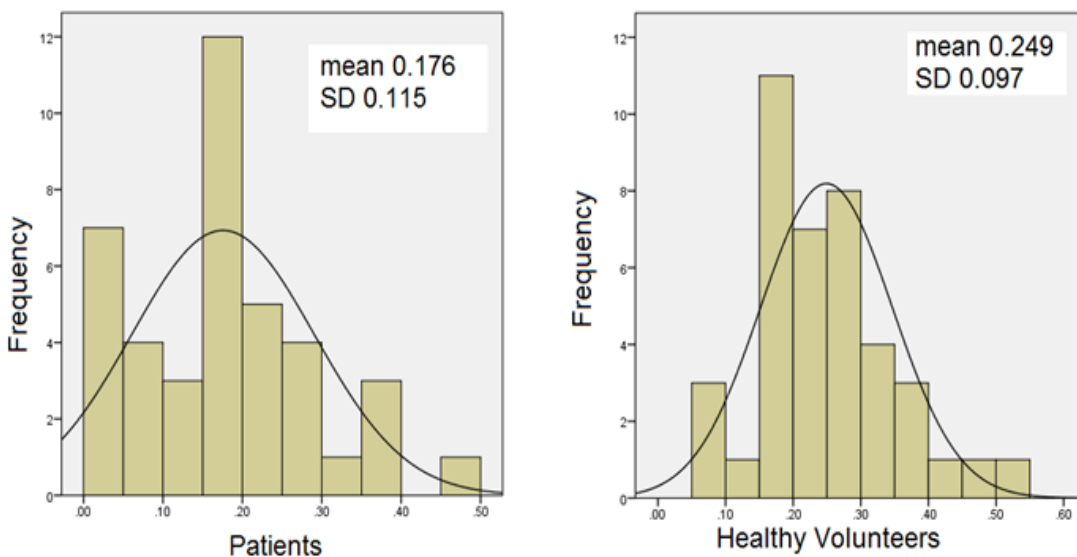
Figure 7-2 The distribution of attainment rate values for patients and healthy volunteers. Left L4/5

Higher attainment rates in healthy volunteers are the opposite of what was expected, and renders upper reference intervals of little use, although before they are dismissed it is worth considering the analysis. Initial attainment rate, as a concept, is not valid for segments that show restricted rotation, or less than a minimum sustained range throughout the corresponding 10° of global rotation. In this thesis all results were

included in this analysis and five patients had an attainment rate of zero but no healthy volunteer did so. Consequently it is recommended that this analysis is repeated excluding segments that demonstrate hypo mobility (see p133). A suitable cut off value for hypo mobility for each segment and direction is suggested as the lower reference range for mIVRs).

No study has previously compared initial intervertebral attainment rates in CNSLBP and healthy volunteers, nor created cut off values to define abnormal, thus there is little to compare other than a previous study by the author (Mellor et al. 2009) but the obvious criticism is the low sample size in Mellor et al (2009) and the less rigorous standardisation of positioning. Additionally the previous study captured one coronal sequence, rather than separating them into left and right. This meant that the intervertebral segments may not have been in the neutral position for the measurements for right bending in Mellor et al (2009). Nevertheless, values were similar as displayed in Figure 7-3 p139 where the upper reference limits in this study are mostly larger than those previously reported (with the exception of right L2/3).
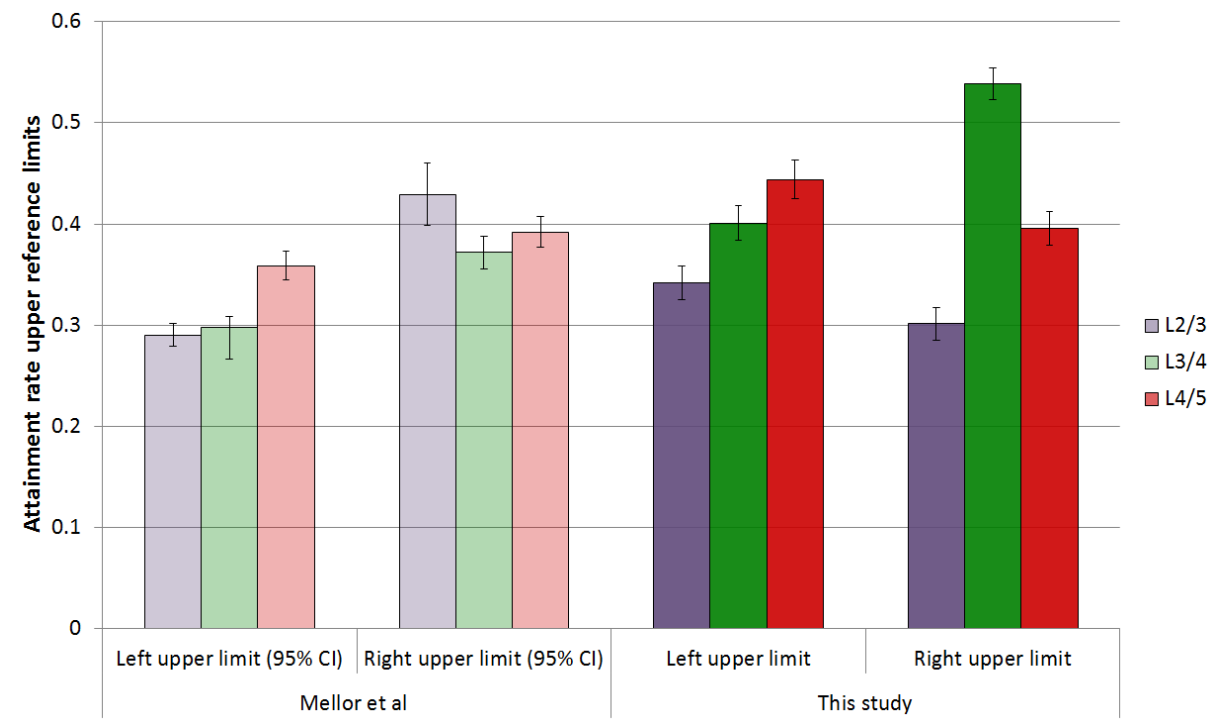
Figure 7-3 Comparison of upper reference intervals and 95% confidence limits in the coronal plane for attainment rate. Mellor et al (2009) and this study.

7.10.4   Interpretation of initial intervertebral attainment rate

The measurement of the neutral zone *in vivo* is one of the seven recommendations for measuring and comparing *in vivo* kinematics with QF (Breen et al. 2012), there is no objective information as to what aspects of the motion this would represent and it is acknowledged that 10° of table rotation is an arbitrary value.. Mellor et al (Mellor et al.

2009) selected the first 10° of passive table rotation based upon both Wong et al (Wong et al. 2004) and Teyhen et al (Teyhen et al. 2007b) who both compared the slope, or attainment rate at varying sections of the continuous motion. It is acknowledged that determining which section of the mid plane is a suitable proxy for the neutral zone is arbitrary and the optimum has yet to be defined given that speed is a proxy for resistance, and in engineering terms resistance is related to force.

Wong et al (Wong et al. 2006) measured the slope of motion in healthy volunteers divided into 10° sections of unstandardised trunk rotation. They reported decreased overall outward motion slopes from L1/2 to L5/S1 in descending order in the weight-bearing sagittal motion study. This is the opposite of this thesis, which measured passive recumbent motion and the slope only in initial outward 10°. The results from Wong et al may be evidence of the phase lag effect (Kanayama et al. 1996) and may be further evidence that the trunk or hip swing protocol would affect attainment rate (see Figure 6-4 p113).

Given that attainment rate still suffers from variation it may be prudent to normalise the values and present them as a proportion of overall motion. Teyhen et al normalised their values and demonstrated sensitivity and specificity >78% for flexion attainment rate in the first 10% of flexion RoM (Teyhen et al. 2007a; Teyhen et al. 2007b). Another suggested method of analysis is the fitting of polynomials to describe the slope. Fourth order polynomials have been shown to have high reliability when used for overall global motion (Williams et al. 2013) and they may be more responsive to attainment rate than the slope.

7.10.5   Limitations and recommendations for future work

It is not clinically meaningful to measure attainment rate in hypo mobile segments although the definition of the cut off value for this is arbitrary. The lower mIVR reference intervals in this study could be used as cut offs, and excluding those participants whose mIVR was less than this may alter the results somewhat. A further analysis could exclude all segments that do not rotate over the full corresponding 10° of corresponding table rotation and it is suggested that this is undertaken with this this data as a further study.

A limitation of this study is that variation at 10° of corresponding table rotation was not considered. Teyhen et al (Teyhen et al. 2005; Teyhen et al. 2007b) accounted for this by normalising slopes as a proportion of L3 to S1, and a recommendation for future work would be to look at normalised attainment rate and compare their variance, in a similar method to proportional continuous motion patterns (see Chapter 9 p159).

Although the NZ did not demonstrate differences in all segments between groups, cadaveric studies have determined that it only increases in the presence of damage to passive structures and disc degeneration (Mimura et al. 1994; Thompson et al. 2003) or is altered in the presence of a transitional vertebral body (Mahato 2013). Therefore a recommendation for further study would be to examine the attainment rate values of participants in this study with known disc degeneration, or transitional vertebrae, and compare their values to the reference values from healthy volunteers on a case by case basis.

7.10.6   Clinical implications

The question of how to measure the neutral zone *in vivo* and its clinical significance remains unanswered. Various proposals include measuring the whole or initial part of the slope of continuous motion (Kumar and Panjabi 1995; Wong et al. 2006; Auerbach et al. 2007; Teyhen et al. 2007b; Ahmadi et al. 2009; Mellor et al. 2009) and the NZ ratio defined as the *"quotient of the NZ and the overall RoM"* (i.e NZ/RoM) (Mimura et al. 1994; Kumar and Panjabi 1995), while others have subjectively classified the quality of the motion based on motion graphs (Breen et al. 2003), or by fitting polynomials to the dynamic motion curves (Thompson et al. 2003). Although these methods have provided fascinating insights into spinal stability there is no strong relationship between pain and attainment rate in this thesis.

The approach in this thesis was purely to determine passive system laxity, which is important because muscle activity can mask this in weight bearing motion leaving the patient prone to injury if caught in a loading situation with no muscle protection (Sahrmann 2002). Clearly further work in this area is required, including both a comparison of weight bearing and passive movement to determine the size and variation of the attainment rate, initially in healthy volunteers.

If attainment rate is a useful kinematic parameter in passive motion then it may be of value in determining differences between groups. However, it is unknown from previous literature whether it is appropriate to measure initial motion in the coronal plane, and also the importance of passive motion in an un-axially loaded spine. It is reasonable to presume that failure in the passive motion structures would increase the initial attainment rate, even if unloaded, thus differences shown in this study in left L4/5, which were opposite to expected, are unexplained. Based on previous literature, targeting segments that demonstrate laxity to increase stabilisation with muscle and motor control could lead to an improvement in LBP symptoms (O'Sullivan 2000).

7.11 Conclusion

The primary hypothesis, which was that there will be differences in the attainment rate between groups, was rejected because only left L4/5 demonstrated a significant difference. The two secondary hypotheses relate to diagnostic accuracy and reference intervals and were also rejected.

Attainment rate in the corresponding 10° of passive table rotation may be useful as a kinematic parameter if combined with others, although further investigation is needed. There appear to be differences for one segment, but in the opposite direction than expected. This may be due to a flawed analysis, hence the values presented here are for introduction only and it is recommended that these analyses are repeated, excluding those whose segments are hypo mobile (a group to whom attainment rate is not pertinent).

7.12 Contribution to new knowledge

For the first time this thesis presents mid-plane continuous data from passive motion in patients and healthy volunteers and recommends the gradient of initial IVR over the corresponding 10° of trunk rotation as a proxy measurement for the neutral zone.

The ability to measure continuous mid plane *In vivo* intervertebral motion with good reproducibility is now possible (Chapter 5 p79) and cadaveric studies have pointed towards the initial motion near to the neutral position as being different in damaged spines (see The Neutral Zone p18). However, the cadaveric neutral zone is tested under weight-bearing conditions with a pre load (Panjabi 1992b), which increases intervertebral joint stiffness (Stokes et al. 2002), and the ends of the NZ are defined by the positions of the segment prior to the 3rd cycle in each direction. Thus it is a quasi-static measurement of residual deformation (Gay et al. 2005) that is not suitable for *in vivo* use and a suitable alternative needs to be investigated. Such an alternative, which uses continuous kinematic data and a neutral starting position, was provided in this chapter.

It may be argued that passive motion does not test active (muscular) or motor control and that the slope at the onset (if it can be analogous to the NZ or LZ) would only be of value if the studies were weight-bearing with a loaded spine. This requires a comparison beyond this thesis, but the difference in the attainment rate in this study points to the role of the passive motion structures alone without contamination from muscular or motor control.

Chapter 8   Reference limits for continuous

intervertebral rotation

8.1   Chapter overview

Maximum intervertebral range of rotation (mIVR) and attainment rate do not use the whole motion pattern; therefore a kinematic parameter that would consider abnormal or normal continuous rotation was based creating reference interval data ($\overline{X} +/-2SD$) for every tenth of a degree of table motion (n=approximately 780). Continuous motion data from both groups were then compared to determine proportions exceeding the intervals (either above or below the reference interval).

The exploration of the diagnostic accuracy of continuous intervertebral rotation (cIVR), reference intervals were undertaken on the proportions exceeding the reference intervals using sensitivity and specificity calculations but, as previously mentioned, the nature of comparing healthy volunteer data with reference intervals derived from the same group is potentially problematical.

8.2   Rationale for study

The rationale for this study was to develop a method of determining normal and abnormal continuous intervertebral rotation patterns by exploring whether there were higher proportions of patients than healthy volunteers whose continuous motion pattern moved outside the reference limit, indicating hyper or hypo mobility at any point throughout the bend. Abnormal motion from static positions has previously been determined based on reference intervals (Schneider et al. 2005; Kulig et al. 2007; Abbott et al. 2009) although these measurements were end of range. The use of reference intervals for cut offs for continuous IV motion data has never been undertaken but it is reasonable to presume that hyper and hypo mobility may occur at any point throughout the bend. Additionally reference intervals showed initial promise for mIVR (see Table 6-6 p109), despite the low proportions of patients or healthy volunteers with mIVRs outside the reference intervals.

A secondary analysis used the proportions (counts out with the reference intervals) to determine the diagnostic accuracy (sensitivity and specificity) of cIVR. It is acknowledged that using cut off values based on data derived from the same group is

erroneous, hence the introduction of cIVR reference intervals are exploratory. For logistical reasons an independent reference group is not included in this chapter.

8.3   Literature review

8.3.1 Continuous intervertebral motion

Information from mid-range positions is believed by many to hold the key to understanding the link between the biomechanics of the spine and back pain. *In vitro* this data can be semi static, where a series of images are taken at points throughout the bend, or dynamic, where data are collected at the same time as motion. Hoag et al (Hoag et al. 1960) was the first to investigate mid-range motion using quasi static functional radiography to look at the quality of intervertebral motion. This method was complicated and affected by reliability of anatomical landmark definition, additionally measurements from the quasi static method can be affected by soft tissue creep (King et al. 2009), which introduces another source of variability.

As discussed on p35, only fluoroscopy can truly measure dynamic *in vivo* motion in a non-invasive way. In recent years fluoroscopy has been combined with computer automated measurements to create quantitative fluoroscopy (QF) (Cholewicki et al. 1991; Harada et al. 2000; Takayanagi et al. 2001; Lee et al. 2002; Wong et al. 2004; Teyhen et al. 2005; Breen et al. 2006; Wong et al. 2006; Auerbach et al. 2007; Teyhen et al. 2007b; Mellor 2009). Although QF may suffer from the same errors of radiographic positioning, measurement error and lack of standardisation, which may account for up to 15% of the variation (Danielson 1988), these have been overcome with automated measurement algorithms such as the DCRA method (Frobin 1996), and standardised positioning, both of which are used in this thesis.

Results from continuous motion studies *in vivo* have suggested that mid-range motion plays an important part in back pain (Auerbach et al. 2007; Teyhen et al. 2007b; Ahmadi et al. 2009) but the identification and measurement of kinematic parameters from continuous motion is problematical. Lehman notes the complexity of analysing the shape, velocity and symmetry of complex movements (Lehman 2004), although advances in mathematical modelling have allowed more complex analyses, such as artificial neural networks (ANN). Bishop et al claimed a neural network classifier had 85% accuracy as a classification model for LBP (Bishop et al. 1997) although they studied global trunk motion. Dickey et al used ANNs in their analysis of intervertebral motion and concluded a strong correlation between intervertebral motion and pain (R^2=0.997) compared to a discriminant linear analysis (R^2=0.5) (Dickey 2002). The

complexity of ANN's (they require training for each specific situation) means they are not readily transferrable to a clinical environment.

Continuous motion has also been modelled by combining initial *in vivo* images from MRI/CT and/ or fluoroscopy with computer algorithms to predict the motions of the spine. Artificial models are more suitable for investigation of kinematic processes, such as the response to loading (Najarian et al. 2005), and while finite element models can be used to explain experimental results, their predictive power is limited by inadequate knowledge of the material, loading, and movement properties of spine tissues. Thus they are unsuitable for clinical use (Jirková et al. 2007).

Conversely, advances in computer aided measurements, digital imaging and radiation dose reduction have now enabled the use of QF to study spine biomechanics with promising results in both research and clinical settings (Cholewicki et al. 1991; Kanayama et al. 1996; Okawa et al. 1998; Harada et al. 2000; Takayanagi et al. 2001; Lee et al. 2002; Vander Kooi et al. 2004; Wong et al. 2004; Teyhen et al. 2005; Breen et al. 2006; Wong et al. 2006; Teyhen et al. 2007b; Wang et al. 2008; Ahmadi et al. 2009; Lam et al. 2009; Mellor et al. 2009). With the exception of Mellor et al (Mellor et al. 2009) and Breen et al (Breen et al. 2006) these studies have all examined continuous weight-bearing motion in the sagittal plane. Additionally they have used differing acquisition and measurement protocols, cannot disaggregate the biomechanical subsystems (see Figure 2-5 p20) and thus cannot be directly compared.

There is currently no simple method for determining normal from abnormal continuous intervertebral motion that could be transposed to clinical practice. Studies using QF have found subtle differences between patients and controls in the mid-plane, but they have used complex statistical modelling (Bishop et al. 1997; Dickey and Gillespie 2003), or combined a number of kinematic factors into a multivariate model (Teyhen et al. 2007a; Teyhen et al. 2007b). These studies have not categorised hyper and hypo mobility from continuous motion but McGregor et al noted that those with spondylolisthesis tend to be hyper mobile while those with stenosis, disc prolapse, or degenerative disc disease, tend to be hypo mobile (McGregor 1997), thus some kind of differentiation would be useful in directing treatment.

8.4   Research question

Can continuous intervertebral rotation (cIVR) upper and lower reference limits distinguish between patients and healthy volunteers?

8.5   Aim

The aim of this study was to examine cIVR reference limits in both CNSLBP and healthy volunteers when variability in positioning, range and rate of trunk motion; and errors in analysis were reduced.

8.6   Hypothesis

Using sensitivity and specificity derived from reference limits, cIVR measured from passive recumbent motion can distinguish between patients with mechanical low back pain and healthy volunteers

The secondary hypothesis states that there will be significant differences in the proportion of patients with mIVR values outside the reference intervals.

8.7   Method

Data acquisition and raw outputs were described earlier (see p45). Continuous intervertebral rotation is produced for every 10th of a degree of table rotation, thus there are typically up to 780 data points on the x axis (see Figure 3-11 p69).Raw graphical output represented left and flexion data as negative, and right and extension as positive on the y axis. Statistical data analysis is detailed in Table 3-2 p52. Data were accepted as being predominantly normally distributed if more than 50% of the tests were not significant.

Upper and lower reference limits ($\overline{X} +/- 2SD$) for every 10th of a degree of passive table rotation (each data point on the x axis) were created from healthy volunteer data (n=40) in this study and represented graphically against all group data (see example for right L4/5 Figure 8-1 p148) Because this study was exploratory and so many reference intervals were created for each segment, confidence intervals were not calculated. Observed values for each participant (n=80) per level and direction (n=12) were compared to the reference limits and any point throughout the bend were included if they were

    i)   Greater than or equal to the upper reference limit (hyper mobility)

            Or

    ii)   Less than or equal to the lower reference limit (hypo mobility)

In addition, data were combined to examine overall direction and planes of motion (coronal, sagittal and overall). No weighting was attributed; hence in theory one

participant may have 12 counts (out with the reference intervals for each level and direction) but for the purpose of combined analysis was counted as one.

The proportions for hyper and hypo mobility were entered into 2 x 2 diagnostic accuracy tables. Being outside the reference interval was counted as positive. Segments were examined individually and combined.
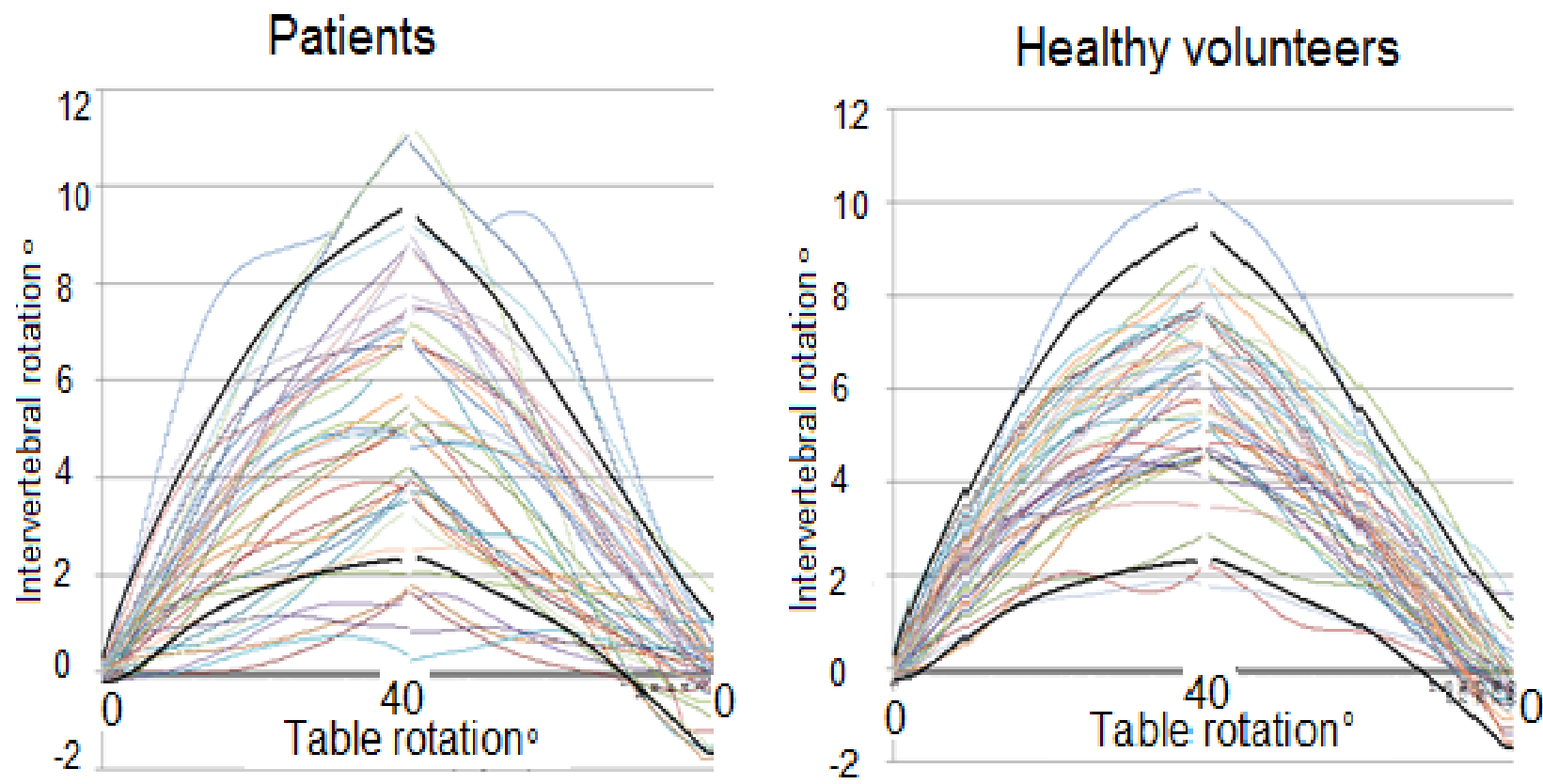
Figure 8-1 Example of L4/5 right bending for patients and healthy volunteers, with upper and lower reference limits in black

8.8   Results

8.8.1 Parametric assumptions

Data at every 10th of a degree was tested for normality (an example for left L4/5 for the first 6 degrees is in the appendix (see Table 13-29 p274)). The percentage of the data that was normally distributed is presented in Table 8-1 p149. Left L2/3 had the lowest percentage of normally distributed data at just 68.8%. It may have been possible to transform this data so that every x axis data point suited a Gaussian distribution but this was not pursued due to logistical reasons and because the assessment of cIVR is exploratory.

Direction	Intervertebral level	% normally distributed
Left n=782	L2/3	68.8
	L3/4	91.8
	L4/5	81.7
Right n = 780	L2/3	90.3
	L3/4	95.3
	L4/5	85.8
Flexion n = 778	L2/3	74.0
	L3/4	95.8
	L4/5	95.9
Extension n = 782	L2/3	68.7
	L3/4	89.4
	L4/5	75.1

Table 8-1   Continuous intervertebral rotation and tests of normality (Shapiro Wilkes)

8.8.2 Continuous intervertebral rotation (cIVR) reference limits

Continuous motion patterns for each segment and direction, along with the continuous reference ranges, are in the appendices (see Figure 13-11 p275 for left, Figure 13-12 p276 for right, Figure 13-13 p277 for flexion and Figure 13-14 p278 for extension). Of note is greater variation in the motion patterns in patients although this was not statistically tested it mirrors the findings of mIVR.

8.8.2.1   *Continuous reference limits for each segment*

Data were separated into hyper and hypo mobility (Figure 8-2 p151 and Figure 8-3 p151), exact counts are in the appendix (see Table 13-30 p279).

Because the reference limits were created from the healthy volunteer data in this thesis, of which the majority was normally distributed, one may expect that 2.5% of the healthy volunteers would have patterns beyond the upper and lower limit. This was not always true for this data however.

8.8.2.1.1 Hyper-mobility in continuous motion

Left L3/4 (p = 0.01) and flexion L4/5 (p = 0.05) had significantly higher proportions of patients exceeding the upper reference interval than healthy volunteers.

8.8.2.1.2 Hypo-mobility in continuous motion

Three conditions had significantly higher proportions of patients than healthy volunteers with hypo mobility. These were: Left L3/4 (p = 0.01), left L4/5 (p=0.003) and right L4/5 (p=0.01).

8.8.2.1.3 Combined data

When data on segments were combined per direction, left (p = 0.001) and flexion (p =0.05) showed significant differences for hypo mobility, but there were no significant differences for hyper mobility. Overall (all directions and segments), hypo mobility is more significantly associated with being a patient (p=0.02) but this is not the case for hyper mobility (p>0.99).
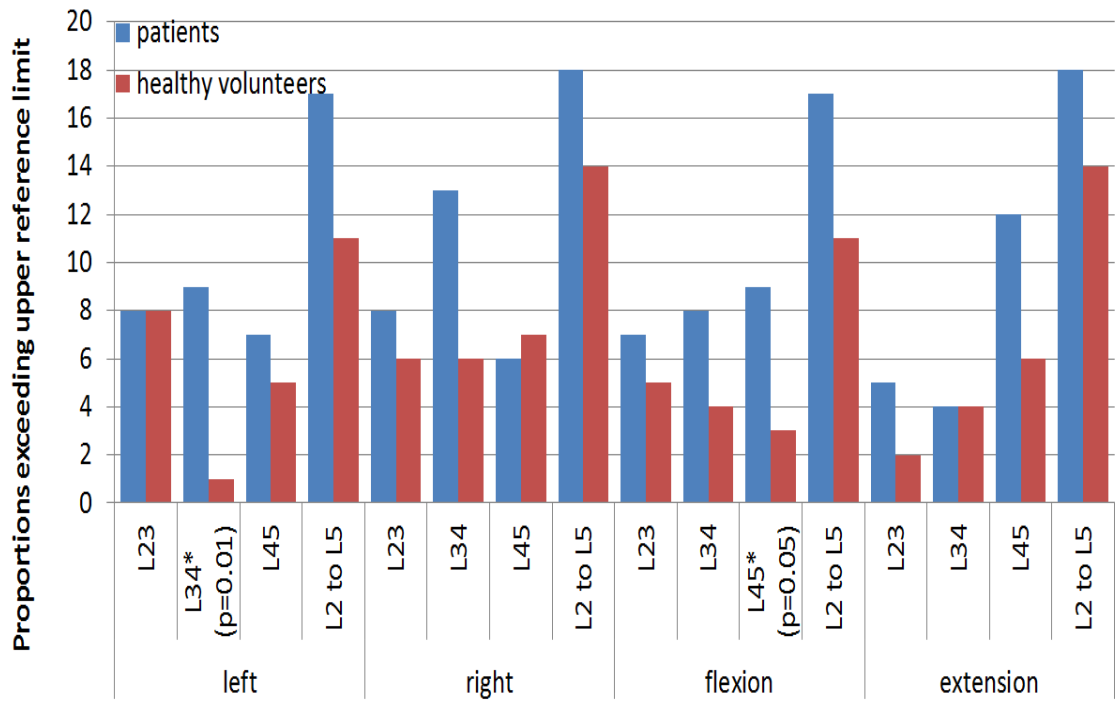
Figure 8-2 Proportions exceeding upper cIVR reference limits
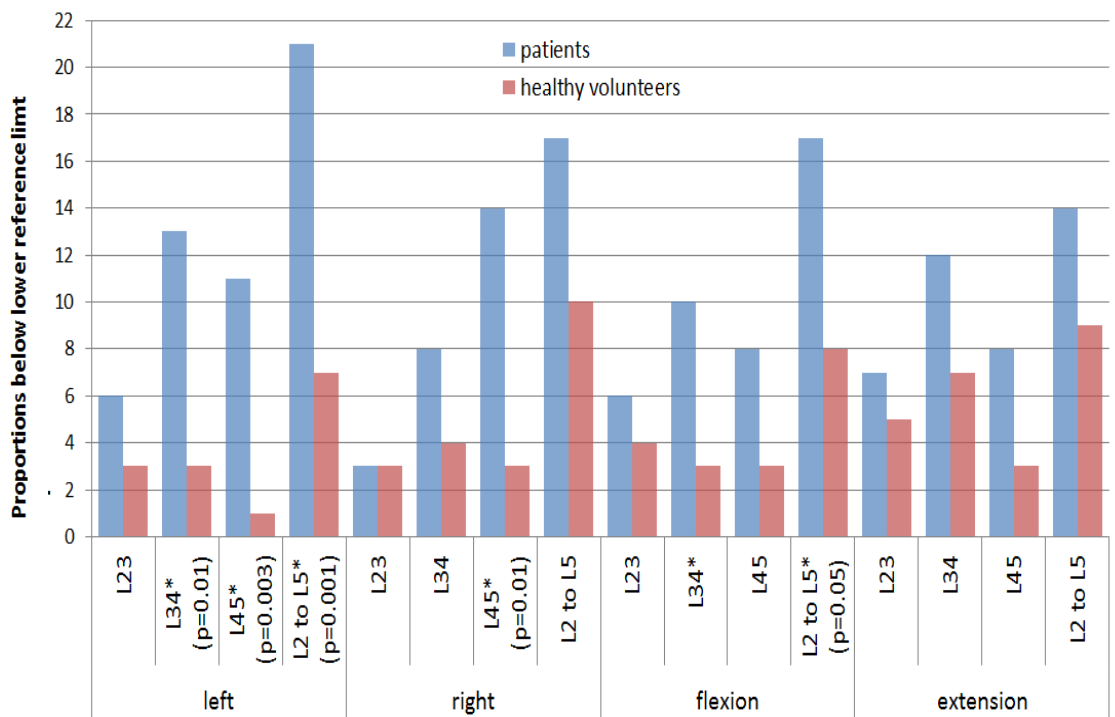
Figure 8-3 Proportions below lower cIVR reference limits

(* significant at the 5% level)

8.8.3 Diagnostic accuracy of cIVR reference limits

The counts (in Table 13-30 p279) were entered into a 2 x 2 table to calculate sensitivity and specificity. The diagnostic accuracy of each segment individually and combined for hyper and hypo mobility are in the appendices (Table 13-31 p280 and Table 13-32 p281). It is acknowledged that sensitivity is dependent on the fact that it is derived from the reference limits from the healthy volunteer group.

For hyper mobility, the trend was for high specificity (the lowest was 0.8) and low sensitivity (the highest per segment was 0.325), and for each direction there were no instances of sensitivity higher than 0.45. For all directions combined, sensitivity was 0.75 (95% confidence interval 0.588 to 0.873) and specificity 0.275 (95% confidence interval 0.146 to 0.439). For hypo mobility the trend was the same, high specificity and low sensitivity. The segment with the lowest specificity was extension L3/4 (0.825 (95% confidence intervals 0.672 to 0.927)), sensitivity was 0.3 (95% confidence intervals 0.166 to 0.465).

Of the three segments that demonstrated significant differences in their means (left L3/4, L4/5 and right L4/5) none demonstrated sensitivity greater than 0.350, and the lowest specificity amongst these segments was 0.925. For all levels and directions combined, sensitivity was 0.85 (95% confidence interval 0.702 to 0.943) and specificity 0.4 (95% confidence interval 0.249 to 0.567).

This points to no hypo and hyper mobility being features that rule out mechanical problems in the passive system (rather than ruling them in) although the nature of this analysis and the increased risk of a type one error need to be appreciated. Overall this leads to the conclusion that hypo mobility may be better at ruling out those with mechanical problems in their passive subsystem, rather than being able to distinguish between patients and healthy volunteers.

8.9 Discussion

Of interest is that a greater number of patient segments demonstrate hypo mobility rather than hyper mobility. This skew in the data that could indicate that the segments are not sufficiently stressed in the passive motion protocol to exceed the upper limit, or that the patients in this group had fewer mechanical issues that led to hyper mobility. In consideration of hyper mobility, it is interesting to compare these results with those in Chapter 6 p95 (mIVRs). The mIVR reference ranges demonstrated just one segment with significantly higher proportions of patients than healthy volunteers above the upper reference limit (see Table 6-6 p109) (flexion L4/5 p=0.03). For cIVR the levels are left L3/4 (p=0.01) and flexion L4/5 (p=0.05) (see Table 13-30 p279). Conversely, no

segments assessed with mIVR demonstrated hypo mobility, whereas five combinations demonstrated significantly more proportions of patients than healthy volunteers below the lower cIVR reference limits. This is important as it demonstrates cIVR may be more responsive than mIVRs for detecting hypo mobility.

It is interesting to note that left L3/4 had a low p value for both hyper and hypo mobility (p = 0.01), which may be due to multiplicity of the statistical tests (thus increasing the chance of a type one error). Conversely it may indicate the mixed nature of conditions that are labelled mechanical CNSLBP. Consequently an advancement of this study would be to determine whether those with known conditions, such as disc degeneration or spondylolisthesis, demonstrated hypo and hyper mobility in continuous motion, as suggested by McGregor et al (McGregor 1997). Fujiwara et al used MRI to grade degeneration and found that intervertebral RoM increased with increasing severity of disc degeneration, but decreased as the degeneration reached its end stage (Fujiwara 2000), which mirrors historical findings by Knuttson et al (Knutsson 1944). Secondly it would be useful to determine the co-dependency of intervertebral motion, for instance if one segment demonstrates hypo mobility does an adjacent segment demonstrate hyper mobility?

Continuous reference intervals did not yield high sensitivity or specificity for cIVR reference ranges to be useful as a standalone kinematic parameter, and they appear to be better at ruling out mechanical CNSLBP rather than ruling it in. This agrees with a systematic review of clinical tests for lumbar instability that concluded the majority had high specificity and low sensitivity (Alqarni et al. 2011). Teyhen et al (Teyhen et al. 2007a; Teyhen et al. 2007b) preselected patients based on their clinical symptoms and found high sensitivity and specificity for continuous motion but they did not distinguish between hyper and hypo mobility, nor use reference limits as cut off values, hence these results cannot be directly compared. It is expected that a pre-selected patient group with spondylolisthesis or disc degeneration would increase the diagnostic accuracy of cIVR values, which demonstrates the heterogenic nature of mechanical CNSLBP.

In this study no participants had a spondylolisthesis between L2 to L5, and the prevalence of disc degeneration greater than grade 1 on the Kellgren and Lawrence scale (Kellgren and Lawrence 1958), was low (see Table 4-3 p75). Additionally agreement between observers was only moderate although both observers agreed that one patient had grade 3 disc degeneration at L4/5. The continuous motion patterns per direction for this patient, along with the cIVR reference intervals are displayed in Figure 8-4 p155 where it can be seen that L4/5 is below the lower reference limit in coronal

motion. Interestingly for left bending, the supra adjacent level (L3/4) exceeds the upper reference limit on its return to neutral.
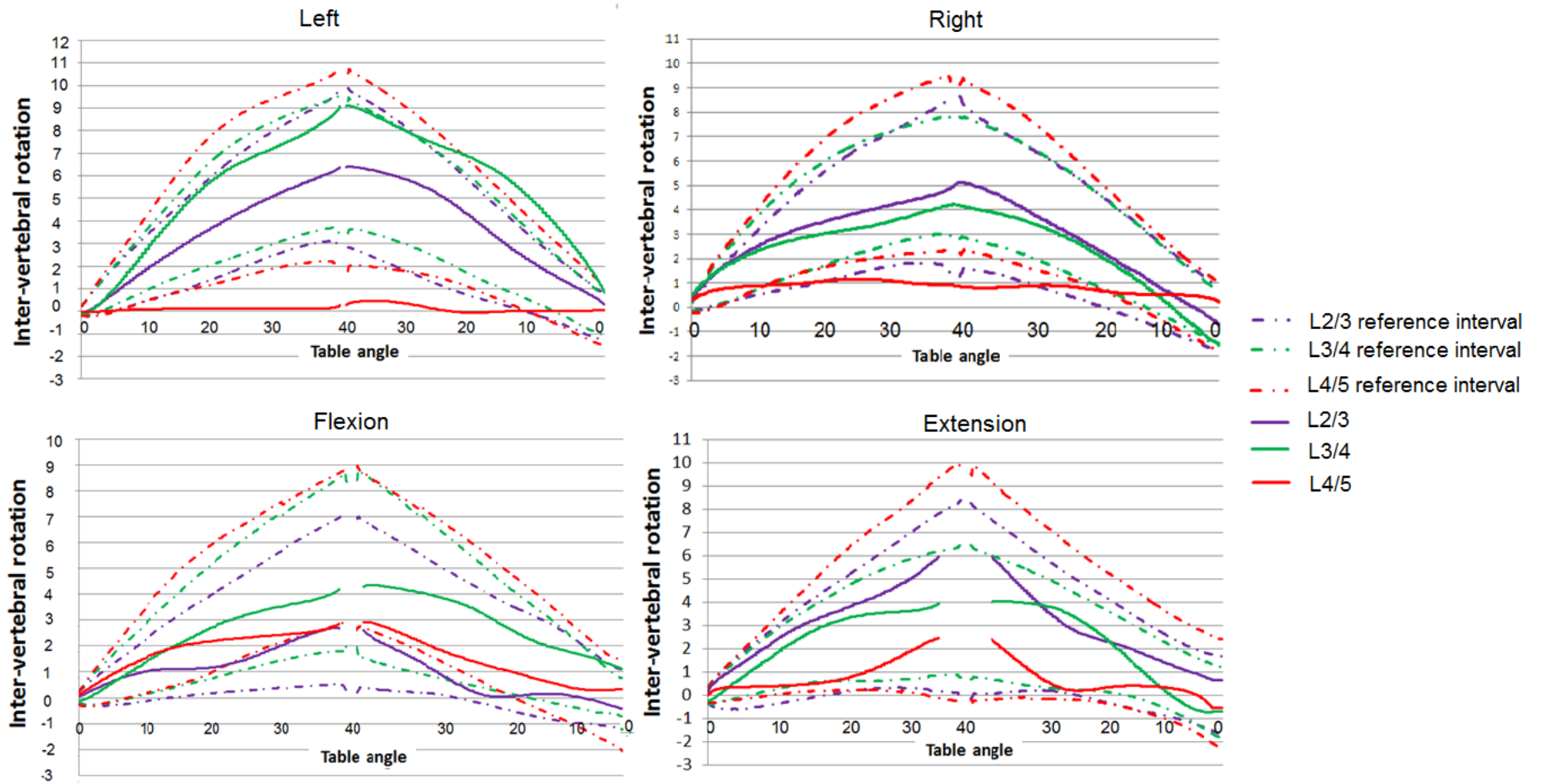
Figure 8-4 Continuous motion patterns for a patient with grade 3 disc degeneration at L4/5[19]

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[19] These results are from a patient who could not achieve 40° extension rotation without coupled motion. The extension graph displays actual rotational values.

Based on the results in this chapter, it appears that continuous reference intervals are more sensitive to the detection of hyper and hypo mobility than mIVR reference intervals. However, this study would need replicating with larger numbers and an independent reference group for firm conclusions to be drawn. Nevertheless these results strengthen the suggestion of a potential sub group of patients for whom hyper or hypo mobility is a feature. In the absence of validated methods for comparing intervertebral continuous motion patterns, the following continuous reference intervals are suggested as an introduction to abnormal motion, defined as moving outside reference intervals.

8.9.1 Limitations and recommendations for future work

It may be reasonable to claim that the cIVRs are reproducible because they come from the same data as mIVRs, which have excellent agreement and repeatability (see Chapter 5 p79). Theoretically mIVRs could be the same and the motion pattern very different. To overcome this, all data included in the reproducibility study was visually checked and deemed to be suitably similar, although it is noted that this was subjective. An advancement of this method would be to undertake a correlation between the cIVR intervertebral outputs of different observers using a similar method to William's et al (Williams et al. 2013) who assessed the reliability of continuous global motion patterns.

Using counts as a way of expressing normal/abnormal motion reduced continuous data into dichotomous data. If a method of objectively quantifying a motion pattern can be determined then comparing these in a RoC curve analysis would yield optimum sensitivity and specificity. To firmly determine whether this method has diagnostic accuracy would require the upper and lower reference limits to be calculated from a separate group of healthy volunteers and with a larger reference group of n=120 as recommended by the CLSI (see Figure 6-1 p100). An alternative approach to assessing continuous motion patterns includes fitting polynomials, or alternatively employing artificial neural networks to determine their ability to predict those who may have mechanical CNSLBP based on their motion pattern. However, the approach would need to be simplified to be clinically meaningful.

In Chapter 6, the mIVR reference ranges displayed significant differences in proportions when healthy volunteer data from this study were used, but this was not the case when independent healthy volunteer data were introduced. Besides an increased risk of a type one error, this may have been a feature of the different motion protocols (see Figure 6-4 p113), hence independent data were not compared for cIVR.

Despite standardising the procedure, there was more variation evident in the motion patterns of patients (see appendices Figure 13-11 p275, Figure 13-12 p276, Figure 13-13 p277, and Figure 13-14 p278). One way of accounting for between subjects variation is to normalise the data[20]. Analysis of normalised rotational values were undertaken by both Abbot et al for end of range values, (Abbott et al. 2006) and Teyhen et al for attainment rate values (Teyhen et al. 2007b). However, while normalised values reduce between subject variations, it is difficult to compare these across studies if the segments are not comparable. For instance Teyhen et al normalised their values to L3-S1 intervertebral motion, whereas this study examines motion between L2 to L5. Nevertheless, an improvement upon the study of continuous motion patterns would be to consider the same once normalised, and this is pursued in Chapter 9 p159.

8.9.2 Clinical implications

The method of continuous intervertebral motion reference intervals appear to be more responsive for detecting hyper and hypo mobility than mIVR lower reference limits, and this is important in considering treatment options as it could lead to mobilisation of segments that were not previously appreciated as hypo mobile. Continuous reference intervals appear to be a reasonable method for determining problems throughout the motion pattern and identifies differences in segments that are not identified from maximum intervertebral rotation (see Chapter 6 p95) or the initial intervertebral attainment rate (see Chapter 7 p129). However, the variation in intervertebral rotation, which is greater in patients, may still be a confounding factor. Further research with a separate independent healthy volunteer group, compared to known subgroups of patients with mechanical disorders, is recommended.

8.10 Conclusion

The hypothesis was that cIVR reference intervals can distinguish between patients and healthy volunteers. This was not supported because no segment, individually or combined, had a sensitivity and specificity that would be acceptable for a standalone diagnostic test. The limitation of deriving cut off values from healthy volunteer data included in the study is noted.

The second hypothesis was that there will be a greater number of patients who have motion patterns that move outside the reference intervals. This was partially supported

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[20] Normalised intervertebral rotation is the proportional contribution of the segment to the global measurement.

because some segments showed significant differences between groups, but the issues of multiple statistical testing and the possibility of a type one error are noted.

Reference intervals for passive recumbent continuous motion may be more penetrating in the search for biomechanical problems as they essentially assess rotation throughout the bend, both outward and return, based upon standardised motion. Thus any deviations outside the reference intervals may point to issues in the discs, ligaments and vertebral articulations. Focussing on particular directions may further shed light on the biomechanical problem, for instance patients with facet joint disease may show problems only in extension, whereas disc degeneration may manifest in all planes of motion. Further research using passive recumbent QF is necessary to confirm or deny this.

8.11 Contribution to new knowledge

Previous studies have examined *in vivo* mid-range motion (Cholewicki et al. 1991; Okawa et al. 1998; Harada et al. 2000; Takayanagi et al. 2001; Lee et al. 2002; Powers et al. 2003; Zheng et al. 2003; Teyhen et al. 2005; Wong et al. 2006; Kulig et al. 2007; Landel et al. 2008; Ahmadi et al. 2009; Lam et al. 2009; Lee B. et al. 2011) using either semi static radiographs, MRI or fluoroscopy. However, the results are typically sampled at points in the trunk bend whereas in this study the whole sequence is used (n=approximately 780 per level and direction).

This is the first time that reference intervals for continuous motion have been calculated and compared in both patients and healthy volunteers. Most studies have only examined the sagittal plane but is the first study to use passive cIVR data in both the sagittal and coronal plane with a method that has high reproducibility for the automated tracking algorithms.

Chapter 9   Proportional lumbar spine intervertebral motion patterns; a comparison of patients with chronic, non-specific low back pain and healthy controls

9.1 Chapter overview

This chapter presents a peer reviewed research paper published in the European Spine Journal (Mellor et al. 2014b) authored by the CI and three supervisors [21] (see Figure 13-15 p292). The paper is given here in full hence it may replicate prior sections of this thesis. The rationale for the study, the hypothesis, and the contribution to new knowledge were not included in the research paper.

9.2 Introduction[22]

It has been noted that intra and inter subject variation contributes to high variability. To overcome this, some authors have normalised results for intervertebral rotation and translation by expressing them as a percentage of the global RoM (Abbott et al. 2006; Auerbach et al. 2007; Teyhen et al. 2007b; Wu et al. 2010). Subjectively evident from mIVR values is the larger variation in patients than healthy volunteers (see Table 6-3 p104), which was also observed by Abbott et al (Abbott et al. 2006) who proceeded to develop a novel way of addressing this by creating 'normalised within subjects approach'. This approach has also been undertaken by Wu et al the cervical spine (Wu et al. 2010).

Normalising intervertebral motion accounts for co-dependency of the segments because the contribution of each segment is expressed as a proportion. This has been useful when considering adjacent segment kinematics following surgery (Auerbach et al. 2007; Passias et al. 2011) but previous studies have only measured static or semi static measurements, and have concentrated on the sagittal plane. Abbott et al (Abbott et al. 2006) compared a 'normalised within subjects' contribution (proportional) approach, with RoM measurements from end ranges. Reference intervals were

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[21] Sections in this chapter that were not published are marked with a footnote. The CI undertook all data collection and analysis. All three supervisors were involved in statistical analyses or editing.
[22] Introduction was not published

provided for both a standard Gaussian ($\overline{X} +/- 2SD$) approach and a normalised approach and they found a statistically significantly higher prevalence of lumbar intervertebral motion disorders when the normalised approach was used. Reference intervals for continuous proportional motion based on upper and lower percentiles (CLSI 2008) were considered but the data were not normally distributed and initial exploration of upper and lower quartiles as cut off values proved untenable due to their irregular nature (see the example from extension in Figure 9-1 p161). Consequently the analysis concentrated upon the production of a variable that would capture the variation of the continuous proportional motion for each participant.

9.3   Rationale for study[23]

Subjective observation of the CPM patterns in patients and healthy volunteers (see Figure 9-2 p162) revealed greater variation in the percentage motion absorbed by each segment in the patient group when compared to the healthy volunteer group. A method of quantifying this variation is proposed as a new kinematic parameter. The parameter reflects the variation of the proportional ranges for each direction (proportional range variance (PRV)) and combined for all four directions (combined proportional range variance CPRV)). Subsequently these were compared for differences in means and diagnostic accuracy, and relationships to patient characteristics of pain and disability. The work was submitted for peer reviewed publication and forms the body of this chapter.

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[23] Rationale for study was not published but is included here for completeness
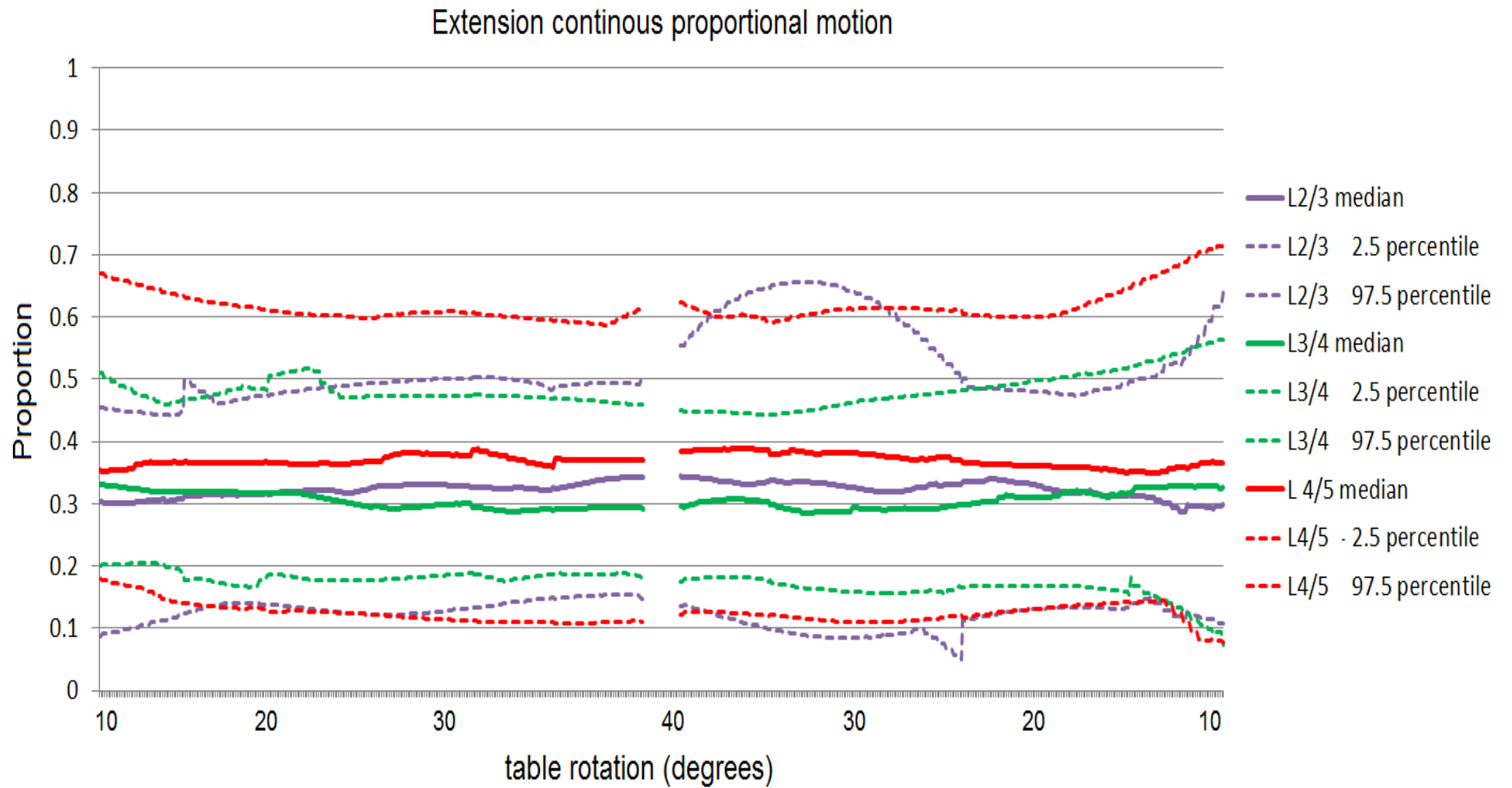
Figure 9-1 Example of median and upper and lower percentiles for continuous proportional motion in extension
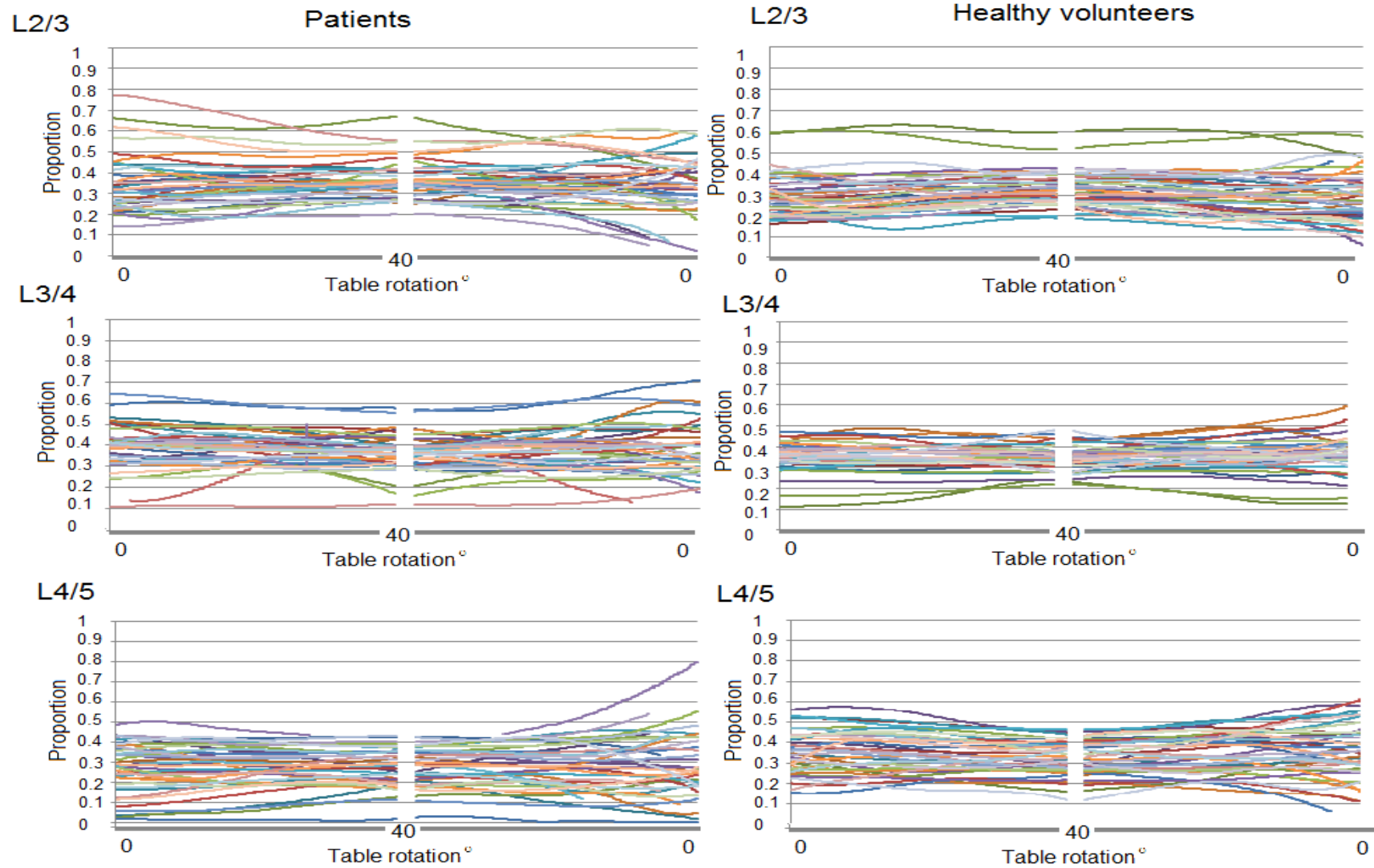
Figure 9-2 Participants' proportional motion for left bending for each segment

9.4 Hypothesis[24]

Primary hypothesis:

i) Patients will have greater variability in proportional continuous motion (PRV) than healthy volunteers.

Secondary hypotheses:

ii) Combined proportional range variance (CPRV) can distinguish between patients and healthy volunteers.
iii) There will be a relationship between pain and disability and combined proportional range variances in the patient group.

9.5 Abstract

Identifying biomechanical subgroups in chronic, non-specific low back pain (CNSLBP) populations from intervertebral displacements has proven elusive. Quantitative fluoroscopy (QF) has excellent repeatability and provides continuous standardised intervertebral kinematic data from fluoroscopic sequences allowing assessment of mid-range motion. The aim of this study was to determine whether proportional continuous IV rotational patterns were different in patients and controls. A secondary aim was to update the repeatability of QF measurement of range of motion (RoM) for intervertebral (IV) rotation.

Fluoroscopic sequences were recorded of passive, recumbent coronal and sagittal motion, which were controlled for range and velocity. Segments L2 to L5 in 40 primary care CNSLBP patients and 40 matched controls were compared. Patients also completed the von Korff Chronic Pain Grade and Roland and Morris disability questionnaire. Sequences were processed using automated image tracking algorithms to extract continuous intervertebral rotation data. These were converted to continuous proportional ranges of rotation, which were determined for each image frame throughout the motion. The continuous proportional range variances (PRV) were calculated for each direction and combined to produce a single variable representing their fluctuation (CPRV). Inter and intra-rater repeatability were also calculated for the maximum intervertebral motion measurements obtained during controlled trunk motion to provide an updated indication of the reliability and agreement of QF for measuring spine kinematics.

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[24] The hypotheses were not published but are included here for completeness

CPRV was significantly higher in patients (0.011 vs 0.008, Mann Whitney 2-sided p = 0.008), implying a mechanical subgroup. Receiver operating characteristic curve analysis found its sensitivity and specificity to be 0.78% (60-90) and 0.55% (37-73) respectively (area under the curve 0.672). CPRV was not correlated with pain severity or disability. The repeatability of maximum intervertebral range was excellent, but range was only significantly greater in patients at L4-5 in right side bending (p=0.03).

9.5.1 Key words:

Spine kinematics, subgroups, movement disorders, repeatability, reliability, agreement.

9.6 Literature review

Low back pain makes a large contribution to the burden of disability worldwide, but its pathophysiology in most sufferers is poorly understood (Murray et al. 2012). Despite sub classification into serious spinal pathology, nerve root pain and non-specific low back pain, the majority of cases are in the latter category and defy classification (Deyo et al. 1992). The theoretical framework provided by the bio-psychosocial model (Waddell 1998) has so far focussed mainly on psychosocial components but individual psychosocial factors are not strong determinants of who will experience first-time low back pain (Mannion et al. 1996; Adams et al. 1999), chronic disabling low back pain in the future (Chou and Shekelle 2010), or poor outcomes from recent episodes (Kent and Keating 2008).

There is a need to further study the biomechanics of the lumbar spine, but, information on the mid-range is not possible from flexion extension radiographs (functional radiography) despite their widespread use in research and clinical practice (Leone et al. 2007). Additionally, it is difficult to discriminate between normal and abnormal motion in living people from these due to large differences in techniques and large biological variation (Nizard et al. 2001). Fluoroscopy can reveal both end and mid-range motion and marked improvements are seen in precision when the measurements are automated (Yeager et al. 2014).

Spinal motion underlies the rationales for many commonly used therapies but motion-based classification systems seem to be largely a matter of professional preference. Objective evidence of patient subgroups remains elusive (Karayannis et al. 2012) and there remains a requirement to define the best methods of measuring spinal motion (Laird et al. 2012).

Some recent cross-sectional comparisons of chronic, non-specific low back pain (CNSLBP) in patients and controls using flexion-extension radiographs have reported

good inter-rater reliability and have shown restricted sagittal rotation to be associated with recurrent or chronic low back pain (Taghipour-Darzi et al. 2012). However, these have been undertaken during uncontrolled, weight-bearing maximum trunk bending and are subject to high intra subject variation (Deitz 2010).

Other 2-dimensional motion studies have expressed intervertebral rotation as the proportional contributions of individual intervertebral levels to total lumbar (Teyhen et al. 2005; Abbott et al. 2006) or cervical spine motion (Wu et al. 2010) allowing comparisons without contamination from inter subject variation. Proportional motion, for example in 3 adjacent segments, is expressed as:

$$\text{contribution Lx} = \frac{\text{Lx}}{\text{Lx} + \text{Ly} + \text{Lz}}$$

(Lx, Ly, Lz: Contributions to motion of adjacent segments.)

Abbott et al (Abbott et al. 2006) found that when expressed as a proportion of the sum of the ranges of the segments under consideration , the prevalence of patients exceeding reference intervals derived from healthy controls became highly significant, more so than when only comparing maximum rotation. Although this was an end of range study, which does not provide sufficient information to assess for functional instability, defined as: "the loss of the spine's ability to maintain its pattern of displacement under normal physiological loads" (White and Panjabi 1990).

Quantitative fluoroscopy (QF) provides continuous intervertebral motion data and reduces intra subject variations as participants are guided to the same range at the same velocity (Breen et al. 2012). QF allows kinematic measurements to be extracted from weight bearing (active) and non-weight-bearing (passive) motion in both the coronal and sagittal planes (Wong et al. 2004; Teyhen et al. 2007b; Ahmadi et al. 2009; Mellor et al. 2009) and kinematic outputs have included intervertebral rotations and translations (Abbott et al. 2006), attainment rates (Teyhen et al. 2007b) and centres of rotation (Ahmadi et al. 2009; Taghipour-Darzi et al. 2009). To date, no QF study has used continuous proportional motion data for the comparison of patients and controls.

This study aims to determine whether continuous proportional motion patterns from passive, uni-planar lumbar spine motion can distinguish between patients with CNSLBP and healthy controls. A new way of measuring this is proposed, using the variances of the proportional ranges between levels (proportional range variance (PRV) for each direction, and their sums (combined proportional range variance (CPRV) (see Figure 9-3 p167). The study also sought to update the repeatability of maximum

rotational values to reflect the decreasing errors associated with improvements in the QF technique (Breen et al. 2012).

9.6.1 Objectives

The objectives of this study were:

1. To determine whether the variations in proportional ranges across motion sequences are significantly different between patients and controls.

2. To calculate the sensitivity and specificity of the PRV and CPRV values to discriminate patients from controls

3. To update the observer agreement and reliability (SEM and ICC) of maximum IV-rotational measurements in passive recumbent motion measured with QF.

 4. To determine whether there are relationships between CPRV and pain or disability.
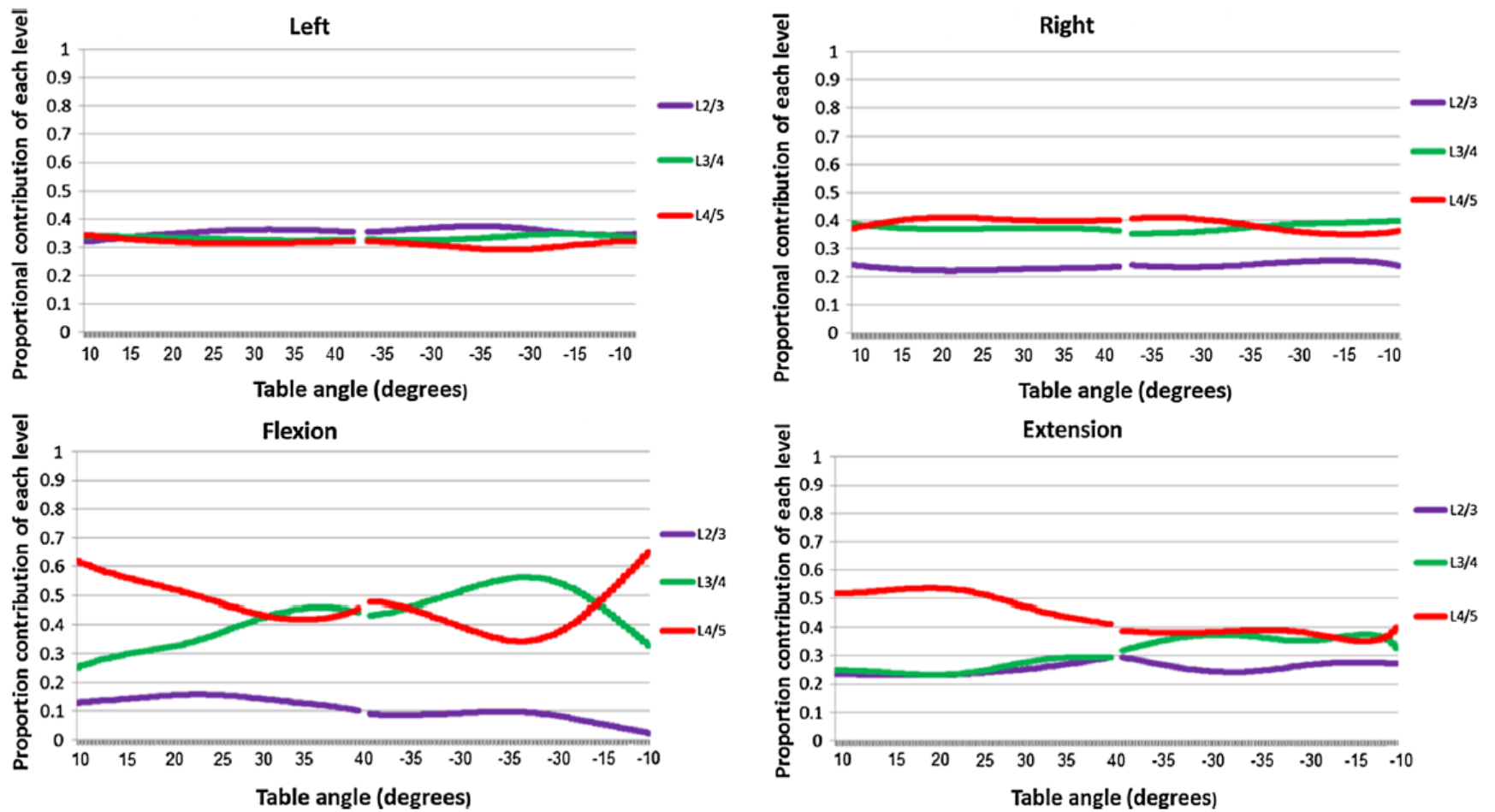
Figure 9-3 Examples of mid-range patterns of L2–5 proportional intervertebral rotation in left, right, flexion and extension motion

9.7   Methods

This was a cross sectional, prospective observational study of passive controlled motion in the lumbar spine.

9.7.1 Participants

A convenience sample of 40 patients aged between 21-50 years presenting to primary care (either chiropractic or outpatient physiotherapy) for CNSLBP was recruited. The age range was kept above 20 and below 51 in an attempt to minimise the influence of age on motion (Wong et al. 2004). Forty pain-free healthy volunteers matched for gender, age and body-mass index (BMI) formed a control group. The eligibility criteria for the study are shown in Figure 3-2 p55 and Figure 3-3 p56.

Patients completed the Roland and Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983) and the von Korff Chronic Pain Grade (Von Korff et al. 1992). Ethical approval was gained from the UK National Research Ethics Service (Southampton A 09/HO5O2/99) and informed consent was taken by the principal investigator (FM).

9.7.2 Sample size

See Sample size calculation p53

9.7.3 Image acquisition and analysis

The study utilised recumbent passive motion as described in other studies (Breen et al. 2006; Yeager et al. 2014). The table moved the lower trunk to a range of 40 degrees and back over a period of approximately 12 seconds in each direction (left, right, flexion and extension). Only L2-5 levels were imaged to minimise image registration failures at S1 due to superimposition of the iliac crests.

Participants first lay supine on a bespoke motion table (Atlas Clinical Ltd) with L3/4 at its fulcrum and the lumbar lordosis flattened by a cushion supporting the knees. Left and right sequences were undertaken separately. Participants then turned onto a left lateral decubitus position and the procedure was repeated for flexion and extension. (See supplementary videos 1 & 2 for examples of left and flexion QF acquisition).

A mobile Siemens Arcadis Avantic (VC10A) image intensifier was positioned with its central ray aligned through L3-4 and fluoroscopy at 15Hz was synchronised with the table motion. Exposure factors were determined by the automatic exposure device (AED) and ranged from 60kVp to120kVp/26.6mA to 63.1mA. Dose was recorded with a Dose Area Product (DAP) meter and converted to mSv using Monte Carlo simulation

software (PCXMC) using the latest tissue weighting factors (ICRP. 2007) and an assumed constant field size of 30cmX30cm .

The fluoroscopic sequences were transferred to a desktop computer and Image J (v 1.47 for Windows OS) was used to separate the individual images from the digital sequences. The images underwent user defined edge enhancement, after which templates were manually placed five times around each vertebral body (L2 to L5) in the first image. Two trained observers undertook this process on a subset of 10 randomly selected participants to allow calculation of the repeatability of this process. Bespoke software written in Matlab (V R2007b, The Mathworks Inc) used a cross-correlation method to obtain automated frame to frame image tracking of the vertebral bodies in subsequent images. Co-ordinates were placed on the vertebral body corners in the first image, linked to the tracking templates and used to register the vertebrae in 2-dimensional space in each frame using a cross correlation method. Tracking was verified for quality assurance by viewing all sequences (see supplementary video 5) and repeating any tracking that failed Averaged intervertebral angles from the five trackings throughout the motion were calculated using the Distortion Compensated Roentgen Analysis method (Frobin 1996). Previous studies using this method found that translation and up to 10° of out-of-plane rotation did not materially influence the accuracy of intervertebral angle measurement (Breen et al. 2006). All patients were recruited and their data acquired, anonymised and analysed by FM.

9.7.4 Repeatability

Table motion was controlled for range. The maximum intervertebral RoM for L2-3, L3-4 and L4-5 achieved at any point throughout the 40° range of the table was calculated as the highest y-value per intervertebral level[25] (see Chapter 5 Figure 5-1 p83). Observers manually identified the maximum and minimum points of the continuous intervertebral motion pattern. Both intra and inter observer repeatability were assessed using intra class correlations (ICC $_{agreement}$ 2,1) (Shrout and Fleiss 1979) and the standard error of measurement (SEM $_{agreement}$) (de Vet et al. 2006).

9.7.5 Statistical analysis

Continuous rotations were converted to proportional contributions for each intervertebral level (n=3) per direction (n=4) (see Figure 9-3 p167). Further examples of continuous proportional motion per level and direction are in the appendix, Figure 13-16 p294. Low overall L2 to 5 rotation at the initial and final 10 degrees of table motion meant that proportional values were only calculated for the middle 80%.

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[25] The actual method was the range between the maximum and minimum y values as reported in this thesis.

To obtain a numerical expression of the fluctuations of the proportional patterns, the range between the maximum and minimum contribution at each frame was calculated (regardless of which intervertebral level contributed to the range). The variance of these ranges was computed and expressed as proportional range variance (PRV) (see Figure 9-4 p170). This was used to measure the fluctuations in the proportional contributions between the 3 levels. The PRVs for all four directions were tested for co-dependency then summed to obtain a combined proportional range variance (CPRV) for each participant.

Statistical analysis of the maximum RoM utilised Stats Direct (V2.7.8) and SPSS (V21 IBM software) to calculate ICC and SEM. Additionally, to find out if the maximum range for any level or direction was different in patients and controls undergoing controlled passive motion, 2-way unpaired t tests were used. As the PRV and CPRV data were not normally distributed, their distributions were compared using a 2-tailed Mann-Whitney U-test. The sensitivity and specificity of the PRVs and CPRV to discriminate cohorts was then determined by receiver operating characteristic (ROC) curve analysis (extended trapezoidal rule method). CPRV was correlated to pain and disability in the patient group.
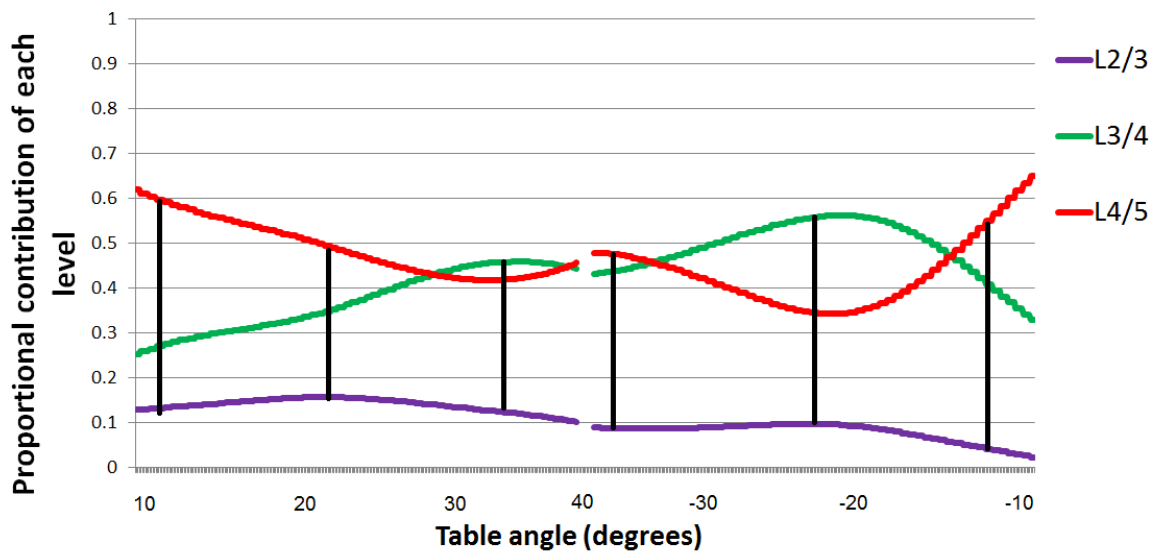
Figure 9-4 Measurement of variability of proportional intervertebral ranges

The range was calculated for each data point (x-axis) to obtain the variance for that direction (black lines). Proportional range variances (PRV) for each direction were summed to give the combined proportional range variance (CPRV). (CPRV = PRVflexion + PRVextension + PRVleft + PRVright.

9.8   Results

9.8.1 Participants

Forty-two consenting patients with a diagnosis of chronic non-specific mechanical low back pain were recruited. Five were from private chiropractic clinics, one from an outpatient physiotherapy department and 34 from a chiropractic college teaching clinic. Two patients underwent fluoroscopy but had unusable data due to poor image quality. One hundred and forty-six healthy volunteers agreed to submit their personal details to a database. Forty of these were matched for gender, age and BMI

The mean effective radiation dose for all participants was 0.561mSv (SD 0.154). Participant demographics are described in Chapter 4 Table 4-1 p74 and maximum intervertebral rotations achieved from a controlled passive protocol are in the appendix (Table 13-16 p257). The only significant difference between patients and controls was for maximum L4/5 left side bending, as reported in Chapter 6 and appendices Table 13-16 p257.

9.8.2 Repeatability

Inter and intra observer reliability and agreement for maximum rotations were high (see Table 13-4 p248,Table 13-5 p248, Table 13-6 p248 and Table 13-7 p249).

The highest ICC was for extension intra observer at L4/5 (ICC =0.990, 95% C.I. 0.962-0.998) and the lowest SEM was 0.081 for right intra observer at L2/3.

The lowest ICC was for inter observer extension at L4/5 (ICC =0.610, 95% C.I. 0.03 to 0.889) and the highest SEM was for inter observer extension at L2/3 (SEM=0.772). Repeatability was excellent for levels and directions combined, the mean inter and intra observer ICCs being 0.956 (95%C.I. 0.837 – 0.989) and 0.990 (0.981-0.999) and the SEM's 0.15° and 0.07° respectively[26].

9.8.3 Variance in ranges between proportional motion patterns

The sensitivity and specificity of PRVs and the CPRV for patients are shown in Table 9-1 p173. There were no significant differences in PRVs (see appendix Table 13-33 p295)[27], but the median CPRV value for patients (0.011) was significantly higher than for controls (0.008), (p=0.008, 2-sided Mann-Whitney).

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[26] These figures, from Chapter 5, differ slightly to those published in Chapter 9 due to a slightly different choice of ICC. The thesis reports a two way random model and the published paper a two way fixed model.

[27] This table was not presented for publication but is included in the appendix for completeness.

The number of patients and controls whose CPRV levels fell above the ROC analysis cut-off value in patients and controls were 31/40 (78%) and 18/40 (45)% respectively (Yates-corrected X^2 = 7.584, p=0.006). The sensitivity and specificity of CPRV for discriminating patients from controls were 0.775 (0.615-0.891) and 0.550 (0.385-0.707). This indicates the possibility of a biomechanical subgroup within the patient population.

9.8.4 Correlation of CPRV with patient characteristics

There were no significant correlations (Kendall's tau) between CPRV and the patient characteristics: age (t=0.215, p=0.0.056), BMI (t=0.046, p=0.683), gender (Fisher exact, 2-sided p=0.901), disability scores (RMDQ) (t=0.155, p=0.181), and three dimensions from the von Korff Chronic Pain Grade. These were based on 10-point visual analogue scales for current pain intensity (t=-0.201, p=0.086), pain intensity over the past 6 months (t=0.207, p=0.067), and worst pain experienced in the past 6 months (t=-0.045, p=0.706).

Variable	Sensitivity	Specificity	AUC	Cut-off	+ve LR	-ve LR	p*
PRV left	0.675 (0.509-0.814)	0.550 (0.385-0.707)	0.579	0.00074	1.500 (1.014-2.297)	0.591 (0.343-0.983)	0.222
PRV right	0.775 (0.615-0.892)	0.500 (0.338-0.662)	0.610	0.00105	1.550 (1.108-2.266)	0.450 (0.231-0.838)	0.090
PRV flexion	0.850 (0.702-0.943)	0.300 (0.166-0.485)	0.568	0.00106	1.214 (0.956-1.591)	0.500 (0.210-1.154)	0.294
PRV extension	0.825 (0.672-0.927)	0.450 (0.293-0.615)	0.623	0.00180	1.500 (1.113-2.118)	0.389 (0.182-0.794)	0.059
Combined (CPRV)Ч	0.775 (0.615-0.892)	0.550 (0.385-0.707)	0.672	0.00865	1.722 (1.203-2.593)	0.409 (0.213-0.749)	0.008

*Mann-Whitney, 2-sided p

ЧCPRV = PRV left + PRV right + PRV flexion + PRV extension

Ø Median CPRV values: patients =0.011, controls =0.008 (p = 0.008 Mann-Whitney)

Table 9-1 Discrimination between patients and controls by proportional range variance (PRV): Sensitivity, specificity and likelihood ratios of PRV for each direction and combined (CPRV), and statistical significance between groups

9.9   Discussion

Many excellent studies have addressed *In vivo* spinal kinematic analysis using advanced imaging technologies. Devices such as bi-planar fluoroscopy (Li et al. 2009; Yao et al. 2012) and upright, kinetic MRI (Kulig et al. 2007; Alyas et al. 2008; Miyazaki et al. 2008) have been used to provide 3D information about the relationships between intervertebral range of motion and structural changes. Such 3-D systems have the added advantage of being able to measure axial rotation, as well as rotations and translation in other planes (Li et al. 2009) but these are mainly research systems, not easily translated into practice, and results are usually reported as 2-D end-of-range measures. By contrast QF has received US Food and Drug Administration clearance for roles that are traditionally filled by flexion-extension radiographs. They require only motion tables to run with existing hospital C-arm fluoroscopy units to output quantifiable rotation, translation, ICR and attainment rates in two planes and in both active and passive motion. Additionally, the calculated radiation dose is less than standard lumbar spine radiographs (UNSCEAR 2010) which makes it suitable for clinical use.

This study updated the inter and intra observer repeatability of maximum intervertebral rotation range (Breen et al. 2006) resulting from improvements in the QF technology and demonstrated a significant difference in maximum rotation between controls and patients for one level and direction only. Additionally, the study used a new measure of combined continuous proportional motion (PRV/CPRV) to compare patients and controls and to determine sensitivity and specificity for mechanical low back pain. The results suggest that combined variances of proportional patterns in patients were not as regular or evenly proportioned as those in controls, suggesting an association between CPRV and CNSLBP and supporting the conclusions of previous studies (Abbott et al. 2006; Teyhen et al. 2007b). The fact that little difference was found in respect of raw values (see appendices Table 13-16 257) despite standardisation of table range, reflects the variable contributions by the segments from L2-5. In this study, L2-5 absorbed an average of between 35-81% of the 40° passive table rotation, a source of extraneous variability that was avoided by calculating proportional motion as recommended by a previous International Forum (Breen et al. 2012).

Using PRV in continuous sequences and combining them to obtain a summary variable (CPRV) is a new concept that focuses on fluctuations in motion patterns within and between levels (Figure 9-3 p167). This addresses subgrouping in terms of movement dysfunction and may reflect patho-anatomical changes in passive components such as discs and ligaments. Such changes may include scarring, dehydration, glycation, calcification, fissuring and annular tears (Karayannis et al. 2012). However, back pain

is unlikely to exist to the exclusion of other biological factors, such as chemical pain stimuli, central sensitisation and abnormal muscle recruitment patterns during active motion.

No significant associations were found between CPRV and the patient characteristics: age, gender, BMI, disability and pain, which is consistent with Abbott et al, however, this study examined a primary care population with low levels of pain and disability.

9.9.1 Limitations and recommendations for future work

The sensitivity and specificity of the combined proportional range values (CPRV) and its area under the curve (AUC) supports the existence of a subgroup based on biomechanics, but it is not intended to constitute a diagnostic test. Additionally, proportional ranges cannot be used to determine hypo or hyper mobility because they cannot be related back to rotational values.

Finally, our study only analysed patients at the lower end of the pain severity scale. Studies of more disabled patients, such as those with spondylolisthesis, spinal stenosis, instability or electing for, or having had spinal surgery, may show greater differences. Additionally only rotation was examined, however, the inclusion of other kinematic parameters such as translation, instantaneous axis of rotation and attainment rate may also improve discrimination and are suggested for further research in this area. Recording during weight bearing motion would help to give a more complete picture of the relationship between intervertebral movement and persistent back pain if the added complexity of loading and muscle contraction can be controlled for.

9.10 Conclusion

The variation in proportional motion between lumbar vertebrae during passive, recumbent motion was greater in patients with CNSLPB than in matched healthy controls, indicating that biomechanical factors play a part. Additional studies with this method should be useful for improving our understanding of the pathophysiology of non-specific low back pain and the relationship of this to treatment outcomes. These would include replication of the present findings in other participant groups, the incorporation of additional kinematic parameters, studies of patient subgroups (e.g. instability, post-surgical disability etc.) and the possible prediction of future back pain disability, including risk of chronicity and poor outcome.

9.11 Contribution to new knowledge[28]

The reader has been introduced to proportional continuous motion and the measurement of variance in a proposed kinematic parameter based on the fluctuations of the proportional motion per direction. When combined, this variable demonstrated highly significant differences between groups This chapter also addressed the objective of analysing the relationship between pain and disability in patients and motion (see Objectives p11) and achieved the secondary aim of establishing any relationship between pain and disability for patients and kinematic parameters generated by passive recumbent QF, finding none (see Secondary aims p10).

Overall the primary hypothesis is accepted (see Hypothesis p10) and for the first time there is evidence that there is a measurable mechanical disruption in clinically diagnosed mechanical CNSLBP. However, the diagnostic accuracy of CPRV is not high enough for QF to be used independently as a 'rule in/rule out' test. Additionally there are no correlations between patient characteristics of pain and disability and CPRV, therefore the secondary hypotheses are both rejected.

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[28] Contribution to new knowledge was not published but is included here for completeness

Chapter 10   The radiation dose received from lumbar spine quantitative fluoroscopy compared to lumbar spine radiographs with suggestions for dose reduction, and diagnostic reference levels (DRL's)

10.1 Chapter overview

This is an original research paper accepted for publication in the peer reviewed journal Radiography (Mellor et al. 2014a) and co- authored by two supervisors[29] (see Figure 13-17 p304). The introduction, rationale, hypothesis and contribution to new knowledge were not included in the research paper[30]. There is also additional information on diagnostic reference levels (DRLs) that are not yet published (Seeram and Brennan 2006; Department of Health 2007). Finally, the research paper was submitted prior to full recruitment, hence the information presented for some of this chapter is from a smaller sample size of n=74. For calculation of DRLs the full sample (n=80) was included.

This chapter achieves the fourth stated objective that was to determine the mean radiation dose for passive recumbent QF with comparisons to published and local data for lumbar spine radiographs. It also determine the upper 1/3 quartile Dose Area Product (DAP Gy.cm^2) for use as a local diagnostic reference levels (DRL's), which are currently unpublished (see Objectives p11),

10.2 Introduction[31]

The calculation of risk from radiation is dependent upon a number of radiographic factors including filtration, voltage, amps, field of view and the distance between the x-ray source and the body (source object distance). The radio-sensitivity of various organs also needs to be considered. Radiation dose is most commonly measured as entrance skin dose (ESD) or absorbed dose (AD) and converted to effective dose (ED), which is an estimated measure of risk. The SI unit for entrance skin dose and absorbed dose is Gray (Gy) and the SI unit for effective dose is Sieverts (Sv). For diagnostic

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[29] Professor Alan Breen and Professor Peter Thomas.
[30] Those sections not published are marked with a footnote.
[31] Introduction to the chapter was not published.

examinations it is more common to quote dose as cGY.cm^2 as this is a direct output of a dose area product (DAP) metre.

Effective dose (ED) is important from a radiation safety perspective (Simpson et al. 2008) because it incorporates different organ radio-sensitivities and the type of ionising radiation (alpha, beta, gamma or x), thus the effective dose is a suitable way of comparing risks from ionising radiation exams. However, it requires complicated mathematical modelling and Monte Carlo simulation software (PCXMC), thus it is often the absorbed dose, which is instantly measurable at the time of making an exposure that is used in diagnostic reference levels.

Deleterious effects from ionising radiation include deterministic and stochastic effects, which are explained below.

- Deterministic effects have a linear relationship between severity and radiation dose, and there is a threshold below which these effects are not seen (Table 10-1 p178). These include ailments such as skin erythema, cataracts and infertility and are rarely seen in diagnostic radiographic examinations.
- Stochastic effects are independent of dose and there is no known threshold, although the probability increases as the dose increases. Such effects include cancers and genetic effects.

	Effect	One single exposure (Sv)	Prolonged exposure (Sv-year)
Testis	Permanent infertility	3.5 to 6.0	2
Ovary	Permanent infertility	2.5 to 6.0	> 0.2
Lens of eye	Milky lens	0.5 to 2.0	> 0.1
	Cataract	5.0	>0.15
Bone marrow	Blood forming deficiency	0.5	>0.4

Table 10-1 Threshold for deterministic effects (ICRP. 1991)

Although stochastic effects have never been observed in animal or human studies in doses less than 100mSv (Tubiana 2006; Tubiana et al. 2009), the potential exists for just one x ray photon to damage a strand of DNA in its path and set off oncogenesis (Wall et al. 2006). Thus, the risks of a lifetime cancer from medical radiation examinations are banded according to the effective dose. Table 10-2 p179 replicates information currently available in UK diagnostic imaging departments regarding dose

and cancer risks for certain procedures (HPA. 2008) along with the estimated doses for the same procedures (Mettler 2008).

More recently, research suggests that the risk of developing cancer or tissue damage after exposure to ionising radiation varies among people because of genetic and lifestyle factors (Advisory Group on Ionising Radiation 2013) but there is still some way to go before personalised risks can be calculated. Therefore the UK adheres to the Linear No Threshold (LNT) model in its approach to medical ionising radiation exposure where any exposure must conform to the principle of ALARA (As Low as Reasonably Achievable).

X ray examination	Equivalent period of background radiation	Estimated effective dose (mSv) (Mettler 2008)	Lifetime additional risk of cancer per examination*
Chest Teeth Hands/Feet	A few days	0.1 0.01 0.005	Negligible risk Less than 1 in 1,000,000
Skull Neck	A few weeks	0.2 0.2	Minimal risk 1 in 1,000,000 to 1 in 100,000
Mammography Hip Spine Abdomen Pelvis CT scan head	A few months to a year	0.4 0.6 1.5 0.6 0.7 2.0	Very low risk 1 in 1,000,000 to 1 in 10,000
Barium enema CT scan of chest CT scan of abdomen	A few years	7.0 7.0 10.0	Low risk 1 in 10,000 to 1 in 1,000

Table 10-2 Risks of cancer from some common x-ray examinations

* In addition to the1/3 lifetime risk of cancer

The LNT model is not adopted worldwide and there is evidence to suggest that a small amount of radiation may have a protective effect. There is a 'healthy worker' effect in studies of those who are exposed to low levels of occupational radiation (Muirhead 2009), and an adaptive response has been proposed, called hormesis (Kaiser 2003; Gori 2011). With supporting evidence from radiobiological and epidemiological studies, some now claim that the LNT model over-estimates risk (Harbron 2012) although

others claim that it is still a suitable model that provides a sufficiently robust risk estimate for justification purposes in medical imaging (Wall et al. 2006).

10.3 Rationale for study[32]

When comparing imaging methods, it is prudent to include an examination of the radiation dose and an estimation of risks against the benefit of the increased diagnostic accuracy. This thesis has shown that QF is better than functional radiography for both reproducibility and detecting mechanical problems in the spine. However, no research has directly compared to radiation doses from other QF studies, nor compared QF with functional radiography. Additionally there are no existing DRL's for QF.

An aim of this thesis was to examine radiation dose for QF and establish diagnostic reference levels (DRLs) (see Aim p10). The stated objective was to determine the mean radiation dose with comparisons to published and local data for lumbar spine radiographs (see Objectives p11). This thesis therefore sought to determine the doses from passive QF and compare this to existing data for standard and functional radiographs of the lumbar spine.

10.4 Diagnostic reference levels[33]

In addition to the ALARA principle and the LNT model, the UK implements DRLs for common radiographic examinations based on the upper 3rd quartile of the national average dose (Seeram and Brennan 2006). These are calculated from national data and the most recent UK survey, in 2010, included 29 NHS English hospitals (Hart et al. 2010). If doses consistently exceed the DRL then an investigation into equipment and practice is triggered and departments are encouraged to develop local DRLs if they undertake non-standard examinations, or their equipment is non-standard (for instance using an ultra-low dose CT algorithm) (Compagnone et al. 2005; Department of Health 2007; Matthews and Brennan 2009)

10.5 Hypothesis[34]

The primary hypothesis is that the radiation dose for QF will be the same order of magnitude as standard (AP and lateral) and functional (flexion extension) radiographs of the lumbar spine. Both absorbed dose and effective dose will be compared.

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[32] Rationale for study was not published; it is included here for completeness.
[33] Diagnostic reference levels were not published
[34] The hypothesis was not published

10.6 Abstract

10.6.1   Purpose

Quantitative fluoroscopy is an emerging technology for assessing continuous intervertebral motion in the lumbar spine, but information on radiation dose is not yet available. The purposes of this study were to compare the radiation dose from quantitative fluoroscopy of the lumbar spine with lumbar spine radiographs, and identify opportunities for dose reduction in quantitative fluoroscopy.

10.6.2   Methods

Internationally reported dose area product (DAP) and effective dose data for lumbar spine radiographs were compared with the same for quantitative fluoroscopy and with data from a local hospital for functional radiographs (weight bearing AP, lateral, and/or flexion and extension) (n=27). The effects of procedure time, age, weight, height and body mass index on the fluoroscopy dose were determined by multiple linear regression using SPSS v19 software (IBM Corp., Armonck, NY, USA).

10.6.3   Results and conclusion

The effective dose (and therefore the estimated risk) for quantitative fluoroscopy is 0.561mSv, and this is lower than most published data for lumbar spine radiography.

The dose area product (DAP) for sagittal (flexion+extension) quantitative fluoroscopy is 3.94 $Gy.cm^2$, which is lower than local data for two view (flexion and extension) functional radiographs (4.25 $Gy.cm^2$), and combined coronal and sagittal dose from quantitative fluoroscopy (6.13 $Gy.cm^2$) is lower than for four view functional radiography (7.34 $Gy.cm^2$).

Conversely DAP for coronal and sagittal quantitative fluoroscopy combined (6.13 $Gy.cm^2$) is higher than that published for both lumbar AP or lateral radiographs, with the exception of Nordic countries combined data.

Weight, procedure time and age were independently positively associated with total dose, and height (after adjusting for weight) was negatively associated, thus as height increased, the DAP decreased.

10.6.4   Keywords

Flexion-extension, spine kinematics, low back pain, intervertebral, continuous motion, movement disorders.

10.7 Literature review

Quantitative fluoroscopy (QF) of the lumbar spine allows intervertebral motion to be measured from fluoroscopic sequences where trunk motion is standardised for velocity and range. Sequences can be recorded using passive recumbent (i.e. no muscle or motor control) or active weight-bearing protocols in both the coronal and sagittal planes. Automated frame-to-frame image registration relies upon good digital image quality and provides continuous intervertebral rotational and translational data, giving more information about the function of the spine than AP, lateral, or flexion-extension (functional) radiographs (Mellor et al. 2009; Breen et al. 2012)

Functional radiographs have long been used for measuring spinal movement and for diagnosing instability (Leone et al. 2009). However, such measurements are unreliable due to errors from positioning, distortion and magnification, with mean test-retest errors of up to 4.9^o (Mayer et al. 1995). By contrast, QF is reported to be accurate to 0.32^o for coronal, and 0.52^o for sagittal plane intervertebral rotation (Breen et al. 2006) with inter observer errors below 1.5^o for rotation and 1.5mm for translation (Cholewicki et al. 1991; Lee et al. 2002; Auerbach et al. 2007; Ahmadi et al. 2009)

QF technology is mainly limited to research, although a new system for clinical use has recently gained 510(K) clearance from the United States Food and Drug Administration (KineGraph VMA, Ortho-Kinematics, Austin, Texas, USA (Ortho-Kinematics 2014)). However, few authors have published radiation dose data and none have compared these to published data from radiographic images. The present study sought to provide this, with suggestions for further optimising radiation doses by analysis of the characteristics that contribute to dose.

The aim was to determine if quantitative fluoroscopic investigation of the lumbar spine imparts a similar dose-area product (DAP) and effective dose (ED) to lumbar spine radiographs .To determine this, published data for AP and lateral radiographs were interrogated. Because no published data exists for functional radiographs, local hospital data were used to represent this dose for comparison. A secondary aim was to determine which factors may contribute to a reduction of the dose from quantitative fluoroscopy.

10.8 Methods and Materials

This was a retrospective study comparing the radiation dose from an on-going QF study with AP and lateral lumbar spine radiographs, functional radiographs, and other QF studies. The comparisons were Dose Area Product (DAP) measured in Gray

multiplied by area (Gy*cm2) and the estimated effective dose (ED) measured in miliSievert (mSv).

10.8.1   Published dose data

National and international surveys (Gron et al. 2000; Hart 2005; Hart et al. 2010; UNSCEAR 2010; US Food and Drug Administration 2010), and peer reviewed scientific literature reporting radiation doses of lumbar spine radiographs and quantitative fluoroscopy/cineradiography/video-fluoroscopy were examined (Almen et al. 2000; Lee et al. 2002; Breen et al. 2006; Mettler et al. 2008; Simpson et al. 2008). Literature was excluded if only entrance skin doses (ESD's) were reported leaving six references reporting DAP values and eight reporting   effective dose. DAP and ED were extracted and compared to the dose from QF in this study.

10.8.2   Quantitative fluoroscopy

Ethical approval was obtained from the UK National Research Ethics Committee Southampton A (09/H0502/99). Recruitment of all participants and their written informed consent were carried out by the principal researcher prior to screening. QF was undertaken in the recumbent coronal and sagittal planes, in a cross-sectional mixed gender study (n=74) of *in vivo* lumbar spine biomechanics, and movement was controlled by a specially designed motorised motion table (Figure 1-2 p6). Data collection was undertaken by the principal researcher using a portable digital C-arm fluoroscope with a 30cm Image Intensifier (Siemens Avantic, Germany), and a pulse rate of fifteen frames per second was selected to minimise movement blurring.

DAP, procedure time, age, gender, height and weight of the participants was obtained. DAP was then converted to ED using PCXMC v2 software(stuk.fi) and 2007 ICRP 103 tissue weighting factors (ICRP 2007). For QF, The mean kVp was 67 for coronal and 79 for sagittal plane, and the mean focus skin distances (FSD) were 75cm and 60cm respectively.

10.8.3   Hospital radiographs

A local hospital database of referrals by spinal surgeons for functional radiographs was inspected. The search covered the previous 12-month period and the cumulative DAP was recorded for patients who had a four series examination (weight-bearing AP, lateral, flexion and extension) or a two series examination (weight-bearing flexion and extension). The collection of retrospective hospital dose data did not require ethical review; however, hospital and radiology department R&D approvals were gained.

No identifying details were recorded and patients who had images that were repeated were excluded, as were those who only had supine AP and lateral lumbar radiographs. Examinations were undertaken by different practitioners using the same room equipped with a GE Medical Systems DEFINIUM 8000 System. ED was estimated using generalised conversion coefficients from the NRPB-R262 report (Hart et al. 1994).

10.8.4 Statistical Analysis

For QF, the relationships between DAP (outcome variable) and procedure time, age, gender, height, weight and body mass index (BMI) (predictor variables) were examined. A 2-sided 5% significance level was used. Initially, a least squares linear regression (IBM SPSS Statistics Version 19) of total dose was conducted to calculate unadjusted regression and correlation coefficients. Next, a multiple linear regression model including only height, weight and BMI determined whether all 3 variables independently predicted dose. Large changes in the standard errors of the regression coefficients from values seen in the unadjusted analyses were used to identify collinearity.

A variety of different models containing different combinations of these three predictor variables were also run, using adjusted R-squared values to help choose the best. From this, the best anthropometric variables were chosen and included with all the other remaining predictor variables in a single regression model. Variables that were not statistically significant were dropped from the analysis in order to obtain a parsimonious model. Adjusted regression (95% CI) and partial correlation coefficients of all statistically significant variables in the resultant model are presented.

10.9 Results

10.9.1 Demographics

Table 10-3 p185 summarises the participant demographics for QF (n=74) and functional radiographic studies (n=27).

10.9.2 QF and lumbar spine radiation doses

Data from the functional radiographs were separated into 2 view (n = 12) and 4-view series (n = 15). The mean kVp, DAP and effective doses, along with the same from QF, are summarised in Table 10-4 p186. The mean age of patients undergoing functional radiography (63 years) was much higher than the participants in this study (37years). The age of the functional radiographic sample is indicative of the population

in the local area, whereas the QF study participants were limited to an age range of 20-51 years.

	QF this study N = 74	Local hospital N = 27
Gender (%)	Male = 42 (57%) Female =32 (43%)	Male =11 (41%) Female = 16 (59%)
Age years. Mean (SD)	36.9 (8.49)	63.2 (17.2)
Weight Kg. Mean (SD)	74.97 (12.73)	-
Height m. Mean (SD)	1.716 (0.127)	-
BMI Mean (SD)	24.77 (2.57)	-

Table 10-3 Demographics of participants imaged with QF versus local hospital data of weight-bearing lumbar radiographs (2 or 4 series) for instability

10.9.3   Dose Area Product (DAP)

Figure 10-1 p187shows the internationally published DAPs for lumbar spine radiographs compared to two series functional radiography, one previous QF lumbar spine study, and the mean DAP for coronal and sagittal QF in this study.

DAP data for separate coronal or sagittal QF studies (2.19 $Gy.cm^2$ (SD 0.78) 3.94$Gy.cm^2$ (SD 0.86) respectively) were higher than UK dose reference levels AP (1.6$Gy.cm^2$) and lateral (3$Gy.cm^2$) lumbar radiographs, whereas sagittal QF was lower than local data for functional radiographs two view series (4.25 $Gy.cm^2$) and lower than data reported from Sweden (6.5 $Gy.cm^2$).

When combined coronal and sagittal, (see Figure 10-2 p188), DAP for QF (6.13 $Gy.cm^2$) were smaller than combined Nordic countries (9.15 $Gy.cm^2$) and the Nordic guidance level (10 $Gy.cm^2$). Conversely DAP for QF was higher than individual Nordic countries data; however, data for the latter were reported 10 years later than the combined data, which may reflect updates in practice and equipment. Combined QF is lower than four view functional radiography (7.34 $Gy.cm^2$), which is the examination it is compared to in the USA (Ortho-Kinematics 2014).

	Coronal QF (n=74)	Sagittal QF (n=74)	Total QF (n=74)	Radiographic views 4 series (weight-bearing AP, lateral, flexion and extension) (n = 15)	Radiographic views 2 series (weight-bearing flexion and extension) (n = 12)
kVp Mean(SD)	66.99 (4.25)	79.09 (8.95)	73.04 (9.26)	90	90
DAP Gy.cm^2 Mean (SD)	2.19 (.78)	3.94 (.86)	6.13 (1.5)	7.34 (4.4)	4.25(1.98)
ED mSv Mean (SD)	0.321 (0.115)	0.24 (0.529)	0.561 (0.154)	-	2.2 (2.1)
Procedure time (seconds). Mean (SD)	36.08 (3.52)	39.27 (4.55)	75.35 (6.11)	-	-

Table 10-4 DAP and effective (ED) radiation dose data for QF recumbent sagittal and coronal plane sequences and weight bearing AP, lateral, flexion and extension radiographs from a local hospital database
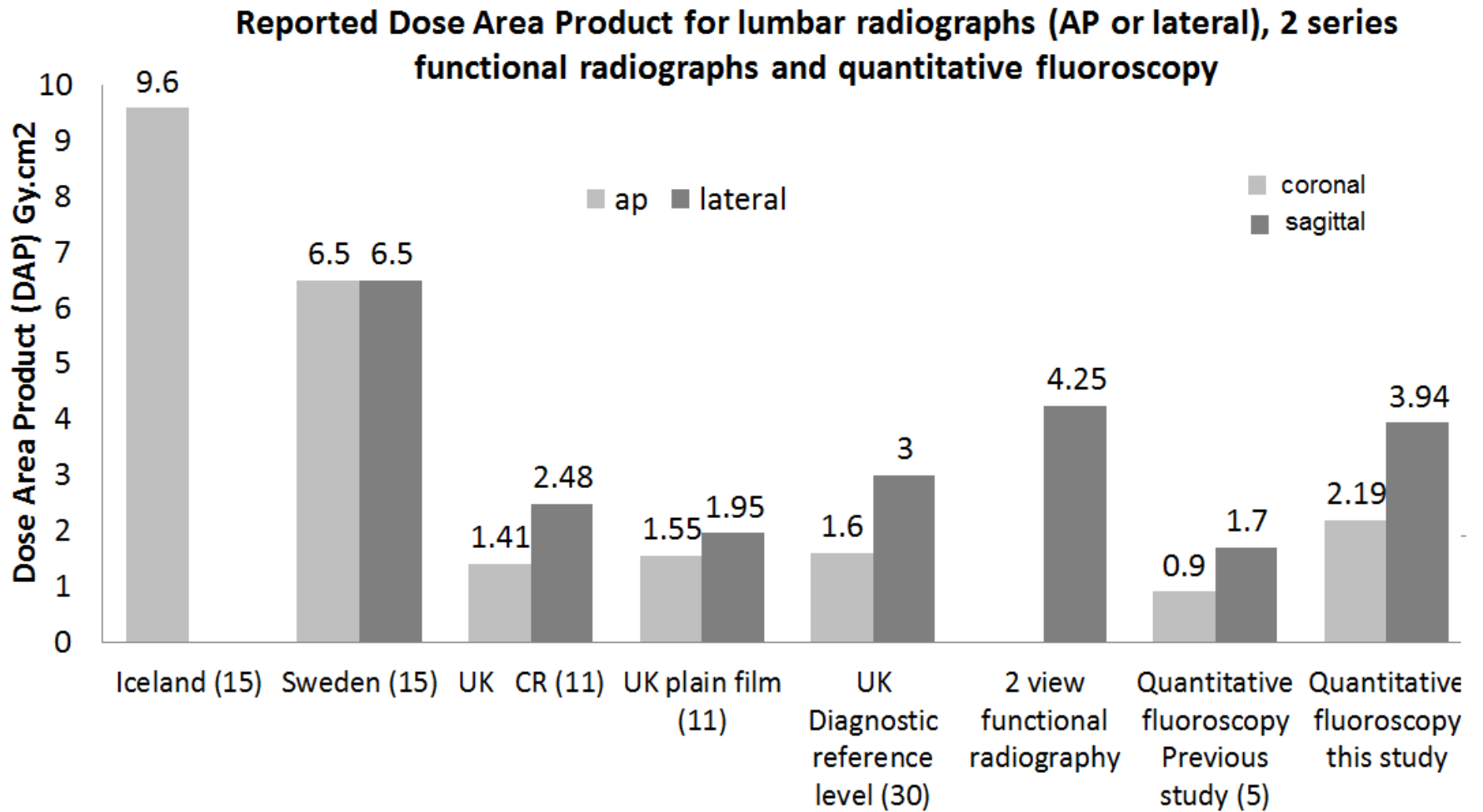
Figure 10-1 The reported DAP of AP and lateral lumbar spine radiographs compared to quantitative fluoroscopy and local data for 2 view (flexion and extension) functional radiographs.
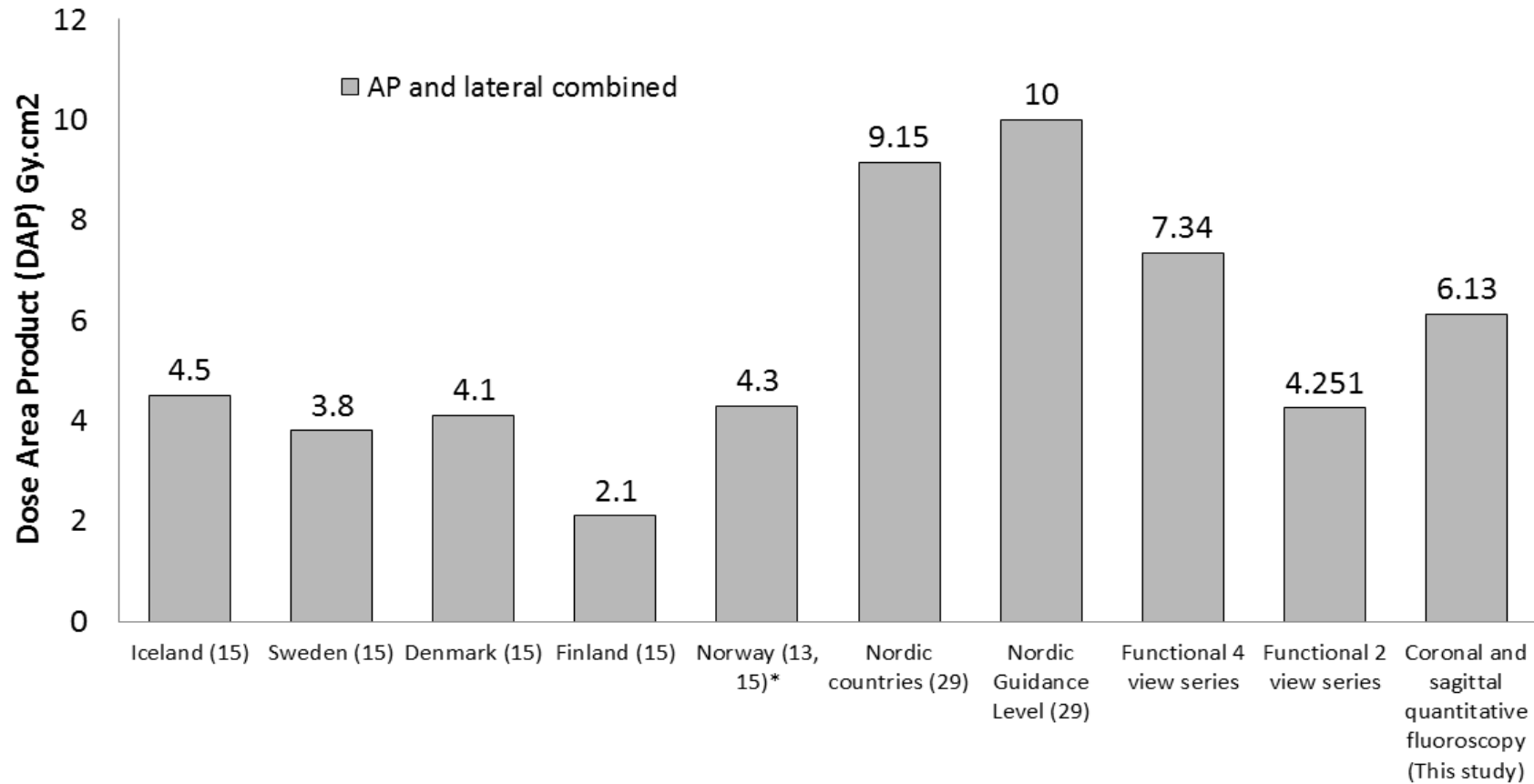
Figure 10-2 The reported DAP of combined lumbar spine radiographs (AP + lateral) compared to quantitative fluoroscopy and local data for functional radiographs.

*Data for Norway has been reported as 4.2 Gy.cm^2 and 4.4 Gy.cm^2 in two separate references. The average of 4.3 Gy.cm^2 is shown here
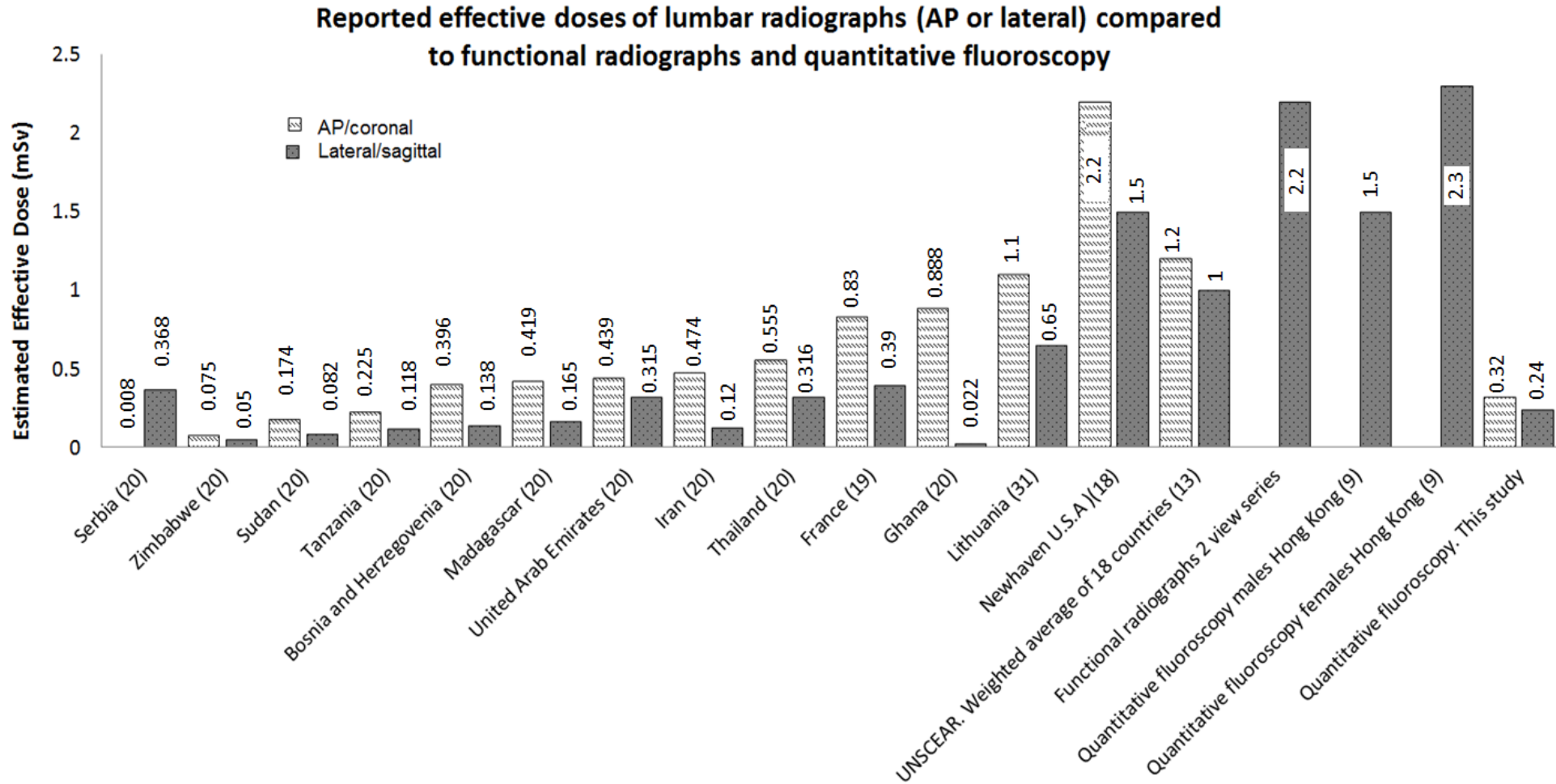
Figure 10-3 Reported effective dose for lumbar spine radiographs (AP or lateral) compared to quantitative fluoroscopy

.
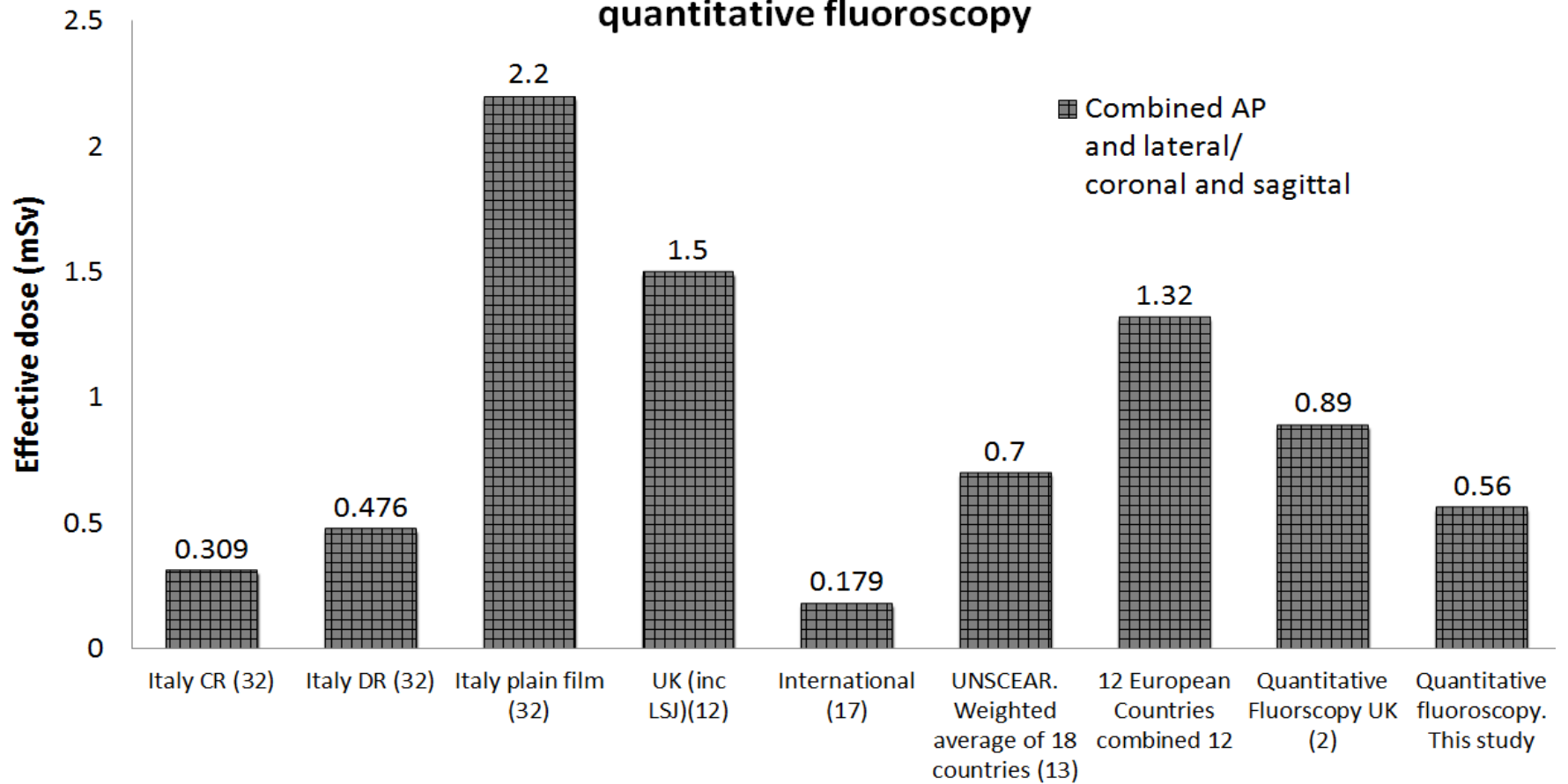
Figure 10-4 The effective dose of combined lumbar spine radiographic series compared to quantitative fluoroscopy and local data for functional radiographs.

10.9.4   Comparison of Effective Dose (ED)

Figure 10-3 p189 shows that the effective doses for QF coronal (0.32mSv) or sagittal (0.24mSv) were less than the estimated ED for 2 view functional radiographs (2.2mSv) and the weighted average for AP and lateral lumbar spine radiographs across 18 countries (1.2mSv and 1mSv respectively) (UNSCEAR 2010). In comparison with individual countries, ED for coronal QF was less than that reported for AP lumbar spine radiographs in 9/12 regions, and for sagittal QF the ED was less in 5/12 regions.

ED data for lumbar radiographs (see Figure 10-3 p189 and Figure 10-4 p190) comes from international sources where there is greater variation in the number of radiographs that make up the series. Additionally these studies did not quote their conversion coefficients, which may have influenced the resultant estimation; hence a margin of error is expected when interpreting these comparisons. One previous QF study undertaken in Hong Kong (Lee et al. 2002) reported an ED of 1.5mSv for males and 2.3mSv for females. No other exposure factors were reported but these estimates are between 1-2mSv higher than the EDs in this study.

 Page 190 shows the reported EDs for AP and lateral radiographs combined, a previous report from QF in 2011 (Breen et al. 2006), and QF in this study. The EDs from this study are lower than the QF data reported in 2011 where the imaging technique was similar but the sample size was smaller. When combined the ED for QF is again lower than the averages of 18 countries (UNSCEAR 2010).

10.9.5   Relationship of patient characteristics to QF dose

Inspection of the histogram and the result from the Kolmogorov-Smirnov test (p=0.30) suggested that it was reasonable to assume that total dose was normally distributed. Unadjusted regression and correlation coefficients relating potential predictors to DAP are shown in Table 10-5 (p192). All variables were significantly associated with total dose. The regression model of total dose against height, weight and BMI displayed substantial collinearity so not all could be included. A model containing weight and height together had a larger adjusted R squared (69%) than BMI alone (56%), and slightly larger adjusted R squared than BMI and height together (67%) and BMI and weight together (68%). Thus BMI was dropped from subsequent models. The effect of gender on total dose appears to be explained by height and weight differences. The remaining statistically significant variables are shown in Table 3. Increased average total dose was associated with greater age, longer procedure time, increased weight and smaller height (after weight is taken into account). The partial correlation coefficients suggest that, of the predictors of total dose, the association is greatest for weight. The adjusted R squared for this final model was 82%.

Predictor	Unadjusted regression coefficient (95% CI) p-value	Correlation	Adjusted regression coefficient for parsimonious model (95% CI) p-value	Partial correlation
Age (years)	6.03 (2.14, 9.92) P=0.003	0.34	3.64 (1.79, 5.49) p<0.001	0.43
Procedure time (mins)	9.30 (3.98, 14.62) p<0.001	0.38	8.47 (5.96, 10.97) p<0.001	0.63
Weight (kgs)	9.56 (7.90, 11.22) p<0.001	0.80	11.83 (9.77, 13.90) p<0.001	0.81
BMI (Kgs/m2)	43.62 (34.67, 52.57) p<0.001	0.75	A	
Height (m)	829.46 (508.06, 1150.87) p<0.001	0.52	-543.24 (-814.5, -271.97) p<0.001	-0.43
Sex (M relative to F)	149.15 (87.98, 210.32) p<0.001	NA	B	

Table 10-5 Linear regression analyses of total absorbed dose on potential predictor

Regression coefficients represent mean change in total dose ($cGy.cm^2$) per unit increase in predictor

NA – sex is a nominal variable so Pearson's correlation not presented

A – BMI excluded because of collinearity with weight and height

B – Effect of sex explained by height, weight and other variables when added to the model (p=0.87)

10.10   Discussion

There is large variation in methods and reporting of dosage data in existing literature, which is reflected in the conflicting results presented here. However, we can confidently say that the mean effective dose for QF in this study was less than one mSv. When undertaking research involving ionising radiation the risk to the individual versus

societal benefit must be considered. A dose of less than one mSv places this research in the International Commission for Radiological Protections (ICRP) category of 'IIa Intermediate', which means the risk to the individual is minor and the benefit to society is intermediate to moderate (ICRP 1991). Alternatively stated, the risk of inducing cancer from 1mSv is 1:20 000 (HPA. 2008) is in addition to the lifetime risk of 1:3 (Sasieni et al. 2011). The mean background radiation dose received annually in the UK is 2.7mSv (Hart et al. 2010). Thus the mean effective dose of 0.561mSv from QF is equivalent to approximately 11 weeks' background radiation.

When considering risks to health from radiation, epidemiological evidence currently states that there is insufficient statistical power to detect excess carcinomas for doses below 100mSv (Tubiana et al. 2009), although a more recent editorial summarised the evidence on the health effects of low level radiation (Zeeb 2012) and agreed that it remains prudent to stay within the linear no threshold (LNT) model and adhere to the ALARA principle because it is possible for a single radiation track to cause significant DNA changes (Harbron 2012).

Considering dose reduction strategies for QF, patient weight appears to be the strongest predictor, followed by procedure time. It is interesting to note the statistically significant correlation between age and dose that cannot be explained by other factors in the model. The negative association between height and total dose after adjusting for weight can be explained by the fixed field of radiation exposure during the procedure. That is, people of the same weight but greater height will have less of their bodies within the field.

10.10.1   Implications for clinical practice

Quantitative fluoroscopy has advanced our understanding of the biomechanics of the spine and it can be used with any portable image intensifier, a motion platform, and bespoke tracking software. This technique is currently being adopted in some centres in the USA[23] and could be used to replace functional radiographs without adding to the medical radiation burden. However, QF has an examination time of 15 minutes for one plane of motion, which is longer than functional radiographs. Hence departments would need to consider the extra information gained in light of the increased examination time.

Quantitative fluoroscopy ensures that trunk movement is highly standardised to reduce inter and intra subject variation, hence all participants were bent to 40 degrees, rather than their maximum voluntary trunk bend. Adopting the standardisation of trunk movement in functional radiography would advance upon the current technique by reducing inter and intra subject variation. However, not bending to the maximum may

not stress intervertebral segments sufficiently to establish a diagnosis of radiological instability, thus if standardisation of trunk motion was to be adopted, revised normative values would also be required.

10.10.2   Limitations

Studies reporting effective dose did not give details of their standard radiographic series or conversion coefficients so these comparisons are provided as an overview. The ED for 2 series functional radiographs was estimated using generalised coefficients (Hart et al. 1994) because of the limited retrospective data available, but it is acknowledged that they are less accurate than those used for QF. Additionally the sample size for functional radiography is small and limited to one site; hence it is unlikely to be representative of the dose received from functional radiographs, it is presented here as an introduction and a suggestion that further research could examine radiation doses received from functional radiographs.

It is acknowledged that comparing QF (dynamic) with published AP and lateral (static) lumbar radiographs is not ideal, as the image quality and clinical indications differ. However, it is necessary to show that new and emerging medical technologies are at least equal to, if not superior to, existing examinations and thus the nearest proxy data for radiation dosage was used.

The effective doses for QF in this study were calculated using Monte Carlo simulation software (PCXMC) and used the latest tissue weighting factors (ICRP 2007) with an assumed constant field size of 30cmX30cm. In practice, collimation was used throughout ensuring the field size was smaller than this and thus the EDs reported here are likely to be overestimated.

10.10.3   Options for further dose reduction

QF reduces the intra and inter subject variation in lumbar spine kinematics, which allows for better comparisons of populations. Linear regression/correlation showed that QF procedure time had a significant correlation with DAP. Therefore, since range and velocity are controlled, increasing the velocity of the trunk motion should lead to a reduction in procedure time and thus a reduction in dose. However, this needs to be carefully balanced against motion blurring that would render the objective automated tracking templates ineffective.

Another way to reduce dose from QF would be to reduce the pulse rate. The method currently in use employs a rate of 15fps but the system in the USA employs a pulse rate of 8fps. If the motion output is equally accurate and reproducible with the pulse rate halved, then it could be safely reduced.

As patients' weight increases so too does the amount of scatter that degrades the image quality upon which the QF tracking algorithms depend. One way of reducing the collective dose to patients undergoing QF would be to impose a maximum weight limit. In some diagnostic centres maximum weight limits are already imposed for CT and MRI although this is mainly for logistical reasons. When undertaking QF, tracking algorithms are likely to fail if image quality is poor hence in larger participants there would be no benefit to those who exceed a certain weight limit. Further analysis would be needed to determine what that weight limit may be. In the present study a BMI limit of 30 was imposed due to the maximum output of the mobile C arm.

10.10.4 Diagnostic reference levels[35]

These were calculated from n=80 and are the 75th percentile. Because data from one site is available these are an introduction to the magnitude of dose one would expect for passive recumbent QF. At the host institute (AECC) doses for QF will be regularly reviewed in conjunction with the DRL's and these will be displayed close to the imaging equipment as a quick reference (see Table 10-6 p195.). If doses are consistently exceeding the DRL (more than 50%) an investigation be triggered, although it is expected that approximately 25% of examinations will exceed the DRL due to the nature of their derivation.

	Mean absorbed dose (SD) $Gy.cm^2$	Diagnostic reference level
Left	114.62 (48)	135.38
Right	101.24 (34.1)	117.98
Flexion	203.7 (41.1)	219.13
Extension	184.18 (57)	197.34

Table 10-6 Diagnostic reference levels for passive motion QF

The DRL is higher for right than left motion because left motion includes initial low dose images to ensure the participant is positioned with L3/4 centred over the table fulcrum. The same is also true for flexion versus extension.

10.11 Conclusion

Quantitative fluoroscopy of the lumbar spine has a similar radiation dose to AP, lateral and functional radiographs. Because QF can provide more reliable and comprehensive information about intervertebral motion, which improves the clinical decisions about the

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[35] Diagnostic reference levels were not published but are included here for completeness

functional integrity of the spine, this technique could be used as a replacement for functional radiographs without an increase in radiation dose.

However, QF requires careful standardisation of patient movement and bespoke tracking algorithms, which are essential for accuracy and reliability. Hence its wider adoption within clinical departments will require careful management. This technique has already been adopted in the U.S.A. and work is underway to improve its accessibility in the U.K.

Finally, caution is advised when referring to published studies comparing radiation dose because of the variation in methods used to both obtain the image, and calculate effective dose. It is therefore recommended that this paper should only be used to compare the order of magnitude of the radiation dose between QF and other lumbar spine radiography.

10.12 Contribution to new knowledge[36]

Absorbed and effective radiation dose data for passive recumbent QF are expressed and, for the first time, they have been demonstrated to be of the same magnitude as functional radiographs and standard radiographs. Additionally techniques for further reducing the radiation dose are suggested, and DRL's established for the passive motion QF examination.

Consequently the primary hypothesis (based on descriptive comparisons) that the radiation dose for QF will be the same order of magnitude as radiographs of the spine is accepted.

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[36] Contribution to new knowledge was not published but is included here for completeness

Chapter 11   General discussion

11.1   Chapter overview

The thesis detailed the method and analysis of passive recumbent QF and developed four kinematic parameters that were tested for differences between groups, and diagnostic accuracy. In addition reference limits were developed, and the radiation dose compared with standard and functional radiographs. A critical evaluation of the proposed kinematic parameters is advanced in the general discussion.

Individually, the kinematic parameters (mIVR, initial intervertebral attainment rate, cIVR and CPM) are discussed in their respective chapters but are discussed collectively to examine whether measurements from passive intervertebral motion aid our understanding of the relationship between spinal biomechanics and pain.

The overall hypotheses and aims (see Hypothesis p10 and Aim p10) were addressed, setting out what is now known about passive recumbent intervertebral motion in patients with CNSLBP and healthy volunteers. A discussion of the limitations of the methods used in this thesis is undertaken, ending with suggestions for further directions for research.

11.2   Introduction

The idea for this thesis came from subjective observations that continuous intervertebral motion can differ in those with CNSLBP compared to healthy volunteers. This guided the study towards investigating the primary care population because this represents 75% - 85% of sufferers for whom no patho-anatomical cause can currently be found (Deyo 2002a). However this figure is contentious and, as argued by Abrahim and Killackey-Jones, is based upon

> "flawed and inadequate data to support the assertions that most LBP cannot be diagnosed".(Abraham and Killackey-Jones 2002).

A call for further subgrouping of CNSLBP has been shared by others (Henschke et al. 2007) and practitioners use subgroups to inform treatment (Gombatto et al. 2013), but subgroups based on pathology, such as disc degeneration (Hughes et al. 2012) or vertebral endplate signal changes (VESC) on MRI (Weishaupt et al. 2001) have not proven responsive to distinguishing between patients and healthy volunteers with a high number of false positives (Boden et al. 1990). Additionally studies that have created sub groups within the CNSLBP population have not agreed on their definitions

(Abraham and Killackey-Jones 2002). For instance some practitioners label mechanical CNSLBP as made better or worse by movement or position (NHS 2010), whereas others would investigate further and sub classify patients with facet joint degeneration (Hasegawa et al. 2011; Li et al. 2011), spondylolisthesis (Niggemann et al. 2010) and disc degeneration (Hughes et al. 2012) based either on medical imaging (Fritz et al. 2005) or clinical signs and symptoms (Cook and Hegedus 2011) and use classifications such as instability (Alqarni et al. 2011). It has been theorised that different pathologies would manifest in altered movement such as altered facet joint biomechanics following fusion (Botolin et al. 2011), and this is the basis behind many clinical kinematic models for CNSLBP (Sahrmann 2002; O'Sullivan 2005; Karayannis et al. 2012) (see Models of chronic non-specific low back pain p16).

The link between pain and restricted motion is debateable with some authors finding a link (Lundberg and Gerdle 2000; Kulig et al. 2007) while others find the opposite is true (Stokes and Frymoyer 1987; Soini et al. 1991; Okawa et al. 1998) or no association (Adams 1995). Studies demonstrate that altered movement occurs when the intervertebral disc is damaged and this, along with ligaments and facet joints, is part of the passive subsystem. It has also been previously demonstrated *in vivo* that degenerate discs do not always lead to back pain (Takatalo et al. 2011), hence CNSLBP from the passive subsystem may be attributable to more than the disc.

Active weight-bearing studies using fluoroscopy have shown some differences in the movement patterns of normal controls and those with CNSLBP (Teyhen et al. 2007a; Teyhen et al. 2007b; Ahmadi et al. 2009) but it is impossible to segregate the action of muscular and motor control in these studies. This study found some subtle differences between patients and healthy volunteers with the kinematic parameters obtained from passive continuous intervertebral rotation, and although the differences between groups and diagnostic sensitivity were not outstanding. It is clearly shown that passive recumbent QF reduces variability (see Chapter 5 p79 and Figure 6-6 p123), which increases the confidence in the differences found. The four kinematic parameters developed in this thesis are collectively discussed in 'A review of the four kinematic parameters in this thesis' (p200).

This thesis sits within the biomechanical model, of which there has been a resurgence of interest. This could be due to increased computing power and advances in medical imaging allowing answers to previous biomechanical questions to be better explored, or it may be driven by the lack of strong determinants of who will experience first-time low back pain (Mannion et al. 1996) . The bio-psycho social model gained popularity in the 1990's as an alternative framework for predicting outcomes, but never addressed

the likely causes of back pain; merely the characteristics that are likely to lead to its chronicity (see Models of chronic non-specific low back pain p16). The increased interest in the biomechanical approach was noted by Karayannis et al who stated that that a biomechanical assessment predominated in most treatment approaches with limited consideration of the psycho-social aspects (Karayannis et al. 2012).

Previous research into spinal motion has been criticised for its variability, with standardisation called for; from posture (Breen et al. 2012), to acquisition and analyses (Pearcy et al. 1985; McGregor et al. 2002a), with a need for analyses to be automated to improve reliability (Vrtovec et al. 2009b). These issues were addressed in this thesis by reducing the influence of the active and motor control subsystems, standardising participant range and velocity, and using an automated measurement algorithm. Additionally the passive recumbent motion protocol reduces associated coupled motion in the coronal plane (see p27), which is evident by the high reproducibility of the tracking algorithms in this plane (see Chapter 5 p79). Reducing extraneous variables reveals that there are some differences in the biomechanics of those with CNSLBP compared to a healthy population, although there is no consistency across the kinematic parameters suggested in this thesis when examined individually.

The improved ability to measure continuous motion brings forth a new set of questions, most notably; which kinematic parameters are of use in determining whether there are mechanical differences, some of which may be subtle. Teyhen et al measured continuous intervertebral sagittal weight-bearing motion and divided the motion curve into sections, comparing the attainment rate of each division. They found that a combination of kinematic parameters, including mid-range attainment rate, demonstrated greater sensitivity and specificity between patients and healthy volunteers than when tested individually (Teyhen et al. 2007b) but their method is not easily transferrable to clinical practice.

Besides this thesis, there is little research into which continuous kinematic parameters are useful. Brownhill examined active intervertebral motion from recumbent MRI scans in a cohort of patients with mechanical low back pain and analysed the whole motion pattern using principle component analyses (PCA) (Brownhill 2010). It was found that those with a lesser history of non-specific LBP had higher amplitude and motion variability than those with more severe non-specific LBP, which supports the raw data and variability found in patients in this thesis. However, PCA is not easily transferable to clinical practice and both Teyhen et als and Brownhill's results include the influence of the motor and active control subsystems. Finally neither study has been replicated

and Teyhen et al pre-screened the patient group for aberrant movement, whereas Brownhill et al did not include a healthy volunteer group.

This study measured four kinematic parameters obtainable from continuous data and these demonstrated subtle mechanical differences between groups, although the differences were not consistent across each parameter. It would be useful to conduct further analyses to determine if combinations of variables are better at distinguishing between patients and healthy volunteers, and what these may be. From a clinical standpoint the understanding of the differences needs to be relevant to pain and informative of treatment. From a biomechanical viewpoint, Hasegawa et al noted that intervertebral properties of the spine cannot be determined by measuring stiffness alone. Measurements of multiple parameters, including the NZ, are necessary (Hasegewa et al. 2009). Thus a multiple regression analysis of kinematic parameters in this thesis may yield greater differences and diagnostic accuracy between groups. Such an analysis was beyond the scope of this thesis, but it is noted as a recommendation for further study.

11.3 A review of the four kinematic parameters in this thesis

Lehman (Lehman 2004) called measurements from continuous motion 'higher order kinematics' and called for further research into assessment techniques to understand these (see Continuous intervertebral motion p144). Passive recumbent QF addressed this challenge and may further help categorise patients with mechanical CNSLBP by discerning subtle differences. The challenge now is to determine which kinematic parameters are useful in guiding treatment options. An international forum on QF measurement of intervertebral motion recommended both cut off values for intervertebral hypo mobility, and the investigation of the initial intervertebral attainment rate (called laxity) (Breen et al. 2012) and both were explored in this thesis[37], along with further exploration of hyper mobility and continuous proportional motion. Segments, directions and overall motion have been examined by differences in mean values, diagnostic accuracy, and differences in proportions falling out with reference intervals.

A summary of all these results are in the appendices (see Table 13-34 p306, Table 13-35 p309, Table 13-36 p310 and Table 13-37 p311) and demonstrate that as a whole the differences between patients and healthy volunteers is quite small, suggesting that back pain is either not a major mechanical problem in the patients' passive subsystem,

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[37] Hypo mobility was investigated via lower reference limits for mIVR and cIVR

or the selected kinematic parameters, individually, are not responsive enough to detect differences. Overall, cIVR appears more responsive than mIVR in determining hypo mobility (see Table 13-36 p310) although the derivation of the reference limits needs consideration. A previous study of weight-bearing QF motion patterns by Wong et al declared continuous motion to be loosely linear (Wong et al. 2006)., however, the data in this study shows that the cIVR patterns are more complex and not linear, with more variability in patients than healthy volunteers (see Figure 8-1 p148).

In an attempt to address this variability, continuous proportional motion graphs were developed (see Chapter 9 p159) and the variation of the fluctuations measured to determine a new kinematic parameter (PRV and CPRV), which showed promising initial sensitivity and specificity per direction. Continuous proportional motion accounts for inter-dependency of adjacent segments and this is the first time this has been developed for continuous intervertebral motion data. For clinicians, knowing that segments are not sharing the motion equally throughout the bend, and being able to identify which segments are restricted in the bend and in which direction, would help to focus treatments based on mobilisation. Although PRV and CPRV further reduces variability it is not recommended that they are used alone in reporting abnormal biomechanics. This is because they cannot measure the beginning of the motion, where problems in the neutral zone may be identified. The limitations of CPRV as a diagnostic tool currently lie in its lack of explanatory power and further research is needed to improve this. One promising line of investigation would be into the association between CPRV and structural changes in the intervertebral disc. McNally and Mulholland demonstrated that high variations in *in vivo* disc stress predict pain on discography (McNally 1996) and Passias et al demonstrated altered motion in disco-genic pain (Passias et al. 2011). As these variations were caused by anisotropic discs it would be useful to see if motion pattern variation is related to the stage of disc degeneration.

The only segment to show differences between groups for two kinematic parameters was left L3/4 for both mIVR and attainment rate (see Table 13-34 p306). This is of particular interest because patients had higher mean mIVR values than healthy volunteers, but lower attainment rate values. The possible reason for the lower attainment rate values in patients (the opposite of what was expected) is discussed in Chapter 7 Discussion p136, but it could also be interpreted as attainment rate not being dependent upon mIVR. Hence laxity in the neutral zone may be detectable with passive recumbent QF without the need to maximally stress the segment, and further research into the effects of loading on measuring the neutral zone *in vivo* is required.

For diagnostic accuracy, no segment demonstrated high sensitivity and specificity (defined as greater than the lower confidence interval of 0.65 for sensitivity and 0.70 for specificity (see Sample size calculation p53) for each kinematic parameter, although as noted by Alqarni et al, clinical tests do not have both high sensitivity and specificity (Alqarni et al. 2011) tending towards higher specificity and lower sensitivity when considered alone. If the patient population had been pre-selected in this study (in a replication of the method used by Tehyen et al (Teyhen et al. 2007b), then a higher diagnostic accuracy would be expected. However, as noted by Rutjes et al, the danger of over-estimating diagnostic accuracy is higher when healthy controls are compared with more severe cases (Rutjes et al. 2006). Additionally it is also over-estimated if the reference standard is constructed in the event of no existing gold standard (Rutjes et al. 2007) as was the case in this thesis.

Understanding the diagnostic accuracy of kinematic parameters allows assessment of whether they are useful at 'ruling in' or 'ruling out' a mechanical issue. In this thesis the majority of the results returned higher specificity than sensitivity, demonstrating that the variable was more responsive to ruling out a mechanical issue (see Table 13-35 p309). For a test to be diagnostically useful it is preferable to have both high sensitivity and specificity. The blue highlighted segments in Table 13-35 p309 are those where both sensitivity and specificity are greater than 0.5 but there is no pattern to this across segments or kinematic parameters.

Brownhills findings of differences in amplitude and motion variability in patients' points to a further need to sub classify CNSLBP. Greater amplitude and variability could be a feature of early stage disc degeneration, and lesser amplitude and variability a sign of later stage degeneration (Kettler et al. 2011). Thus, including all mechanical CNSLBP based on clinical diagnoses (as is the case in this thesis) would include both those who are in the early and late stages of disc degeneration.

The majority of medical imaging for diagnosis of pathological and anatomical abnormalities in the spine relies predominantly upon subjective assessment and interpretation. The kinematic parameters presented here are one option for objectively quantifying intervertebral motion, but because cIVR and CPM were exploratory variables it is recommended that the reproducibility of these are assessed, perhaps by adapting the fitting of polynomials as described by Williams et al. in his assessment of global motion patterns (Williams et al. 2013). Additionally, undertaking the analyses of these kinematic parameters with a repeated measures design would yield intra subject variation, which is crucial for their interpretation. A repeated measures QF study of passive and recumbent motion is currently underway designed to create a normative

database of recumbent and weight-bearing guided intervertebral motion (Breen et al. 2013).

11.4 A healthy volunteer with radicular pain.

As stated in Study population p53, an exclusion criterion for patients was radicular pain. It was an oversight to not include this for healthy volunteers (whose exclusion criteria were based on whether they had activity limiting back pain over the previous 12 months) and it subsequently came to light that a healthy volunteer was later being treated at the AECC for leg pain, thought to be radicular in origin (with no reported mechanical LBP). This information was received prior to anonymising the participants' data thus it was possible to examine their results, of which, cIVR and CPM are presented in Figure 11-1 p204 and Figure 11-2 p205). This participant had higher variation than the average values across all healthy volunteers for left, right and flexion, which is interesting given that the cIVR motion graphs show extension L4/5 has the most abnormal motion pattern. When normalised, this irregularity is not as apparent because L4/5 shares the motion reasonably equally with the other segments. This demonstrates the adaptive nature of intervertebral motion, which may be more relevant to clinical practice rather than individual examination of segmental motion.
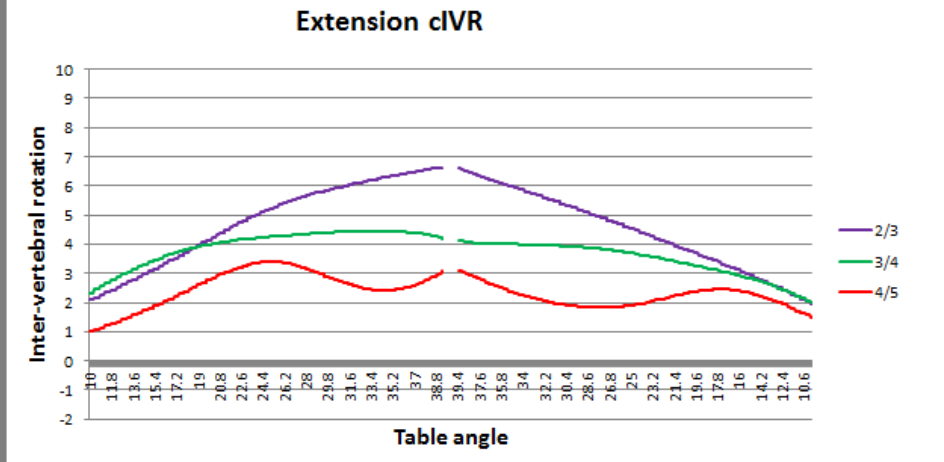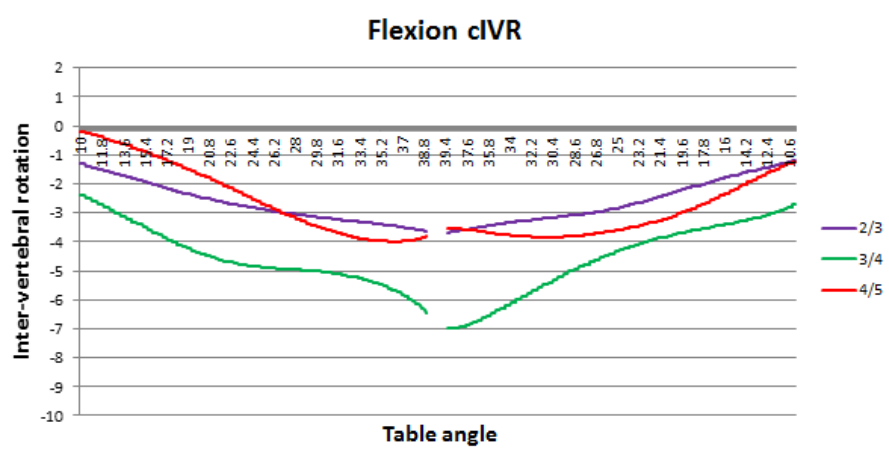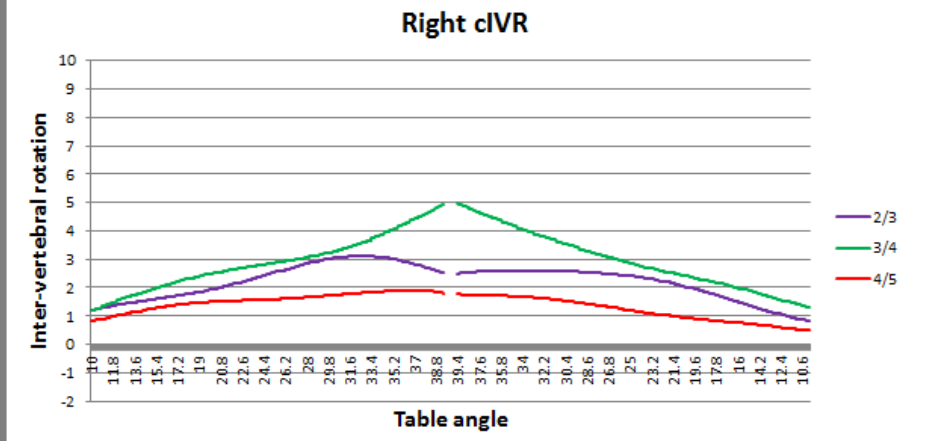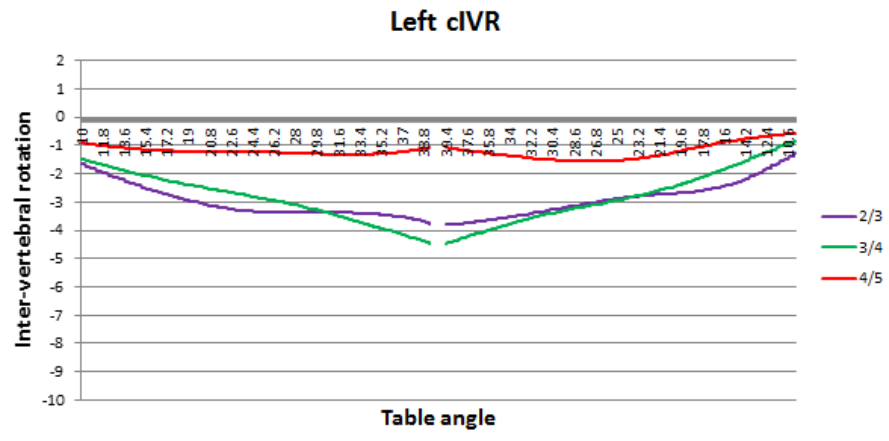
Figure 11-1 Continuous intervertebral rotation for a healthy volunteer with radicular pain
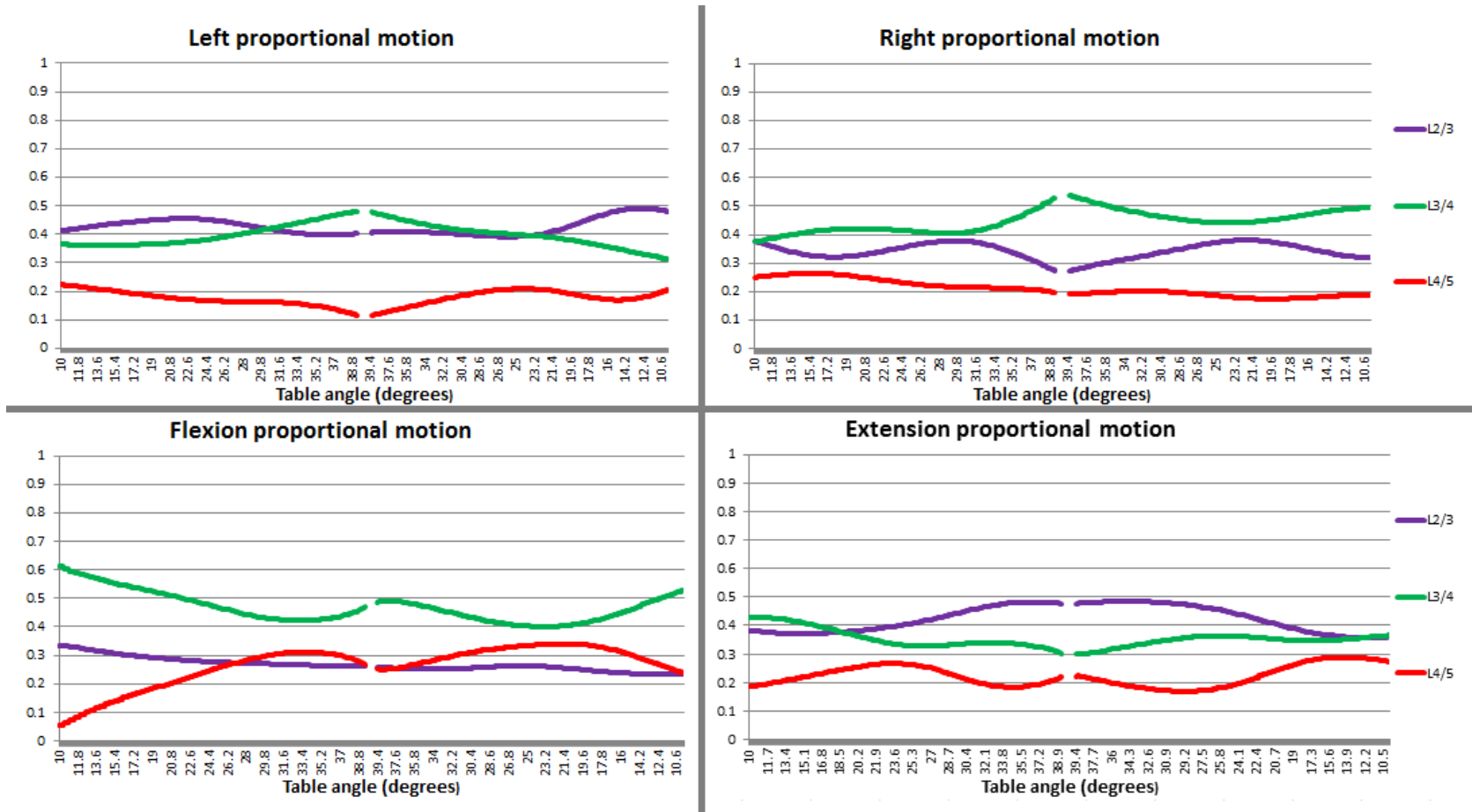
Figure 11-2 Continuous proportional motion patterns for a healthy volunteer with radicular pain

11.5 Limitations and recommendations for further work

A limitation of QF is that it may not account for subtle out-of-plane rotations. Large out-of-plane rotations would manifest as template tracking failure [38] and although bi-planar fluoroscopy would overcome this, (see Bi planar imaging p35) it is less applicable to a clinical setting. Breen et al (Breen et al. 2006) are the only group to have developed a standardised patient positioning and motion protocol, and the fluoroscopy sequences with templates were subjectively viewed for quality assurance, thus out-of-plane rotations are not thought to be a major issue in these results. It is noted as a limitation that QF cannot accurately measure axial rotation, and the exclusion of this plane may provide an incomplete picture of in vivo passive biomechanics. Future research combining 3D imaging methods with QF may address this limitation.

Seven participants were unable to achieve 40^0 extension without associated axial rotation (see 'Sagittal plane intervertebral data collection' p59) although the inclusion/exclusion criteria stated participants should tolerate up to 40° of table motion. While globally these participants could achieve 40^0 global rotation, the associated out-of-plane intervertebral axial rotation would have caused terminal failure of the automated tracking, thus passive rotation was reduced to a point where out-of-plane rotation was not evident. For logistical reasons it was decided to keep these participants in the study, and no weighting was given to their reduced trunk motion. In practice this represented 11.5% of the sample but it is interesting to note that there are no significant associations for any kinematic parameter for extension. Future studies could first ascertain that patients can achieve 40° in all direction without out-of-plane rotation, although this would require a single fluoroscopy image at the end range to check vertebral positions, and may be ethically unfeasible. An alternative could be to use stabilising devices to hold the participant in place during the passive motion, as demonstrated by Ortho-kinematics, a company in the USA currently commercialising the QF technology (Ortho-Kinematics 2014).

Tracking templates are reliant upon pixel information within their border, and a limitation of the QF automated tracking is that overlap of other structures (i.e. bowel gas or the iliac crests) can change the appearance of the pixels. In practice this can generally be overcome by replacing the templates at the point of change, but in some instances it causes complete tracking failure. Previous studies have dealt with this by analysing segments individually and discounting missing data (Breen et al. 2006; Mellor et al. 2009; Yeager et al. 2014), but this does not appreciate the inter-dependency of segmental motion. This thesis disregarded the whole data from that

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[38] Because out-of-plane rotations causes the vertebral shape to change

participant if one level failed to track in any direction. In practice two participants were excluded following data collection because L5 was not reliably tracked throughout extension.

As with functional views, QF relies upon good image quality and images that are degraded due to radiographic scatter decreases template tracking ability. For this reason, S1 in the sagittal plane has a higher failure rate than other vertebral bodies[39] and thus was excluded from this thesis. It is for the same reason that a limit on BMI was imposed and it is interesting to note that the two participants whose data were rejected both had a BMI of 30. A further limitation in this thesis is the lack of a pre-determined time interval between patients being recruited and undergoing QF. In most instances the time interval was less than two weeks (exact figures are not available) but it is likely that patients received treatment in this period; consequently their CPG and RMDQ scores may have altered at the time of imaging. However, it was not intended to use these questionnaires as outcome measures.

Despite positioning participants with L3/4 centred at the fulcrum of the table, no measurement of this standardisation was taken (of the initial lumbar lordosis). It was assumed to be 'flattened' in both sagittal and coronal imaging but there were clearly subjective differences between participants. The influence on initial lordosis on segmental motion is unknown, although it is theorised that a segment that is not within its neutral zone may react differently to load (Smit et al. 2011) but the *in vivo* applications of this are unknown. Additionally, inconclusive evidence exists for association between lordosis and low back pain, the optimal lordotic range remains unknown, and it may be related to a variety of individual factors such as weight, activity, muscular strength, and flexibility of the spine and lower extremities (Been and Kalichman 2014). Given this, it is unknown whether standardising the lordotic angle would be an improvement or hindrance, and a better method of standardisation to the lordosis is achieved by proportionally representing segmental motion (see Chapter 9 p159)

Overall there were few differences demonstrated between both groups and one reason for this may be heterogeneity in the participants. No consideration was given to anatomical variations such as facet joint tropism (Hasegawa et al. 2011) due to their low incidence in the sample and difficulties in viewing from fluoroscopic images. This may have accounted for some of the variation in the results given that previous studies indicate these play a part in lumbar motion (Gombatto et al. 2013). It is recommended that further investigation of the effects of anthropomorphic variables is studied with

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[39] Because of superimposition of the iliac bones in the sagittal plane

passive recumbent QF and a larger sample size. Relationships may have been found if the kinematic variables in this thesis were combined in a multivariate model, similar to an approach undertaken by Teyhen et al (2007a, 2007b) and this is recommended as further research to better understand any relationships between CNSLBP and biomechanics.

Cadaveric studies demonstrate that altered movement occurs when the intervertebral disc is damaged (Mimura et al. 1994; Adams 1995) and the disc, along with ligaments and facet joints, are part of the passive subsystem but degenerate discs do not always lead to back pain (Carragee 2000; Carragee 2006). Hence, CNSLBP from the passive subsystem may be attributable to more than the disc, but it is impossible to pin point the exact feature that may be causing aberrant motion in this sample due to limitations in image quality of fluoroscopic images. Combining QF with MRI could shed further light on how passive structures relate to pain and motion.

Heterogeneity of the patient group may also have been influenced by central sensitisation and chemical pain rather along with passive subsystem mechanical factors (Breen 2014). There are specific conditions that cause these, such as disc protrusion, disc herniation, cysts, end-plate and disc inflammation, and stenosis. Although the inclusion/exclusion criteria in this study were tightly defined to capture mechanical low back pain and screen out psychosocial factors, it is feasible that problems in the passive subsystem are just one aspect of mechanical low back pain, as theorised by Breen et al (Breen 2014) (see Figure 11-3 p209).
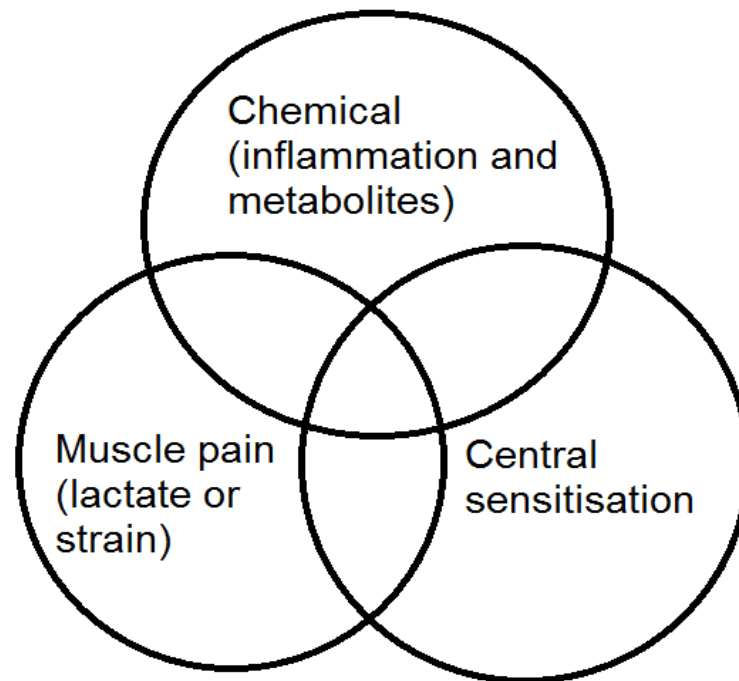
Figure 11-3 Factors contributing to mechanical low back pain

A further limitation of this study is that it only considered kinematic parameters from intervertebral rotation, although the QF procedure has now been validated for translation and ICR measurements (Breen 2011) and it is recommended that these are further studied retrospectively with this data. Eventually this could lead to a model of biomechanics and CNSLBP and further delineate the pathologies and anatomical variants that influence motion.

It would be interesting to follow up healthy participants from this study and determine whether any subsequently suffered LBP [40], which would then be examined in light of their motion patterns. The majority of healthy volunteers did not have remarkable motion but one in particular, from a healthy volunteer, was noticeable because it had the greatest variation of all participants for extension PRV (see Figure 11-4 p210). No longitudinal QF studies have yet been undertaken for this purpose; hence it is a recommendation for future research to determine whether aberrant motion patterns can predict future back pain and echoes Borenstein who called for clinical correlation with abnormal patterns as the 7 year follow up study for MRI (Borenstein et al. 2001).

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[40] Unfortunately this is not possible due to anonymised data
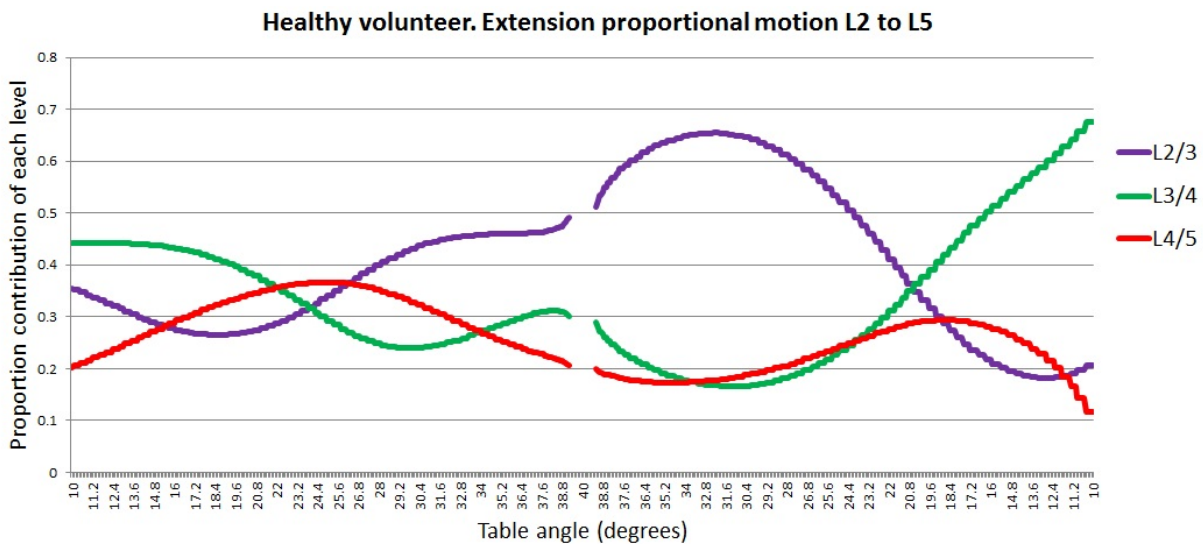
Figure 11-4 Proportional continuous motion for a healthy volunteer (extension)

11.6 Potential implications for clinical practice

It is acknowledged that the translation from research to clinical practice requires further research with larger populations. The kinematic variables would need simplifying to aid understanding, and this would include reducing the number of decimal places of mIVR and initial segmental attainment rate. Discussion with clinical colleagues indicates that one decimal place is a favourable figure to report for mIVR, although it is standard practice in research to report RoM to two decimal places (Breen 2006, Yeager 2014). Whether QF can better select patients for treatment, such as spinal surgery is recommended for further study.

The 'non-specific' aspect of CNSLBP has emerged as a consequence of failure to identify anatomic or physiologic changes that clearly explain symptoms (Deyo 2002b). Patients are thus currently grouped by clinical findings (Abraham and Killackey-Jones 2002) but these 'sub classifications' are indistinct and psychosocial elements appear to have more relation to prognosis than physical examinations (Deyo and Diehl 1988). Treatment options recommended for those with CNSLBP (NICE. 2009) include mechanical interventions such as spinal manipulation, which claims to improve the motion in a joint, or exercise, which aims to strengthen the stability of a joint. These treatments have opposing actions and may be offered based upon the clinician's experience, but predicting which patients will have the best outcome is impossible. The measureable kinematic parameters obtained from QF may therefore help better target the treatment currently offered and thus improve prognosis.

It is not intended that every patient with CNSLBP would undergo QF as it is clear that psychosocial elements, central sensitisation and chemical factors play their part and there is a need to limit imaging investigations for economic and clinical reasons; but for those patients who are not responding to conservative therapy and have no identifiable psycho-social problem, QF could help identify the cause.

In the words of Richard Deyo

 "Everyone would be delighted if we could define clear cut new diseases [for back pain] but they should have pathologic, prognostic or therapeutic importance and not be based simply on clinical lore or inference" (Deyo 2002b).

Demonstrating a mechanical component in some CNSLBP patients goes some way to justifying the treatments currently offered, albeit the differences between groups in this thesis are small. If this study is replicated with similar findings then further research will be necessary to identify what tissues are disrupted when passive intervertebral motion is aberrant, and also identify other kinematic parameters obtainable from QF technology.

11.7 Contribution to new knowledge

The uniqueness of this study and its contribution to the area of spinal biomechanics is the ability to measure the passive intervertebral motion with high reproducibility. It provides an initial data base of healthy volunteer data by which to compare that of CNSLBP for the first time. The main contribution to care is better selection of treatments, especially where spinal surgery is being considered.

The promise of this is not with spinal pain of mild and recent onset, but with conditions that are disabling, recurrent and/or chronic. Quantitative fluoroscopy provides a detailed look at the continuous intervertebral biomechanics and, if the differences found in this thesis are replicated, it would be a step forward in understanding non-specific mechanical back pain. If replication of this study does not determine differences in groups then it signals that non-specific back pain may not be unduly influenced by passive elements and is probably not worth pursuing. Instead the focus should remain on motor control and loading in biomechanics research and/or stay with chemical and neurological explanations.

This thesis also contributes to new knowledge by standardising the procedure for QF and developing kinematic parameters for the classification of normal and abnormal movement in the passive subsystem. The differences found between groups begin to illuminate the need for further study in this area, and given that the majority of differences were in the coronal plane, it is recommended that this plane be

reconsidered in the radiological assessment of intervertebral motion. In addition, relating passive to active weight bearing motion may illuminate issues that are influenced by muscular and motor control. If differences are greater in weight-bearing studies then future research into the relationship between altered biomechanics and CNSLBP should be concentrated in these areas.

Chapter 12   Conclusion

The study was originally justified on the basis that "knowing if CLBP is mechanical or not will facilitate treatment." This is the first study to show that there are some measurable biomechanical differences in the passive subsystem patients with CNSLBP and healthy volunteers when variation in data acquisition and analysis, and measurement errors are reduced, opening up a new direction for objective diagnosis and management. These results require replication and if they are reproducible, the resulting increase in understanding of motion patterns and the implications for CNSLBP management may be compared in randomised trials and considered in treatment strategies.

Although the kinematic differences were weak, they indicate that biomechanics may be partly responsible for clinically diagnosed mechanical CNSLBP, but this is not detectable by any one kinematic parameter. It is likely that other factors such as loading, central sensitisation and motor control may also be responsible for back pain that is considered mechanical. QF is easily adapted to clinical practice and is recommended to replace functional radiography, but further work is needed to determine which kinematic parameters are clinically useful.

The increased reproducibility and information gained from QF means it could replace functional radiography, particularly for the conditions listed in Table 12-1 p213, but it is not yet known whether weight-bearing or recumbent motion protocols would be preferable for this.

Clinical indications for the use of QF (active or passive)
Determining fusion status
Identifying adjacent level instability
Assessing clinical stability of spondylolisthesis
Internal disc disruption/laxity/functional instability
Clinical and functional stability at specific levels/directions
Detection of dynamic stenosis

Table 12-1 Indications for the use of QF

Furthermore, if the motion abnormalities are related to MRI abnormalities, this could lead to a further study of ways to diagnose mechanical CLBP without radiation and reveal associations between structural abnormalities and abnormal motion patterns. To conclude, QF, both passive recumbent and active weight-bearing is easily adaptable for clinical use. It is currently undergoing commercialisation in the USA (Ortho-

Kinematics 2014) and can detect subtle mechanical differences between patients and healthy volunteers. Further work is now necessary to determine which kinematic parameters (individually or combined) are most clinically useful.

Chapter 13   Appendices

Appendices for Chapter 3 Methodology

CM/STA/hph

02 October 2009

NHS

National Research Ethics Service
SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEE (A)
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Park Street, Shirley
Southampton
Hampshire
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Miss Fiona E Mellor
Research Radiographer
Institute for Musculoskeletal Research and Clinical Implementation
Anglo-EuropeanCollegeofChiropractic
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Bournemouth
BH5 2DF

Tel: 023 8036 2466
          023 8036 3462
Fax: 023 8036 4110

Email: scsha.SWHRECA@nhs.net

Dear Miss Mellor

Study Title: **Chronic non-specific low back pain: Biomechanical assessment of inter-vertebral motion in the mid-lumbar spine in symptomatic and healthy participants.**
REC reference number: 09/H0502/99
Protocol number: 1

Thank you for your letter of 29 September 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The favourable opinion applies to the following research site(s):

Research Site	Principal Investigator / Local Collaborator
Anglo-European College of Chiropractic.	Miss Fiona E Mellor

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Participant Information Sheet: Volunteer	2	21 September 2009
Participant Information Sheet: Patient	2	21 September 2009
Participant Consent Form: Transfer of Personal Details	2	25 September 2009
Evidence of insurance or indemnity		04 September 2009
Telephone Script	1	24 September 2009
Recruitment email for Patients	2	21 September 2009
Recruitment Poster	2	21 September 2009
Response to Request for Further Information		29 September 2009
Covering Letter		07 August 2009
REC application		06 August 2009
Protocol	1	07 August 2009
Investigator CV: Miss F Mellor		
Participant Consent Form: Patients	1	07 August 2009
GP/Consultant Information Sheets	1	07 August 2009
Letter from Sponsor		06 August 2009
Letter from Statistician		10 August 2009
Referees or other scientific critique report		07 July 2009
Summary/Synopsis	1	07 August 2009
Questionnaire: Depression Screening		
Letter from Professor Breen		14 July 2009
Investigator CV: Professor A Breen		06 August 2009
Advertisement	1	07 August 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National

Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0502/99	Please quote this number on all correspondence

Yours sincerely

Dr Chris Markham
Vice-Chair

Email: scsha.SWHRECA@nhs.net

Enclosures: "After ethical review – guidance for researchers" SL- AR2 for other studies

Copy to: Haymo Thiel,
Anglo-European College of Chiropractic
13-15 Parkwood Road
Bournemouth
BH5 2DF

Southampton & South West Hampshire REC (A)

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	09/H0502/99	Issue number:	1	Date of issue:	02 October 2009

Chief Investigator:	Miss Fiona E Mellor

Full title of study:	Chronic non-specific low back pain: Biomechanical assessment of inter-vertebral motion in the mid-lumbar spine in symptomatic and healthy participants.

This study was given a favourable ethical opinion by Southampton & South West Hampshire REC (A) on 01 October 2009. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	Post	Research site	Site assessor	Date of favourable opinion for this site	Notes [1]
Miss Fiona E Mellor	Research Radiographer	Anglo-European College of Chiropractic.	Southampton & South West Hampshire REC (A)	02/10/2009	

Approved by the Chair on behalf of the REC:

……………………………………… (Signature of Co-ordinator)

Mrs Sharon Atwill

(1)   *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

Figure 13-1 National Research Ethics Approval gained 02/10/2009

Poole Hospital NHS
NHS Foundation Trust

17 August 2011

Miss Fiona Mellor
Research Radiographer
Anglo European College of Chiropractic
13-15 Parkwood Road
Bournemouth BH18 8LY

Dear Miss Mellor

Re: Chronic non specific low back pain: Biomechanical assessment of inter-vertebral motion in the mid-lumbar spine in symptomatic and healthy participants
REC reference number: 09/H0602/99
EudraCT number: N/A
Protocol Ref: V2

Thank you for the documentation relating to the above study. Poole Hospital NHS Foundation Trust is responsible for Dr Paul Thompson acting as a Participant Identification Centre (PIC) and, in accordance with IRAS guidance, formal research management and governance approval is not required. We note that Dr Thompson may identify and refer NHS patients as potential participants to you at the Anglo-European College of Chiropractic.

Anglo European College of Chiropractic are responsible for the participant-related research procedures specified in the protocol being conducted at their sites

Poole Hospital NHS Foundation Trust has reviewed the request to refer patients, including any resource implications or data protection issues, and this letter confirms their permission for Dr Thompson to act as a PIC and proceed with the identification and referral of potential participants.

I wish you every success with the study

Yours sincerely

Martin Smith
Director of Nursing & Patient Services

Cc: Dr P Thompson

Please send all correspondence relating to this study to:
Research Governance Manager
Research Governance Department
Poole Hospital NHS Trust
Longfleet Road
Poole DORSET. BH15 2JB

Research Governance Department, Durrells House, Poole Hospital NHS Foundation Trust, Longfleet Road, Poole, Dorset BH15 2JB

Figure 13-2 Letter allowing Poole Hospital Foundation Trust to act as a patient identification centre (PIC)

ANGLO-EUROPEAN COLLEGE OF CHIROPRACTIC

IMRCI
Institute for Musculoskeletal Research & Clinical Implementation

Information for patients:
A study to compare motion between the bones in the lower back in people with chronic low back pain and healthy volunteers.

I would like to invite you take part in my PhD research study. Before you decide it is important for you to understand why the research is being done and what it would involve. **My contact details are at the end of this information and I am happy to answer any questions you may have.**

This information leaflet will:

1. Outline the purpose of the research.
2. Explain why you have received this leaflet.
3. Describe what happens next.
4. Describe what will happen if you decide to participate.
5. Clarify the risks and benefits to you of taking part.
6. Inform you about confidentiality and data protection.
7. Describe what to do if you have a problem
8. Explain what will happen to the results of this research
9. Tell you who is funding the research
10. State who has reviewed the study
11. Give contact details so you can ask further questions.

1. Purpose.
This study will investigate whether it is possible to distinguish people who have chronic non specific low back pain (CNSLBP) from those who do not by comparing the movement between the bones in the lower back (lumbar vertebrae) using video x-rays (fluoroscopy). Previous research has shown that normal x-rays and MRI are not able to reliably distinguish individuals with CNSLBP from those without due to a poor relationship between what they show and pain. It is thought there may be a difference in how the lumbar vertebrae move in people with CNSLBP. However until now there has been no way of investigating this theory.

2. Why Have I Received this Leaflet?
You have received this leaflet because you are aged between 21 and 51 years and you have mechanical CNSLBP. This means your back pain has been present for more than 3

Inter-vertebral motion in CNSLBP and healthy participants. Patient information leaflet. V3. 06.09.10   1

months and is made worse or better by movement or position. **I am happy to answer any questions you may have but it is entirely your decision whether or not you decide to join the study. You are free to refuse to participate or withdraw at any time without giving a reason (see Confidentiality and Data Protection). This will not affect the standard of care you receive.**

3. What Happens Next?

I will contact you after 7 days to see if you would like to participate and check with you that you match the initial entry criteria for the study. If you do not want to take part or you do not match the entry criteria I will destroy your personal details and not contact you again.

4. What Will Happen if I Decide to Participate?

If you match the initial entry criteria and you want to take part you will be invited to attend the x-ray department at the AECC. I will meet and go through this information leaflet with you and ask you to sign 2 consent forms, one of which will be for you to keep.

The video x-ray assessment;

Following the questionnaires you will be shown to a changing room and asked to change into a gown ready for the video x-rays of the bones in your spine during bending. To do this, I will use a new method called OSMIA (Objective Spinal Motion Imaging Assessment) which uses a specially designed table and low dose video x-rays. The table is hinged in the middle and the lower half moves slowly from side to side whilst you lie on it. You will firstly be asked to lie on your back on the table with your knees bent. The lower half of the table will swing from left to right/right to left and video x-rays will be taken showing the movement of the lumbar vertebrae as you bend from side to side. Then you will be asked to lie on your side and again the bottom half of the table will swing both ways allowing video x-rays to be taken as you bend forward and backwards. Before I take the x-rays I will demonstrate the movement of the table with you to find the range of bending that you are comfortable with. Previous studies have shown that pre and post surgical patients do not feel pain when bending as the movement is 'passive', which means the movement, is generated by the table moving. **The whole procedure will take no more than 40 minutes.**

5. Risks and Benefits of Participating.

This examination uses radiation (video x-rays). Therefore it is important you understand

the risks and benefits of taking part. **Females please note, x-rays may harm an unborn child. It is therefore vital that you inform the radiographer beforehand if you are pregnant or suspect you might be.** The radiation dose from the examination is roughly the same amount of naturally occurring background radiation you would receive in the UK over a 6 month period. Experts agree that it is very difficult to determine the risk of inducing cancer from such low doses, however it is estimated that **there is a 1 in 16 000 – 1 in 17 000 extra chance of getting cancer from this examination. This is in addition to the quoted 1 in 3 natural lifetime risk of you contracting cancer throughout your lifespan.**

You may wish to consider this risk in relation to some more familiar events as in the table below. There is no direct benefit to you from the radiation dose; however the risk is seen to be minimal.

Some familiar risks (Sedgwick and Hall 2003)	Chance they will happen
Getting three balls in the UK national lottery	1 in 11
Needing emergency treatment in the next year after being injured by a can, bottle, or jar	1 in 100
Death by an accident at home	1 in 7100
Getting five balls in the UK national lottery	1 in 11 098
Death by an accident at work	1 in 40 000
Death playing soccer	1 in 50 000
Death by murder	1 in 100 000
Being hit in your home by a crashing aeroplane	1 in 250 000

Sedgwick, P. and A. Hall (2003). "Teaching medical students and doctors how to communicate risk." BMJ **327**(7417): 694-695.

There is also a risk that an 'incidental' finding will be seen on your video x-ray. An incidental finding is defined as one that is unrelated to your back pain and is discovered unintentionally. To date, more than 100 patients have undergone this examination and there have been no significant incidental findings. All video x-rays will be reviewed by a Diplomate of the American Chiropractic Board of Radiology (DACBR) at the AECC and in the event of an incidental finding you will be referred, if necessary, to the appropriate specialist in consultation with your GP, if that is what you would like. Such detection has the benefit of starting treatment early but in a small number of cases may have

Inter-vertebral motion in CNSLBP and healthy participants. Patient information leaflet. V3. 06.09.10   3

225

implications for future employment and insurance.

There may be no overall benefit to you from taking part in this study but the information I receive might help improve the diagnosis of patients with CNSLBP and allow more targeted treatment. Throughout the video x-ray examination you will have the option of watching the movement of your lumbar vertebrae on a TV screen which many previous patients have found fascinating.

6. Confidentiality and Data Protection

Ethical and legal practice will be followed with respect to any information obtained from you in this study. It is necessary to inform your GP of your participation in this research and you will be asked to provide your GP's details (name and address) on the consent form.

Following review of your video x-rays by a DACBR, all your data will be anonymised which means I will not be able to identify you from any of your answers. Consequently, you will not be able to withdraw your data from the study once it has been collected. This does not affect your right to withdraw from the study prior to, or during data collection. Your anonymised data will also be retained indefinitely for use in further studies.

7. What if there is a problem?

If you have a concern about any aspect of the study you should speak to me in the first instance and I will do my best to answer your questions. If you remain unhappy and wish to complain formally you can do this by contacting Professor Breen at the AECC. In the event that something does go wrong and you are harmed during the research due to someone's negligence, you may have grounds for legal action for compensation against the AECC but you may have to pay your own legal costs.

8. What will happen to the results of this study?

The results from this study will be collated and presented to Bournemouth University for the award of Doctor of Philosophy (PhD). They will also be presented at international conferences including the Society for Back Pain Research, and disseminated in international peer reviewed journals and on the AECC website (www.aecc.ac.uk). You are welcome to keep up to date with the study's progress by periodically checking the website, or contacting me at any time; my details are at the end of this leaflet.

9. Who is funding the research?

This research is being undertaken in fulfilment for the qualification of PhD. It is funded by

Inter-vertebral motion in CNSLBP and healthy participants. Patient information leaflet. V3. 06.09.10   4

the National Institute for Health Research (NIHR) and is supported and sponsored by the Anglo-European College of Chiropractic.

10. Who has reviewed the study?

This research has been extensively reviewed by my academic supervisors Professor Breen, Professor Thomas and Professor Thompson. Additionally, Bournemouth School of Health and Social Care Postgraduate Committee and the Southampton National Research Ethics Committee have reviewed and given a favourable opinion on this study.

11. Further information and contact details

Miss Fiona Mellor

NIHR Clinical Doctoral Research Fellow/Research Radiographer

Anglo-European College of Chiropractic.

13-15 Parkwood Road

Bournemouth BH5 2Df

Tel: 01202 436280

Email: imrci.fmellor@aecc.ac.uk

Figure 13-3 Patient information leaflet

Information for healthy volunteers:

A study to compare motion between the bones in the lower back in people with chronic low back pain and healthy volunteers.

I would like to invite you take part in my PhD research study. Before you decide it is important for you to understand why the research is being done and what it would involve for you.

My contact details are at the end of this information and I would be happy to answer any questions you may have.

This information leaflet will:

1. Outline the purpose of the research.
2. Why you have received this information leaflet.
3. Describe what will happen if you decide to participate.
4. Clarify the risks and benefits to you of taking part.
5. Inform you about confidentiality and data protection.
6. Describe what to do if you have a problem
7. Explain what will happen to the results of this research
8. Tell you who is funding the research
9. State who has reviewed the study
10. Give contact details for the clinical investigator so you can ask any further questions.

1

1. Purpose.

This study will investigate whether it is possible to distinguish people who have chronic non specific low back pain (CNSLBP) from those who do not by comparing the movement between the bones in the lower back (lumbar vertebrae) using video x-rays (fluoroscopy). It is thought there may be a difference in how the lumbar vertebrae move in people with CNSLBP. However until now there has been no way of investigating this theory. Previous research has shown that normal x-rays and MRI are not able to reliably distinguish individuals with CNSLBP from those without due to a poor relationship between what they show and pain.

2. Why have I received this information leaflet?

You have received this leaflet because you are aged between 21 and 51 years and you replied to an email or advertisement asking for volunteers without back pain who would like to take part in the research study. This leaflet will explain the research in further detail. **I am happy to answer any questions you may have but it is entirely your decision whether or not you decide to join the study. You are free to refuse to participate or withdraw at any time prior to the taking of the x-ray video without giving a reason (see Confidentiality and Data Protection p6).**

3. What Will Happen if I Decide to Participate?

If you take part in this research your name, gender, age, height and weight, address and telephone number will be stored on a password protected database. For every patient with CNSLBP who takes part in the research I will match one healthy volunteer based on age, body mass

2

index (BMI) and gender to also take part. It may be that you are NOT matched to a patient, in which case your contact details will be destroyed after 40 patients have been recruited.

If you are matched you will be invited to attend the x-ray department at the AECC at a time convenient to you. I will go through this information leaflet and explain the video x-ray examination. If you are happy to proceed you will be asked to sign 2 consent forms, one of which will be for you to keep. After this, you will be shown to a changing room and asked to change into a gown ready for the video x-rays of your lower spine during bending. To do this, I will use a new method called OSMIA (Objective Spinal Motion Imaging Assessment) which uses a specially designed table and low dose video x-rays. The table is hinged in the middle and the lower half moves slowly from side to side whilst you lie on it.

You will first be asked to lie on your back on the table with your knees bent. The lower half of the table will swing from left to right/right to left and video x-rays will be taken showing the movement of the lower back as you bend from side to side. Then you will be asked to lie on your side and again the bottom half of the table will swing both ways allowing video x-rays to be taken as you bend forward and backwards. Before I take the x-rays I will demonstrate the movement of the table with you to find the range of bending that you are comfortable with. Previous studies have shown that even pre and post surgical patients do not feel pain when bending as the movement is 'passive', which means the movement, is generated by the table moving rather than by you. You will however be provided with a button that will stop the table immediately should you begin to feel pain or discomfort. **The whole procedure will take no more than 1 hour.**

3

4. Risks and Benefits of Participating.

This examination uses radiation (video x-rays). Therefore it is important you understand the risks and benefits of taking part. **Females please note, x-rays may harm an unborn child. It is therefore vital that you inform the radiographer beforehand if you are pregnant or suspect you might be.** The radiation dose from the examination is roughly the same amount of naturally occurring background radiation you would receive in the UK over a 6 month period. Experts agree that it is very difficult to determine the risk of inducing cancer from such low doses, however it is estimated that **there is a 1 in 16 000 – 1 in 17 000 extra chance of getting cancer from this examination. This is in addition to the quoted 1 in 3 natural lifetime risk of you contracting cancer throughout your lifespan.** You may wish to consider this risk in relation to some more familiar events as in the table below. There is no direct benefit to you from the radiation dose; however the risk is seen to be minimal.

Some familiar risks (Sedgwick and Hall 2003)	Chance they will happen
Getting three balls in the UK national lottery	1 in 11
Needing emergency treatment in the next year after being injured by a can, bottle, or jar	1 in 100
Death by an accident at home	1 in 7100
Getting five balls in the UK national lottery	1 in 11 098

4

Death by an accident at work	1 in 40 000
Death playing soccer	1 in 50 000
Death by murder	1 in 100 000
Being hit in your home by a crashing aeroplane	1 in 250 000

Sedgwick, P. and A. Hall (2003). "Teaching medical students and doctors how to communicate risk." BMJ **327**(7417): 694-695.

There is also a risk that an 'incidental' finding will be seen on your video x-ray. An incidental finding is defined as one that is unrelated to your back pain and is discovered unintentionally. To date more than 100 patients have undergone this examination and there have been no significant incidental findings.

All video x-rays will be reviewed by a Diplomate of the American Chiropractic Board of Radiology (DACBR) at the AECC and in the event of an incidental finding you will be referred, if necessary, to the appropriate specialist in consultation with your GP, if that is what you would like. Such detection has the benefit of starting treatment early but in a small number of cases may have implications for future employment and insurance. There may be no overall benefit to you from taking part in this study but the information I receive might help improve the diagnosis of patients with CNSLBP and allow more targeted treatment. Throughout the video x-ray examination you will have the option of watching the movement of your lumbar vertebrae on a TV screen which many previous patients have found fascinating.

5

5. Confidentiality and Data Protection

Ethical and legal practice will be followed with respect to any information obtained from you in this study. Your details will be kept on a password protected database until 40 matched volunteers have been recruited. After this, all identifying details will be destroyed. If you are selected for a video x-ray examination it will be necessary to inform your GP of your participation and you will be asked to provide your GP's details (name and address) on the consent form when you attend. Following review of your video x-rays by a DACBR, all your data will be anonymised. Consequently, you will not be able to withdraw your data from the study once it has been collected. This does not affect your right to withdraw from the study prior to, or during data collection. Your anonymised data will also be retained indefinitely for use in further studies.

6. What if there is a problem?

If you have a concern about any aspect of the study you should speak to me in the first instance and I will do my best to answer your questions. If you remain unhappy and wish to complain formally you can do this by contacting Professor Breen at the AECC.

In the event that something does go wrong and you are harmed during the research due to someone's negligence, you may have grounds for legal action for compensation against the AECC but you may have to pay your own legal costs.

6

7. What will happen to the results of this study?

The results from this study will be collated and presented to Bournemouth University for the award of Doctor of Philosophy (PhD). They will also be presented at international conferences including the Society for Back Pain Research, and disseminated in international peer reviewed journals and on the AECC website (www.aecc.ac.uk). You are welcome to keep up to date with the study's progress by periodically checking the website, or contacting me at any time; my details are at the end of this leaflet.

8. Who is funding the research?

This research is being undertaken in fulfilment for the qualification of PhD. It is being funded through a fellowship awarded by the National Institute for Health Research, and is being supported and sponsored by the Anglo-European College of Chiropractic.

9. Who has reviewed the study?

This research has been extensively reviewed by my academic supervisors Professor Breen, Professor Thomas and Professor Thompson. Additionally, Bournemouth School of Health and Social Care Postgraduate Committee and the Southampton National Research Ethics Committee have reviewed and given a favourable opinion on this study.

7

10. Further information and contact details

Miss Fiona Mellor

Research Radiographer

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Bournemouth BH5 2Df

Tel: 01202 436280

Email: imrci.fmellor@aecc.ac.uk

8

Figure 13-4 Healthy volunteer information leaflet

Inter-vertebral motion in healthy and symptomatic participants.
Inclusion criteria questionnaire V3

What is your current age?   ………………..

Please circle your gender   M   F

What is your current height?   ………………..

What is your current weight? ………………..

Please answer Yes or No to the following 7 questions by circling the answer which is relevant to you.

If you do not understand any question then please do not answer, I will contact you after I receive this questionnaire and explain the questions further to you if you so wish.

1. Have you had a CT scan of your chest, pelvis or abdomen, or angiography in the last 2 years"?
Yes   No

2. "Have you had previous lumbar spine, abdominal or pelvic surgery
Yes   No

3. Are you currently involved in any other research study?
Yes   No

4. Are you currently involved in a claim for compensation that is linked to your back pain"?
Yes   No

5. "Have you suffered from low back pain for more than 3 months"?
Yes   No

6. "During the past month have you often been bothered by feeling down, depressed or hopeless?"
Yes   No

7. "During the past month have you often been bothered by little interest of pleasure in doing things?"
Yes   No

Please continue onto the next page.

1

Inter-vertebral motion in healthy and symptomatic participants.
Inclusion criteria questionnaire V3

Chronic Pain Status

Pain intensity items

How would you rate your back pain on a 0 – 10 scale at the present time, that is right now, where 0 is 'no pain' and 10 is 'pain as bad as it could be'?

0	1	2	3	4	5	6	7	8	9	10
No pain   Pain as bad as
                                                                it could be

In the past 6 months how intense was your WORST pain rated on a 0-10 scale where 0 is 'no pain' and 10 is 'pain as bad as it could be'?

0	1	2	3	4	5	6	7	8	9	10
No pain   Pain as bad as
                                                                it could be

In the past 6 months, on the average, how intense was your pain rated on a 0-10 scale where 0 is 'no pain' and 10 is 'pain as bad as it could be'? (That is, your usual pain at times you were experiencing pain).

0	1	2	3	4	5	6	7	8	9	10
No pain   Pain as bad as
                                                                it could be

About how many days in the last 6 months have you been kept from your usual activities (work, school or housework) because of back pain?

☐ Days

In the past 6 months how much has your back pain interfered with your daily activities rated on a 0-10 scale where 0 is 'no interference' and 10 is 'extreme change'?

0	1	2	3	4	5	6	7	8	9	10
No interference   Extreme
                                                                Change

In the past 6 months, how much as your back pain changed your ability to take part in recreational, social and family activities where 0 is 'no change' and 10 is 'extreme change'?

0	1	2	3	4	5	6	7	8	9	10
No change   Extreme
                                                                Change

In the past 6 months, how much has your back pain changed your ability to work (including housework) where 0 is 'no change' and 10 is 'extreme change'?

0	1	2	3	4	5	6	7	8	9	10
No change   Extreme
                                                                Change

2

Inter-vertebral motion in healthy and symptomatic participants.
Inclusion criteria questionnaire V3

Roland Morris Disability Questionnaire

When your back hurts you may find it difficult to do some of the things you normally do. This list contains some sentences that people have used to describe themselves when they have back pain. When you read them you may find that some stand out because of how you feel. Please tick only those answers on this questionnaire which apply to how you generally feel.

1. I stay at home most of the time because of my back	
2. I change position frequently to try to get comfortable	
3. I walk more slowly than usual because of my back	
4. Because of my back I am not doing any of the jobs that I normally do around the house	
5. Because of my back I use a handrail to get upstairs	
6. Because of my back I lie down to rest more often	
7. Because of my back I have to hold onto something to get out of a chair	
8. Because of my back I try to get other people to do things for me	
9. I get dressed more slowly than usual because of my back	
10. I only stand up for short periods of time because of my back	
11. Because of my back I try not to bend or kneel down	
12. I find it difficult to get out of a chair because of my back	
13. My back in painful almost all of the time	
14. I find it difficult to turn over in bed because of my back	
15. My appetite is not very good because of my back pain	
16. I have trouble putting on my socks (or stockings) because of the pain in my back	
17. I only walk short distances because of my back pain	
18. I sleep less well because of my back	
19. Because of my back pain I get dressed with help from someone	
20. I sit down for most of the day because of my back	
21. I avoid heavy jobs around the house because of my back	
22. Because of my back pain I am more irritable and bad tempered with people than usual	
23. Because of my back I go upstairs more slowly than usual	
24. I stay in bed most of the time because of my back	

Thank You

3

Figure 13-5 Questionnaire for patients, which includes CPG and RMDQ

Low Back Pain Research Study

Study Investigator: Fiona Mellor BSc (Hons)
Phone: 01202 436280
Email: imrci.fmellor@aecc.ac.uk

SCREENING QUESTIONNAIRE FOR LOW BACK PAIN PATIENTS

1. What is the purpose of the study?
To investigate the differences in movement between the bones in the lumbar spine (vertebrae) in those with chronic low back pain and those without which will further our understanding of low back pain.

2. Who is conducting the study?
The study is being organised by the study investigator (see above) who is a PhD candidate at Bournemouth University.

3. What is this questionnaire?
This is an initial screening questionnaire to identify people who may be eligible for the study. Completion of this form does NOT represent your agreement to participate. You will be given an information sheet to help you decide whether or not to take part in the study.

4. What will happen after completing this questionnaire?
The study investigator will review your AECC clinical notes and if you are a suitable participant, she will contact you to ask if you are willing and able to proceed to the next part of the study.

Please answer the questions below and return this form to clinic reception

Q1 Surname: First Name:

Q2 Age (years):

Q3 Do you suffer from low back pain? (Please circle one)   Yes   No

Q4 Is low back pain the main reason for you visiting us today? (Please circle one)   Yes   No

Q5 If yes to the previous 2 questions, have you suffered from low back pain for   Yes   No
more than 3 months, or more than ½ the number of days in the previous year?
(i.e. more than 132 days, which do not have to be consecutive)

Consent

1. I give permission for the investigator to have access to my AECC clinical records and understand they will remain confidential.

2. I understand that I may be contacted by Fiona Mellor (the study investigator) regarding participation in this study. I give permission to be contacted for this purpose.

   Signature: _____   Date:_____

Please indicate the best method of contacting you:
   - Home Phone (indicate phone number): _____
   - Mobile Phone (indicate phone number): _____
   - Email (indicate email address): _____
   - Other (please specify): _____

Clinic attendance questionnaire

Figure 13-6 Clinic attendance questionnaire

Figure 13-7 Healthy volunteer recruitment poster

Anglo European College of Chiropractic

IMRCI Institute for Musculoskeletal Research & Clinical Implementation

OSMIA Data Record Sheet

Participant identification

Date of QF

D.o.B

Height

Referrer Fiona Mellor (PhD Study)

Weight

Examination Requested: Recumbent QF. Hip swing. Left, right flexion extension

Direction	# of frames	kVp	mA	Screening time	Absorbed dose cGYcm2	Range of trunk motion (°)	Comments
Left							Include here is the participant cannot achieve 40 degrees of table motion and why. Also comment here if any acquisition needs to be repeated, and include the factors as a separate examination
Right							
Flexion							
Extension							

If more than one screening per direction please record factors for each screening and the reasons needed to repeat.

Z:\05.Avantic patients\29.10.13

Figure 13-8 Radiation and participant height/weight record sheet

Appendices for Chapter 4 Participant characteristics

Appendices for Chapter 4 Participant characteristics

Tests of Normality			
Patients	Shapiro-Wilk		
(n=40)	Statistic	df	Sig.
Age	0.928	40	0.01
Height m	0.981	40	0.72
Weight Kg	0.977	40	0.57
BMI	0.971	40	0.38

Table 13-1 Normality test (Shapiro Wilkes) for distribution of patient characteristics

Tests of Normality			
Healthy	Shapiro-Wilk		
volunteers	Statistic	df	Sig.
(n=40)			
Age	0.943	40	0.04
Height m	0.974	40	0.49
Weight Kg	0.962	40	0.20
BMI	0.965	40	0.24

Table 13-2 Normality test (Shapiro Wilkes) for distribution of healthy volunteer characteristics

Participant characteristics	Levene's test for equality of variances. Significance p =	Independent student's t test significance (2 tailed) p =
Height (cm)	0.38	0.61
Weight (Kg)	0.36	0.77
BMI	0.49	0.98

Table 13-3 Levene's test and independent samples t test. Participant demographics

Kellgren-Lawrence Grading Scale for joint degeneration

Grade 0: = no degeneration

Grade 1: = doubtful narrowing of joint space and possible osteophytic lipping

Grade 2: = definite osteophytes, definite narrowing of joint space

Grade 3: = moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour

Grade 4: = large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

Figure 13-9 Kellgren and Lawrence scale for grading disc degeneration

(Kellgren and Lawrence 1958)

Appendices for Chapter 5 Reproducibility of two kinematic parameters; maximum intervertebral rotation and initial intervertebral attainment rate

Intra-vertebral level	Intra observer SEM agreement (degrees)			
	Left	Right	Flexion	Extension
L2/3	0.17	0.08	0.13	0.35
L3/4	0.16	0.11	0.13	0.24
L4/5	0.15	0.12	0.10	0.19

Table 13-4 Maximum IVR Intra observer SEM per level and direction

Intervertebral level	Inter observer SEM agreement (degrees)			
	Left	Right	Flexion	Extension
L2/3	0.46	0.55	0.31	0.77
L3/4	0.28	0.18	0.17	0.41
L4/5	0.26	0.20	0.31	0.27

Table 13-5 Maximum IVR Inter observer SEM per level and direction

Direction	Intra observer ICC (95% C.I.)			
	L2/3	L3/4	L4/5	Mean
Left	0.884 (0.539 to 0.971)	0.833 (0.469 to 0.956)	0.987 (0.949 to 0.997)	0.687 (0.176 to 0.911)
Right	0.924 (0.728 to 0.981)	0.962 (0.863 to 0.990)	0.972 (0.890 to 0.993)	0.968 (0.882 to 0.992)
Flex	0.968 (0.870 to 0.992)	0.932 (0.766 to 0.982)	0.985 (0.831 to 0.997)	0.954 (0.770 to 0.989)
Ext	0.905 (0.682 to 0.975)	0.962 (0.857 to 0.990)	0.990 (0.962 to 0.998)	0.909 (0.674 to 0.977)

Table 13-6 Maximum IVR Intra observer reliability (ICC 2, 1) per level and direction

Direction	Inter observer ICC (95%C.I.)			
	L2/3	L3/4	L4/5	Mean
Left	0.888	0.890	0.95	0.651
	(0.562 to 0.972)	(0.640 to 0.971)	(0.812 to 0.987)	(0.129 to 0.898)
Right	0.869	0.943	0.941	0.924
	(0.578 to 0.965)	(0.787 to 0.985))	(0.788 to 0.985)	(0.740 to 0.980)
Flex	0.624	0.853	0.803	0.669
	(0.03 to -0.891)	(0.527 to 0.961)	(0.410 to 0.947)	(0.102 to 0.907)
Ext	0.761	0.763	0.610	0.728
	(0.273 to 0.935)	(0.310 to 0.935)	(0.03 to 8.89)	(0.198 to 0.926)

Table 13-7 Maximum IVR Inter observer reliability (ICC 2, 1) per level and direction

Intra-vertebral level	Intra observer SEM agreement			
	Left	Right	Flexion	Extension
L2/3	0.016	0.013	0.007	0.019
L3/4	0.028	0.014	0.009	0.010
L4/5	0.012	0.015	0.007	0.009

Table 13-8 Initial intervertebral attainment rate; Intra observer SEM per level and direction

Intervertebral level	Intra observer SEM agreement			
	Left	Right	Flexion	Extension
L2/3	0.017	0.019	0.033	0.017
L3/4	0.024	0.017	0.012	0.025
L4/5	0.024	0.020	0.039	0.056

Table 13-9 Initial intervertebral attainment rate; Inter observer SEM per level and direction

Direction	Intra observer			
	Left	Right	Flexion	Extension
L2/3	0.942	0.989	0.977	0.868
	(0.762 to 0.986)	(0.958 to 0.997)	(0.9 to 0.994)	(0.550 to 0.966)
L3/4	0.956	0.976	0.932	0.962
	(0.807 to 0.989)	(0.887 to 0.994)	(0.766 to 0.982)	(0.857 to 0.990)
L4/5	0.993	0.989	0.985	0.990
	(0.964 to 0.998)	(0.960 to 0.997)	(0.831 to 0.997)	(0.962 to 0.998)
Mean	0.890	0.970	0.958	0.909
	(0.573 to 0.973)	(0.869 to 0.993)	(0.781 to 0.990)	(0.674 to 0.977)

Table 13-10 Initial intervertebral attainment rate; Intra observer reliability (ICC 2, 1) per level and direction (SPSS, 2 way mixed model with random effects, absolute and single measures)

Direction	Inter observer			
	Left	Right	Flexion	Extension
L2/3	0.924	0.944	0.621	0.905
	(0.730 to 0.981)	(0.804 to 0.986)	(0.037 to 0.890)	(0.682 to 0.975)
L3/4	0.905	0.953	0.854	0.763
	(0.666 to 0.976)	(0.831 to 0.988)	(0.532 to 0.961)	(0.310 to 0.935)
L4/5	0.972	0.968	0.803	0.610
	(0.898 to 0.993)	(0.863 to 0.992)	(0.401 to 0.947)	(-0.30 to 0.889)
Mean	0.811	0.926	0.671	0.728
	(0.435 to 0.949)	(0.730 to 0.981)	(0.107 to 0.907)	(0.198 to 0.926)

Table 13-11 Initial intervertebral attainment rate; Inter observer reliability (ICC 2, 1) per level and direction (SPSS, 2 way mixed model with random effects, absolute and single measures)

Recommendations from the GRRAS report (de Vet et al. 2006)	How they are addressed in this chapter
Identify in the title that inter/inter rater reliability or agreement was investigated	See title p79
Name and describe the diagnostic or measurement device of interest explicitly	Passive controlled motion measured by QF (see Raw data extraction p66)
Specify the subject population of interest	Adults aged 21-50 years with/without CNSLBP (see Justification of inclusion/exclusion criteria p53)
Specify the rater population of interest	Trained observers with at least four years' experience of placing templates and interpreting outputs.
Describe what is already known about reliability and agreement and provide a rationale for your study	See Literature review p80, and Rationale for study p79 and Comparison of these results with other studies p90)
Explain how the sample size was chosen. State the determined number of raters, subjects, and replicate observations	Random sample chosen by rater B. Two independent raters. 10 participants each consisting of 12 individual observations (L2/3, L3/4 and L4/5 in left, right, flexion and extension). Observed twice (placing templates and interpreting results).
Describe the sampling method	Rater B selected random participants from the sample of n=20 using a manual method of selecting names from a hat.
Describe the measurement/rating process (time interval between measurements/blinding)	Two months between observations, each rater blind to each other's results
State whether measurements were conducted independently	Independent measurements
Describe the statistical analysis	SEM agreement (Shrout and Fleiss 1979) and ICC (2,1) (Cook et al. 2012)

State the actual number of raters and subjects which were included, and number of replicate observations which were conducted	Two raters, 10 subjects, 2 observations per subject.
Describe the sample characteristics of raters and subjects	Two experienced raters selected by convenience from a potential pool of 3 raters. Justification of inclusion/exclusion criteria p53)
Report estimates of reliability and agreement including measures of statistical uncertainty	ICC's reported with 95% confidence intervals
Discuss the potential relevance of results	See Clinical implications p92

Table 13-12 GRASS guidelines for reporting of reliability and agreement studies

Appendices for Chapter 6 Maximum intervertebral rotation

Section and Topic	Item #		On page #
Title/ Abstract/ Keywords	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	Chapter 6 p95
Introduction	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	Research question p102
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	Study population, Sample size calculation and Justification of inclusion/exclusion criteria p53
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	Recruitment strategy p56
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	Study population p53 Recruitment strategy p56
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	Research design p45
Test methods	7	The reference standard and its rationale.	mIVR values (continuous data)
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	Procedure p59 Literature review p96
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	mIVR values are continuous data and the cut offs were automatically determined from the RoC curve by the statistical software. The reference limits created in this study were not used for diagnostic accuracy
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	The CI executed and read the index test (QF). Musculoskeletal practitioners undertook the reference standard (clinical diagnosis of mechanical CNSLBP)

	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	The CI and MSK practitioners were not blind to the condition of the participant. A full clinical history was not taken, but the RMDQ and CPG were entry criteria
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	Chapter 5 p79
	13	Methods for calculating test reproducibility, if done.	Chapter 5 p79
Results			
Participants	14	When study was performed, including beginning and end dates of recruitment.	Methods p102
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	Chapter 4 p73
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	Table 3-3 p57
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	Methods p102
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	Inclusion and exclusion criteria defines this Figure 3-2 p55 Figure 3-3 p56
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	Not included
	20	Any adverse events from performing the index tests or the reference standard.	No adverse events from QF
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	Table 6-4 p107
	22	How indeterminate results, missing data and outliers of the index tests were handled.	Missing data p70
	23	Estimates of variability of diagnostic accuracy between subgroups of	Accuracy has previously been reported in Breen et

		participants, readers or centers, if done.	al (2006)
	24	Estimates of test reproducibility, if done.	Chapter 5 p79
Discussion	25	Discuss the clinical applicability of the study findings.	Clinical implications p126

Table 13-13 STARD checklist for reporting studies of diagnostic accuracy – for mIVRs

Shapiro Wilkes test for non-normality (p values)					
		L2/3	L3/4	L4/5	L2 to L5
Healthy volunteers	Left	0.85	0.32	0.98	0.77
	Right	0.91	0.67	0.99	0.87
	Flex	0.65	0.41	0.49	0.17
	Ext	0.68	0.03*	0.18	0.81
Patients	Left	0.12	0.03*	0.85	0.86
	Right	0.81	0.26	0.71	0.71
	Flex	0.15	0.91	0.85	0.65
	Ext	0.36	0.69	0.20	0.98

Table 13-14 Normality of mIVR data for patients and healthy volunteers (p values for each levels and direction)

Direction	Levine's test for equal variances p value			
	L2/3	L3/4	L4/5	L2 to L5
Left	0.26	0.31	0.20	0.29
Right	0.72	0.03*	0.02*	0.33
Flex	0.66	0.98	0.03*	0.56
Ext	0.89	0.69	0.91	0.74

Table 13-15 Equality of variance for mIVR data (p values for each levels and direction)

*if $P < 0.05$ then the sample is unlikely to be from a normal distribution

		Patients n=40 mIVR⁰				Healthy volunteers n = 40 mIVR⁰				2 tailed t test*
		Min	Max	Mean	SD	Min	Max	Mean	SD	P =
Left	L2/3	2.92	11.41	6.74	1.53	3.45	11.00	6.80	1.74	0.87
	L3/4	2.07	11.18	7.14	2.00	3.91	10.00	6.92	1.51	0.59
	L4/5	0.51	11.77	5.62	2.63	1.70	12.21	6.82	2.19	0.03*
	L2-5	8.28	27.62	19.49	4.09	10.58	27.52	20.54	3.46	0.22
Right	L2/3	2.91	9.10	5.94	1.48	2.71	9.70	5.72	1.59	0.52
	L3/4	1.97	10.37	6.68	2.01	3.14	9.18	5.96	1.32	0.06*
	L4/5	0.91	12.86	5.81	2.80	1.93	10.35	6.44	1.92	0.25*
	L2-5	9.02	28.73	18.43	4.27	10.18	25.37	18.12	3.43	0.72
Flex	L2/3	1.25	8.64	4.23	1.56	1.14	7.12	4.05	1.54	0.61
	L3/4	1.67	9.19	5.90	1.70	2.05	9.90	5.5	1.75	0.30
	L4/5	1.43	12.33	7.10	2.46	3.04	9.21	6.46	1.51	0.16*
	L2-5	5.87	25.54	17.22	4.03	22.20	8.00	16.00	3.57	0.17
Ext	L2/3	0.60	10.46	5.04	1.98	0.98	8.49	4.64	1.90	0.36
	L3/4	1.15	7.86	4.15	1.67	1.42	7.49	4.11	1.53	0.92*
	L4/5	0.76	9.85	4.78	2.43	1.40	10.25	5.31	2.37	0.32
	L2-5	23.92	3.71	13.97	4.67	24.04	4.71	14.06	4.28	0.92

Table 13-16 Descriptive data for mIVR (degrees) and statistical significance of differences between groups

Shapiro Wilkes test for non-normality (p value)		
	L2/3	L3/4	L4/4
Left n=20	0.55	0.85	0.31
Right n=20	0.03	0.03	0.33
Flex n=17	0.08	0.59	0.91
Ext n=17	0.74	0.09	0.02

Table 13-17 Normality of data for healthy volunteers from the independent QF study

Direction	Levine's test for equal variances (p value)		
	L2/3	L3/4	L4/5
Left	0.67	0.70	0.44
Right	0.85	0.26	0.54
Flex	0.42	0.60	0.07
Ext	0.03	0.92	0.17

Table 13-18 Equality of variance for the independent QF data per direction

*if $P < 0.05$ then the sample is unlikely to be from a normal distribution or have homogeneity of variance

		Mean mIVR^0 Healthy volunteers hip swing protocol (this study) n=40				Mean mIVR ^{0} Healthy volunteers trunk swing protocol (independent data) n = 17-20				2 tailed t test
		Min	Max	Mean	SD	Min	Max	Mean	SD	p=0.05
Left	L2/3	3.45	11	6.8	1.74	1.91	10.24	6.72	1.8	0.867
	L3/4	3.91	10	6.92	1.51	4.3	10.28	7.11	1.52	0.640
	L4/5	1.7	12.21	6.82	2.19	1.69	9.83	6.19	1.97	0.283
	L2-5	10.58	27.52	20.54	3.46	15.08	26.17	20.02	3.45	0.588
Right	L2/3	2.71	9.7	5.72	1.59	1.79	8.87	6.06	1.65	0.437
	L3/4	3.14	9.18	5.96	1.32	4.7	10.57	6.99	1.28	0.006
	L4/5	1.93	10.35	6.44	1.92	2.38	10.19	6.43	1.7	0.993
	L2-5	10.18	25.37	18.12	3.43	13.43	27.49	19.49	3.6	0.157
Flex	L2/3	1.14	7.12	4.05	1.54	1.65	7.38	3.86	1.45	0.660
	L3/4	2.05	9.90	5.5	1.75	1.99	10.28	6.02	1.95	0.296
	L4/5	3.04	9.21	6.46	1.51	1.85	10.25	6.44	2.19	0.968
	L2-5	22.20	8.00	16	3.57	5.49	24.84	15.7	4.27	0.795
Ext	L2/3	0.96	8.49	4.64	1.90	2.46	6.61	4.33	1.14	0.453
	L3/4	1.42	7.49	4.11	1.53	3.25	8.97	5.31	1.66	0.011
	L4/5	1.4	10.25	5.31	2.37	0.01	8.29	3.05	2.85	0.008
	L2-5	24.04	4.71	14.06	4.28	9	18.91	12.68	3.21	0.188

Table 13-19 Descriptive data for mIVR and statistical significance of differences in mean between 2 groups of healthy volunteers

		Total number of intervertebral levels above the reference interval			Total number of intervertebral levels below the reference intervals		
		patients	healthy volunteers	Fisher's Exact 2 sided (by summation) p=	patients	healthy volunteers	Fisher's Exact 2 sided (by summation) p=
left	L2/3	1	2	>0.99	1	0	>0.99
	L3/4	1	0	>0.99	4	1	0.36
	L4/5	2	1	>0.99	5	1	0.20
right	L2/3	0	1	>0.99	0	1	>0.99
	L3/4	2	0	0.24	6	0	0.03
	L4/5	2	2	-	6	2	0.26
flex	L2/3	3	0	0.24	0	0	-
	L3/4	0	1	>0.99	1	1	-
	L4/5	3	0	0.24	1	0	>0.99
ext	L2/3	6	7	>0.99	2	4	0.66
	L3/4	0	0	-	5	1	0.20
	L4/5	2	4	0.68	0	0	-

Table 13-20 Statistical significance of participants outside independent QF study reference intervals per segment

	Total number of intervertebral levels above the reference interval			Total number of intervertebral levels below the reference intervals		
	patients	healthy volunteers	Fisher's Exact 2 sided (by summation) p=	patients	healthy volunteers	Fisher's Exact 2 sided (by summation) p=
left	4	3	>0.99	7	2	0.15
right	3	3	-	10	3	0.07
flex	6	2	0.26	1	1	-
extension	8	10	0.79	6	4	0.74
Coronal	6	5	>0.99	10	4	0.09
Sagittal	12	12	-	6	5	>0.99
All combined	15	15	-	14	9	0.32

Table 13-21 Statistical significance of participants outside independent QF study reference intervals per direction

(Shaded rows were not used in the analysis due to statistically significant differences in mean mIVR values)

Appendices for Chapter 7 Investigation of initial intervertebral attainment rate over 10 degrees of corresponding global rotation

Section and Topic	Item #		On page #
Title/ Abstract/ Keywords	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	Chapter 7 p129
Introduction	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	Research question p132
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	Study population, Sample size calculation and Justification of inclusion/exclusion criteria p53
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	Recruitment strategy p56
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	Study population p53 Recruitment strategy p56 Research design p45
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	Research design p45
Test methods	7	The reference standard and its rationale.	Initial intervertebral attainment rate values (continuous data)
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	Procedure p59 Literature review p130
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	Initial intervertebral attainment rates are continuous data and the cut offs were automatically determined from the RoC curve by the statistical software. The reference limits created in this study were not used for diagnostic accuracy

	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	The CI executed and read the index test (QF). Musculoskeletal (MSK) practitioners undertook the reference standard (clinical diagnosis of mechanical CNSLBP)
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	The CI and MSK practitioners were not blind to the condition of the participant. A full clinical history was not taken, but the RMDQ and CPG were entry criteria
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	Chapter 5 p79
	13	Methods for calculating test reproducibility, if done.	Chapter 5 p79
Results			
Participants	14	When study was performed, including beginning and end dates of recruitment.	Methods p102
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	Chapter 4 p73
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	Table 3-3 p57
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	Methods p102
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	Inclusion and exclusion criteria defines this Figure 3-2p55 and Figure 3-3 p56
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference	Not undertaken

		standard; for continuous results, the distribution of the test results by the results of the reference standard.	
	20	Any adverse events from performing the index tests or the reference standard.	No adverse events from QF
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	Table 13-26 p269
	22	How indeterminate results, missing data and outliers of the index tests were handled.	Missing data p70
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	Accuracy has not yet being investigated
	24	Estimates of test reproducibility, if done.	Chapter 5 p79
Discussion	25	Discuss the clinical applicability of the study findings.	Clinical implications p126

Table 13-22 STARD checklist for reporting studies of diagnostic accuracy for attainment rate

Shapiro Wilkes test for non-normality				
	Direction	L2/3	L3/4	L4/5
Healthy volunteers	Left	0.02	0.004	0.19
	Right	0.01	0.53	0.92
	Flex	0.59	0.66	0.69
	Ext	0.99	0.97	0.10
Patients	Left	0.09	0.14	0.17
	Right	0.14	0.72	0.34
	Flex	0.06	0.40	0.75
	Ext	0.00	0.79	0.11

Table 13-23 Normality of data for attainment rate (p values)

Levine's test for equal variances (p values)			
	L2/3	L3/4	L4/5
Left	0.98	0.14	0.43
Right	0.98	0.05	0.01
Flex	0.91	0.37	0.30
Ext	0.67	0.22	0.02

Table 13-24 Equality of variance for attainment rate

*if $P < 0.05$ then the sample is unlikely to be from a normal distribution

		Patients n=40				Healthy volunteers n = 40				2 tailed t test*
		Min	Max	Mean	SD	Min	Max	Mean	SD	P =
Left	L2/3*	0.079	0.404	0.215	0.076	0.101	0.425	0.196	0.073	0.29
	L3/4*	0.001	0.445	0.262	0.101	0.109	0.540	0.248	0.077	0.12
	L4/5	0.000	0.462	0.176	0.115	0.091	0.533	0.249	0.097	0.003
Right	L2/3*	0.079	0.362	0.196	0.066	0.090	0.371	0.175	0.064	0.14
	L3/4	0.013	0.471	0.254	0.010	0.097	0.359	0.227	0.066	0.16
	L4/5*	0.000	0.575	0.208	0.126	0.068	0.395	0.244	0.076	0.09
Flex	L2/3	0.000	0.317	0.117	0.068	0.000	0.278	0.115	0.062	0.90
	L3/4	0.000	0.378	0.158	0.081	0.032	0.286	0.159	0.063	0.92
	L4/5	0.000	0.391	0.215	0.095	0.056	0.393	0.198	0.081	0.40
Ext	L2/3*	0.000	0.403	0.135	0.076	0.000	0.282	0.135	0.063	0.56
	L3/4	0.000	0.302	0.140	0.059	0.021	0.335	0.162	0.069	0.15
	L4/5*	0.000	0.435	0.166	0.101	0.049	0.375	0.165	0.074	0.96

Table 13-25 Descriptive data for initial segmental attainment rate; statistical significance of differences in means between groups

(* Mann Whitney U test)

Direction and level		sensitivity (95% C.I.)	specificity (95% C.I.)	AUC (Wilcoxon estimate)
Left	L2/3	0.825 (0.672 to 0.927)	0.375 (0.228 to 0.542)	0.569
	L3/4	0.550 (0.385 to 0.707)	0.700 (0.535 to 0.834)	0.602
	L4/5	0.750 (0.588 to 0.873)	0.600 (0.433 to 0.751)	0.683
Right	L2/3	0.825 (0.672 to 0.927)	0.425 (0.27 to 0.591)	0.597
	L3/4	0.425 (0.27 to 0.591)	0.800 (0.644 to 0.909)	0.604
	L4/5	0.300 (0.166 to 0.465)	0.950 (0.83 to 0.994)	0.609
Flex.	L2/3	0.775 (0.615 to 0.892)	0.375(0.227 to 0.542)	0.516
	L3/4	0.725 (0.561 to 0.854)	0.450(0.293 to 0.615))	0.528
	L4/5	0.325 (0.186 to 0.413)	0.850 (0.702 to 0.943)	0.558
Ext.	L2/3	0.600 (0.434 to 0.751)	0.625 (0.458 to 0.773)	0.538
	L3/4	0.600 (0.434 to 0.751)	0.650 (0.483 to 0.793)	0.603
	L4/5	0.350(0.206 to 0.517))	0.825 (0.672 to 0.927)	0.503

Table 13-26 Initial segmental attainment rate. Sensitivity, specificity and area under the curve (AUC)
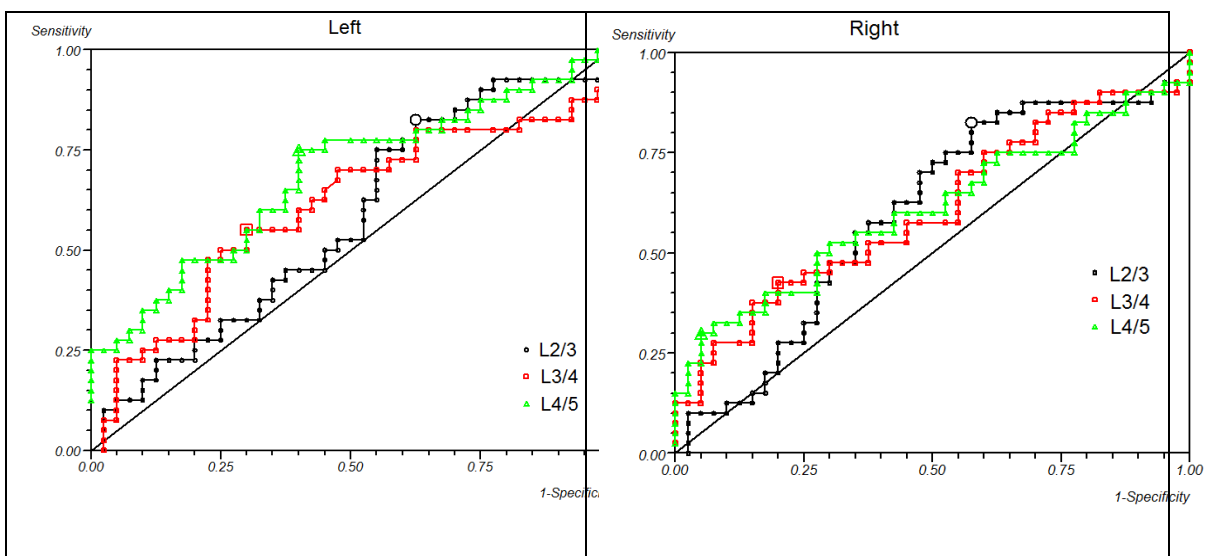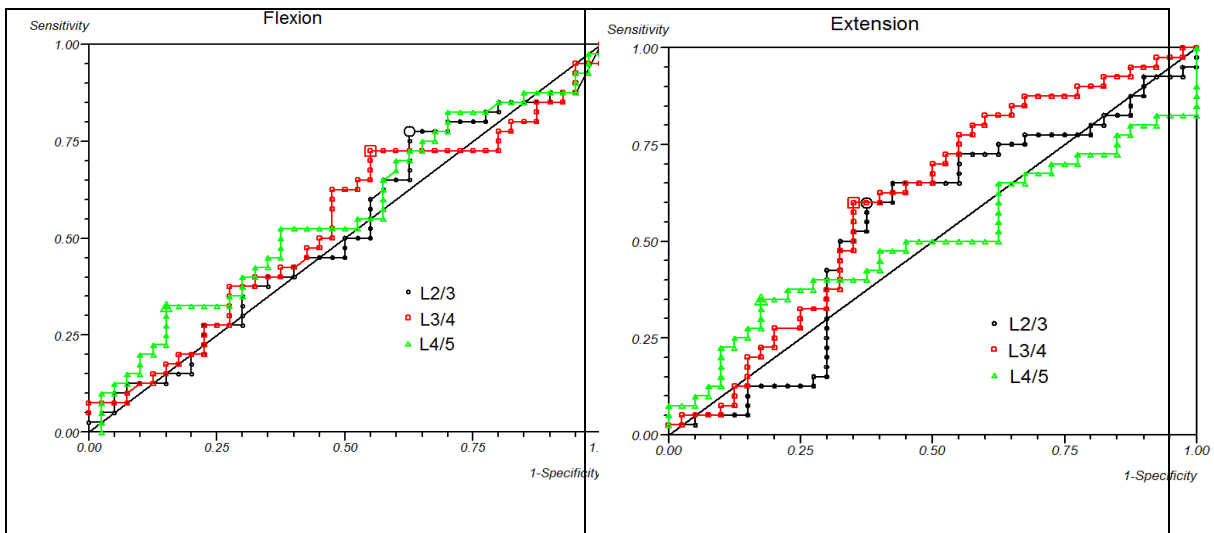
Figure 13-10 Initial segmental attainment rate; receiver operator curves for each level and direction.

Total number of participants with attainment rate values above the upper reference limit per segment		patients	healthy volunteers	Fisher's Exact 2 sided (by summation) p=
left	L2/3	1	2	>0.99
	L3/4	4	1	0.36
	L4/5	5	1	0.20
right	L2/3	3	0	0.24
	L3/4	2	2	-
	L4/5	2	1	>0.99
flexion	L2/3	3	1	0.62
	L3/4	2	1	>0.99
	L4/5	1	1	-
extension	L2/3	4	2	0.68
	L3/4	0	1	>0.99
	L4/5	1	0	>0.99

Table 13-27 Initial intervertebral attainment rate; statistical significance of the differences in proportions that exceed the upper reference limit per segment

Total number of participants with attainment rate values above the upper reference limit				
		patients	healthy volunteers	Fisher's Exact 2 sided by summation (p=0.05)
left	L2/3	7	4	0.52
	L3/4	14	9	0.32
	L4/5	3	4	>0.99
right	L2/3	0	0	-
	L3/4	4	0	0.12
	L4/5	3	1	0.62

Table 13-28 Attainment rate; exceeding upper reference limits from Mellor et al (2009) in the coronal plane

A

ppendices for Chapter 8 Reference limits for continuous intervertebral rotation

Table angle (⁰)	Shapiro-Wilk							
	Statistic	df	Sig.		Table angle	Statistic	df	Sig.
0.10	.853	38	.000		3.20	.873	38	.000
0.20	.911	38	.005		3.30	.874	38	.001
0.30	.924	38	.013		3.4	.885	38	.001
0.4	.913	38	.006		3.50	.872	38	.000
0.50	.896	38	.002		3.60	.872	38	.000
0.60	.880	38	.001		3.70	.884	38	.001
0.70	.849	38	.000		3.80	.884	38	.001
0.80	.836	38	.000		3.90	.884	38	.001
0.90	.855	38	.000		4	.880	38	.001
1	.843	38	.000		4.10	.875	38	.001
1.10	.855	38	.000		4.20	.887	38	.001
1.20	.852	38	.000		4.30	.876	38	.001
1.30	.866	38	.000		4.4	.890	38	.001
1.4	.860	38	.000		4.50	.889	38	.001
1.50	.874	38	.001		4.60	.892	38	.002
1.60	.874	38	.000		4.70	.886	38	.001
1.70	.878	38	.001		4.80	.886	38	.001
1.80	.856	38	.000		4.90	.898	38	.002
1.90	.865	38	.000		5	.897	38	.002
2	.882	38	.001		5.10	.896	38	.002
2.10	.861	38	.000		5.20	.895	38	.002
2.20	.880	38	.001		5.30	.899	38	.002
2.30	.878	38	.001		5.4	.905	38	.003
2.4	.862	38	.000		5.50	.912	38	.006
2.50	.887	38	.001		5.60	.901	38	.003
2.60	.854	38	.000		5.70	.907	38	.004
2.70	.865	38	.000		5.80	.912	38	.005
2.80	.886	38	.001		5.90	.920	38	.010
2.90	.856	38	.000		6	.903	38	.003
3	.871	38	.000					
3.10	.887	38	.001					

Table 13-29 Test of normality from healthy volunteer data (n=40) for left L4/5 first 6 degrees of table motion
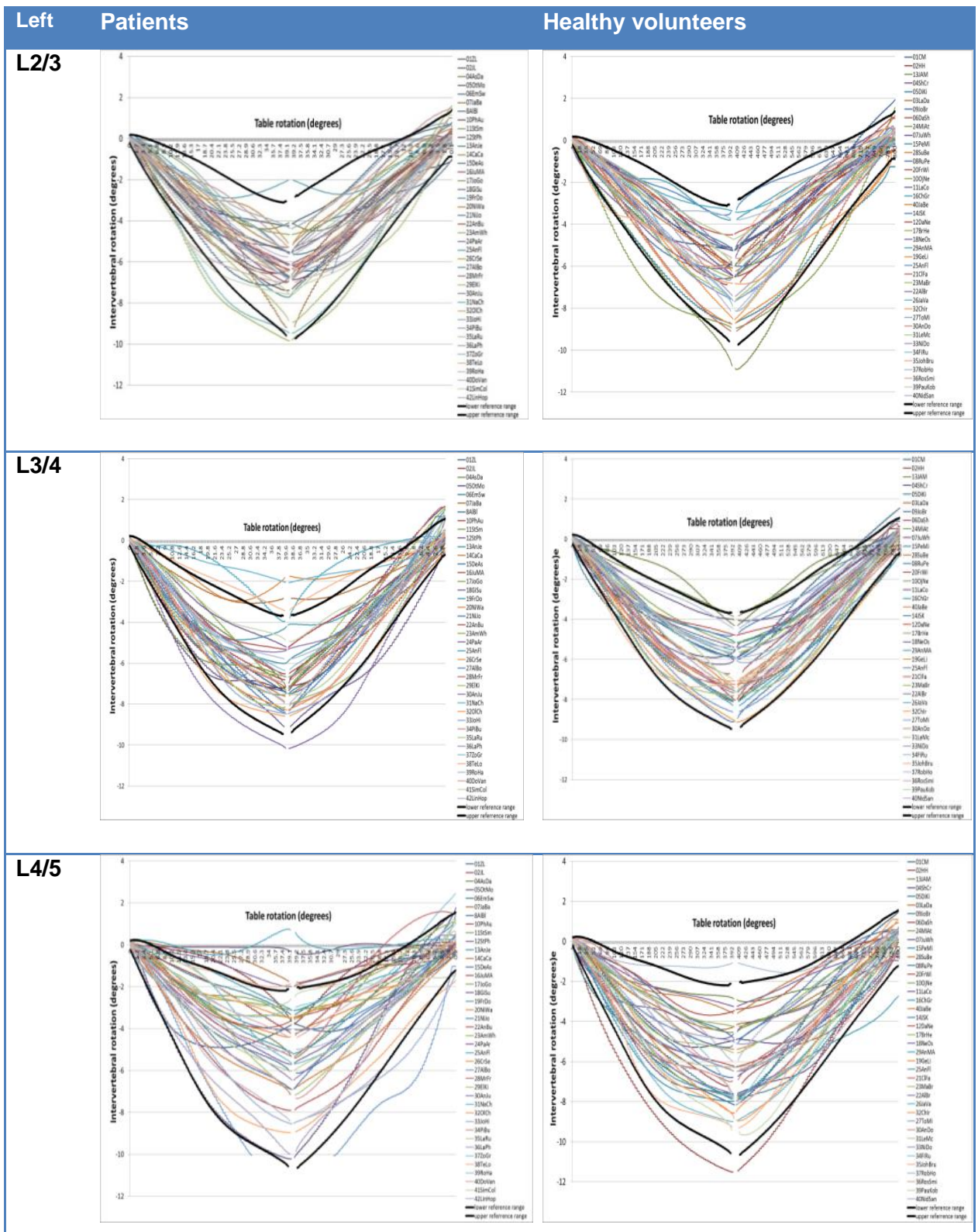
Figure 13-11 Continuous intervertebral motion patterns and reference intervals (black lines) – left
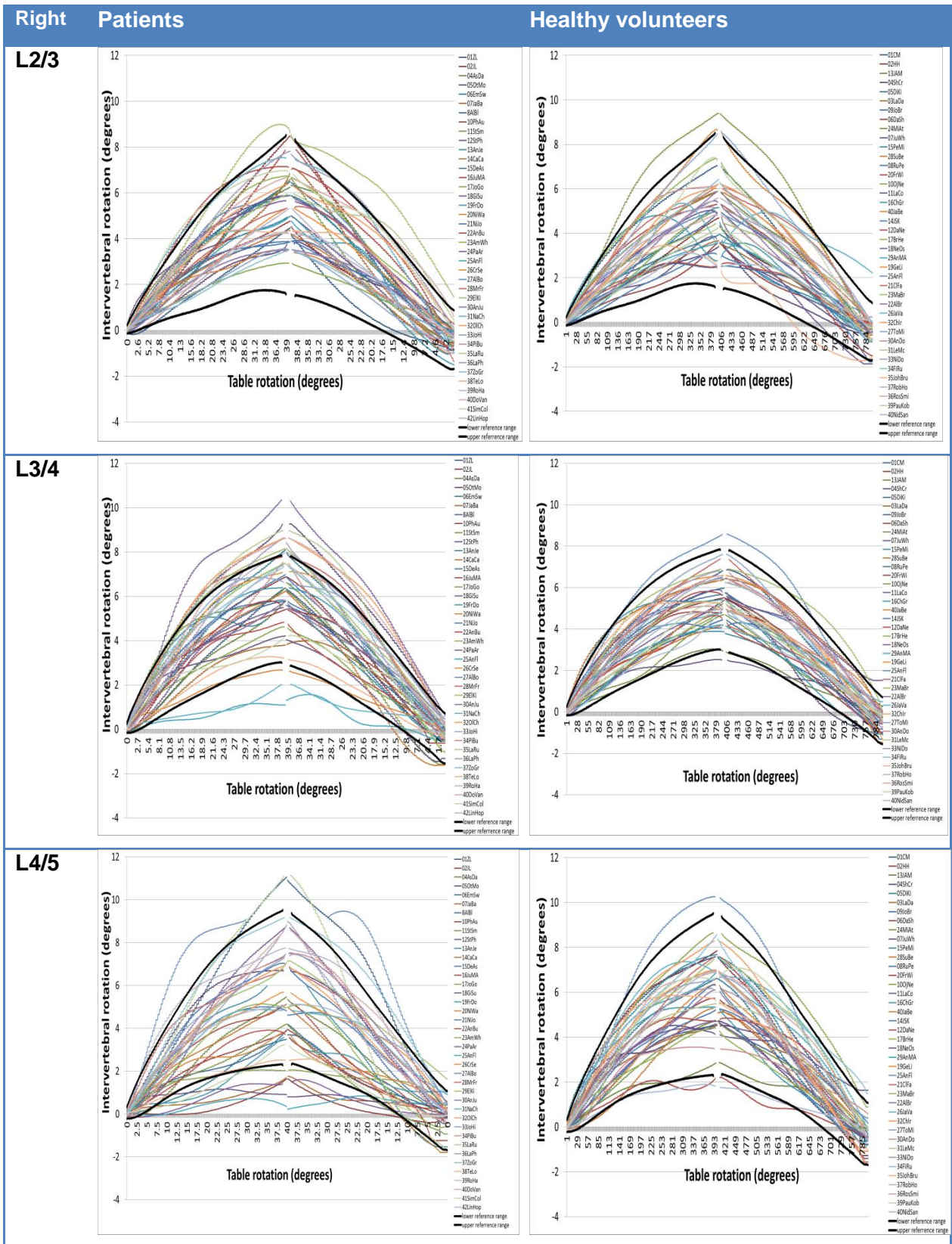
Figure 13-12 Continuous intervertebral motion patterns and reference intervals (black lines) – right
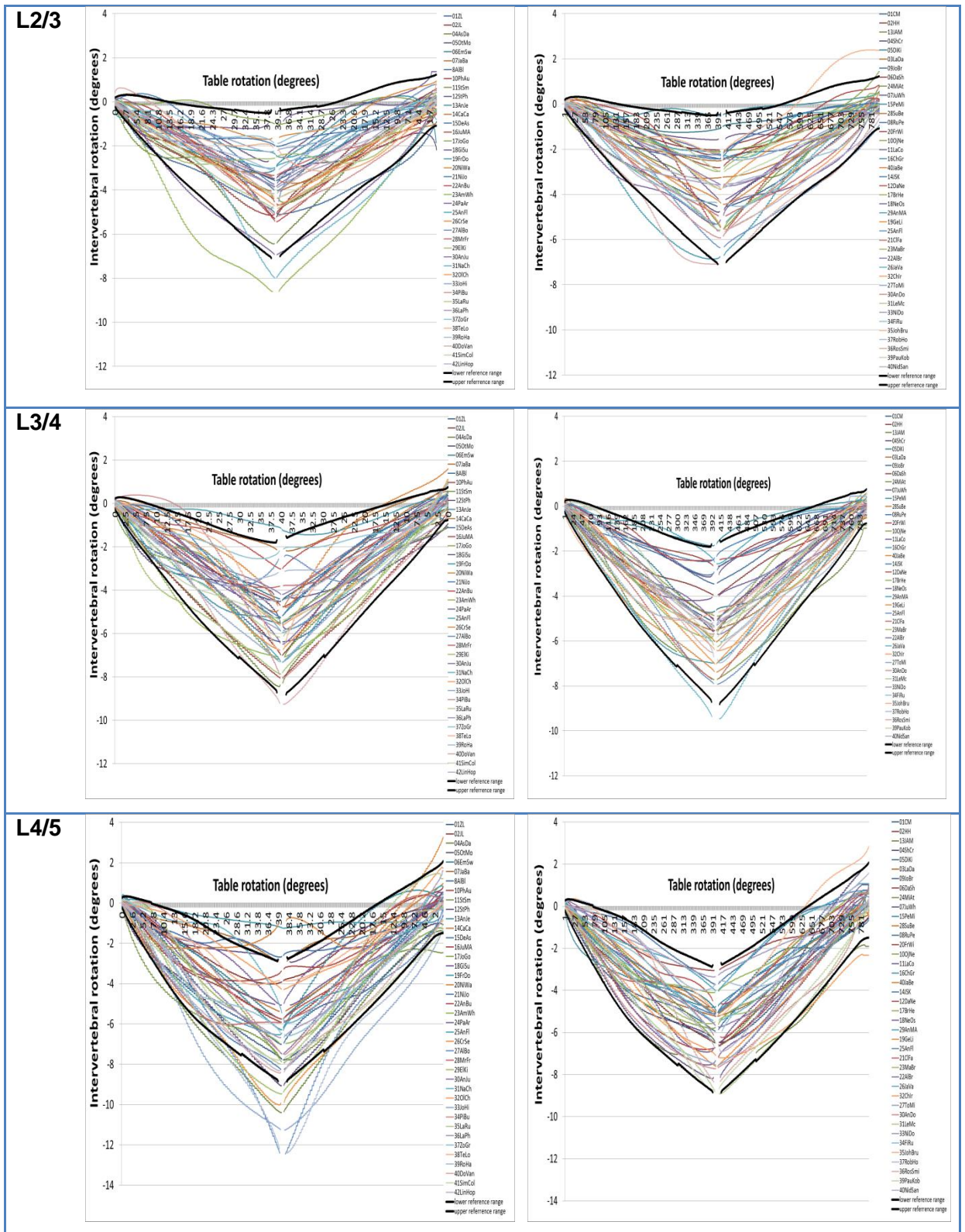
Figure 13-13 Continuous intervertebral motion patterns and reference intervals (black lines) – flexion

Ext	Patients	Healthy volunteers

L2/3

L3/4

L4/5
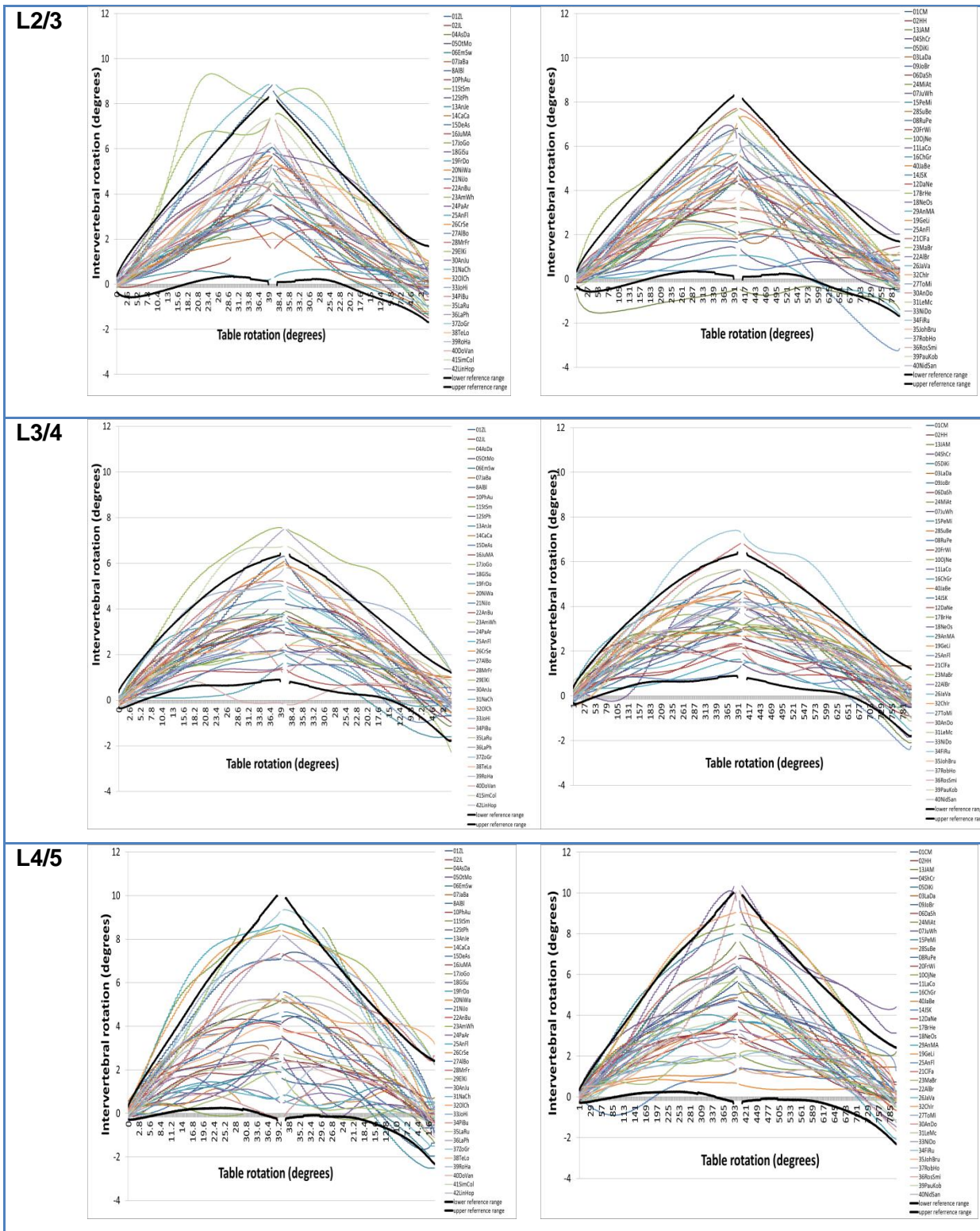
Figure 13-14 Continuous intervertebral motion patterns and reference intervals (black lines) – extension

		Total number of intervertebral levels above the reference interval			Total number of intervertebral levels below the reference interval		
		patients	healthy volunteers	Fisher's Exact 2 sided (by summation) p=	patients	healthy volunteers	Fisher's Exact 2 sided (by summation) p=
Left	L2/3	8	8	-	6	3	0.48
	L3/4	9	1	0.01	13	3	0.01
	L4/5	7	5	0.76	11	1	0.003
Left L2 to L5		17	11	0.24	21	7	0.001
Right	L2/3	8	6	0.77	3	3	-
	L3/4	13	6	0.11	8	4	0.35
	L4/5	6	7	>0.99	14	3	0.01
Right L2 to L5		18	14	0.49	17	10	0.15
Flex	L2/3	7	5	0.76	6	4	0.73
	L3/4	8	4	0.35	10	3	0.07
	L4/5	9	3	0.05	8	3	0.19
Flex L2 to L5		17	11	0.24	17	8	0.05
Ext	L2/3	5	2	0.43	7	5	0.76
	L3/4	4	4	-	12	7	0.29
	L4/5	12	6	0.18	8	3	0.19
Ext L2 to L5		18	14	0.50	14	9	0.32
Any level or direction		30	29	>0.99	34	24	0.02

Table 13-30 Proportions moving above and below continous motion reference intervals

Total number of intervertebral levels above the reference interval			
Direction and level		Sensitivity (95% C.I.)	Specificity (95% C.I.)
Left	L2/3	0.200 (0.090 to 0.357)	0.800 (0.644 to 0.909)
	L3/4	0.225 (0.868 to 0.994)	0.975 (0.868 to 0.999)
	L4/5	0.175 (0.073 to 0.328)	0.875 (0.732 to 0.958)
L2 to L5		0.425 (0.270 to 0.591)	0.725 (0.561 to 0.851)
Right	L2/3	0.200 (0.090 to 0.357)	0.850 (0.702 to 0.943)
	L3/4	0.325 (0.186 to 0.491)	0.850 (0.702 to 0.943)
	L4/5	0.150 (0.056 to 0.298)	0.825 (0.672 to 0.927)
L2 to L5		0.450 (0.296 to 0.615)	0.650 (0.482 to 0.794)
Flex.	L2/3	0.175 (0.073 to 0.328)	0.875 (0.732 to 0.958)
	L3/4	0.200 (0.090 to 0.356)	0.900 (0.763 to 0.972)
	L4/5	0.225 (0.108 to 0.385)	0.925 (0.796 to 0.984)
L2 to L5		0.425 (0.270 to 0.591)	0.725 (0.561 to 0.851)
Ext.	L2/3	0.125 (0.419 to 0.268)	0.950 (0.831 to 0.994)
	L3/4	0.100 (0.028 to 0.237)	0.900 (0.763 to 0.972)
	L4/5	0.300 (0.166 to 0.465)	0.850 (0.702 to 0.943)
L2 to L5		0.45 (0.483 to0.615)	0.650 (0.483 to 0.794)
All levels and directions combined		0.750 (0.588 to 0.873)	0.275 (0.146 to 0.439)

Table 13-31 Sensitivity and specificity of cIVR upper reference limits for hyper mobility

Total number of intervertebral levels below the reference interval			
Direction and level		Sensitivity (95% C.I.)	Specificity (95% C.I.)
Left	L2/3	0.150 (0.057 to 0.298)	0.925 (0.796 to 0.984)
	L3/4	0.325 (0.186 to 0.491)	0.925 (0.796 to 0.984)
	L4/5	0.275 (0.146 to 0.439)	0.975 (0.868 to 0.994)
L2 to L5		0.525 (0.361 to 0.649)	0.825 (0.672 to 0.927)
Right	L2/3	0.075 (0.016 to 0.204)	0.925 (0.796 to 0.984)
	L3/4	0.200 (0.091 to 0.972)	0.900 (0.763 to 0.972)
	L4/5	0.350 (0.206 to 0.517)	0.925 (0.796 to 0.984)
L2 to L5		0.425 (0.270 to 0.591)	0.750 (0.588 to 0.873)
Flex.	L2/3	0.150 (0.057 to 0.299)	0.900 (0.763 to 0.972)
	L3/4	0.250 (0.127 to 0.412)	0.925 (0.796 to 0.984)
	L4/5	0.200 (0.091 to 0.357)	0.925 (0.796 to 0.984)
L2 to L5		0.425 (0.270 to 0.591)	0.800 (0.641 to 0.910)
Ext.	L2/3	0.175 (0.073 to 0.328)	0.875 (0.732 to 0.958)
	L3/4	0.300 (0.166 to 0.465)	0.825 (0.672 to 0.927)
	L4/5	0.200 (0.091 to 0.357)	0.925 (0.796 to 0.984)
L2 to L5		0.35 (0.206 to 0.517)	0.775 (0.615 to 0.892)
All levels and directions combined		0.85 (0.702 to 0.943)	0.400 (249 to 0.567)

Table 13-32 Sensitivity and specificity of cIVR lower reference limits for hypo mobility

Appendices for Chapter 9 Proportional lumbar spine intervertebral motion patterns

ORIGINAL ARTICLE

Proportional lumbar spine inter-vertebral motion patterns: a comparison of patients with chronic, non-specific low back pain and healthy controls

Fiona E. Mellor · Peter W. Thomas · Paul Thompson · Alan C. Breen

Abstract

Introduction Identifying biomechanical subgroups in chronic, non-specific low back pain (CNSLBP) populations from inter-vertebral displacements has proven elusive. Quantitative fluoroscopy (QF) has excellent repeatability and provides continuous standardised inter-vertebral kinematic data from fluoroscopic sequences allowing assessment of mid-range motion. The aim of this study was to determine whether proportional continuous IV rotational patterns were different in patients and controls. A secondary aim was to update the repeatability of QF measurement of range of motion (RoM) for inter-vertebral (IV) rotation.

Methods and Materials Fluoroscopic sequences were recorded of passive, recumbent coronal and sagittal motion, which was controlled for range and velocity. Segments L2–5 in 40 primary care CNSLBP patients and 40 matched controls were compared. Patients also completed the von Korff Chronic Pain Grade and Roland and Morris Disability Questionnaire. Sequences were processed using automated image tracking algorithms to extract continuous inter-vertebral rotation data. These were converted to continuous proportional ranges of rotation (PR). The continuous proportional range variances were calculated for each direction and combined to produce a single variable representing their fluctuation (CPRV). Inter- and intra-rater repeatability were also calculated for the maximum IV-RoM measurements obtained during controlled trunk motion to provide an updated indication of the reliability and agreement of QF for measuring spine kinematics.

Results CPRV was significantly higher in patients (0.011 vs. 0.008, Mann–Whitney two-sided $p = 0.008$), implying a mechanical subgroup. Receiver operating characteristic curve analysis found its sensitivity and specificity to be 0.78 % (60–90) and 0.55 % (37–73), respectively (area under the curve 0.672). CPRV was not correlated with pain severity or disability. The repeatability of maximum inter-vertebral range was excellent, but range was only significantly greater in patients at L4–5 in right side bending ($p = 0.03$).

Conclusion The variation in proportional motion between lumbar vertebrae during passive recumbent trunk motion was greater in patients with CNSLBP than in matched healthy controls, indicating that biomechanical factors in passive structures play a part.

Keywords Spine kinematics · Subgroups · Movement disorders · Repeatability · Reliability · Agreement

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Background

Low back pain makes a large contribution to the burden of disability worldwide, but its pathophysiology in most sufferers is poorly understood [1]. Despite sub-classification into serious spinal pathology, nerve root pain and non-specific low back pain, the majority of cases are in the

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284

latter category and defy classification [2]. The theoretical framework provided by the bio-psychosocial model [3] has so far focussed mainly on psychosocial components, but individual psychosocial factors are not strong determinants of who will experience first-time low back pain [4, 5], chronic disabling low back pain in the future [6], or poor outcomes from recent episodes [7].

There is a need to further study the biomechanics of the lumbar spine, but information on the mid-range is not possible from flexion extension radiographs (functional radiography) despite their widespread use in research and clinical practice [8]. Additionally, it is difficult to discriminate between normal and abnormal motion in living people from these due to large differences in techniques and large biological variation [9]. Fluoroscopy can reveal both end and mid-range motion and marked improvements are seen in precision when the measurements are automated [10].

Spinal motion underlies the rationales for many commonly used therapies, however motion-based classification systems seem to be largely a matter of professional preference. Objective evidence of patient subgroups remains elusive [11] and there remains a requirement to define the best methods of measuring spinal motion [12].

Some recent cross-sectional comparisons of chronic, non-specific low back pain (CNSLBP) patients and controls using flexion–extension radiographs have reported good inter-rater reliability and have shown restricted sagittal rotation to be associated with recurrent or chronic low back pain [13]. However, these have been undertaken during uncontrolled, weight-bearing maximum trunk bending and are subject to high intra subject variation [14].

Other two-dimensional motion studies have expressed inter-vertebral rotation as the proportional contributions of individual inter-vertebral levels to total lumbar or cervical spine motion [15, 16] allowing comparisons without contamination from inter-subject variation. Proportional motion, for example in three adjacent segments, is expressed as

$$\text{Contribution } Lx = \frac{Lx}{Lx + Ly + Lz}$$

(Lx, Ly, Lz: contributions to motion of adjacent segments.)

Abbott et al. [15] found that when expressed as a proportion of the sum of the ranges of the segments under consideration, the prevalence of lumbar motion segments in patients exceeding reference intervals derived from healthy controls became highly significant, more so than when only comparing maximum rotation. However, this was an end of range study, which does not provide sufficient information to assess for functional instability, defined as "the loss of the spine's ability to maintain its pattern of displacement under normal physiological loads" [17].

Quantitative fluoroscopy (QF) provides continuous inter-vertebral motion data and reduces intra subject variations as participants are guided to the same range at the same velocity [18]. QF allows kinematic measurements to be extracted from weight-bearing (active) and non-weight-bearing (passive) motion in both the coronal and sagittal planes [19–22] and kinematic outputs have included inter-vertebral rotations and translations [15], attainment rates [20] and centres of rotation [19, 23]. However, no QF study has used continuous proportional motion data for the comparison of patients and controls.

This study aims to determine whether continuous proportional motion patterns from passive, uni-planar lumbar spine motion can distinguish between patients with CNSLBP and healthy controls. A new way of measuring this is proposed, using the variances of the proportional ranges between levels [proportional range variance (PRV)] for each direction, and their sums [combined proportional range variance (CPRV)] (Fig. 1). The study also sought to update the repeatability of maximum rotational range values to reflect the decreasing errors associated with improvements in the QF technique [18].

Objectives

The objectives of this study were

1. To determine whether the variations in proportional ranges across motion sequences are significantly different between patients and controls.
2. To calculate the sensitivity and specificity of the PRV and CPRV values to discriminate patients from controls.
3. To update the observer agreement and reliability (SEM and ICC) of maximum IV-rotational measurements in passive recumbent motion measured with QF.
4. To determine whether there are relationships between CPRV and pain or disability.

Methods

This was a cross-sectional, prospective observational study of passive controlled motion in the lumbar spine.

Participants

A convenience sample of 40 patients aged between 21 and 50 years presenting to primary care (either chiropractic or outpatient physiotherapy) for CNSLBP was recruited. The age range was kept above 20 and below 51 in an attempt to minimise the influence of age on motion Wong et al. [22]. Forty pain-free healthy volunteers matched for gender, age and body-mass index (BMI) formed a control group. The eligibility criteria for the study are shown in Table 1.
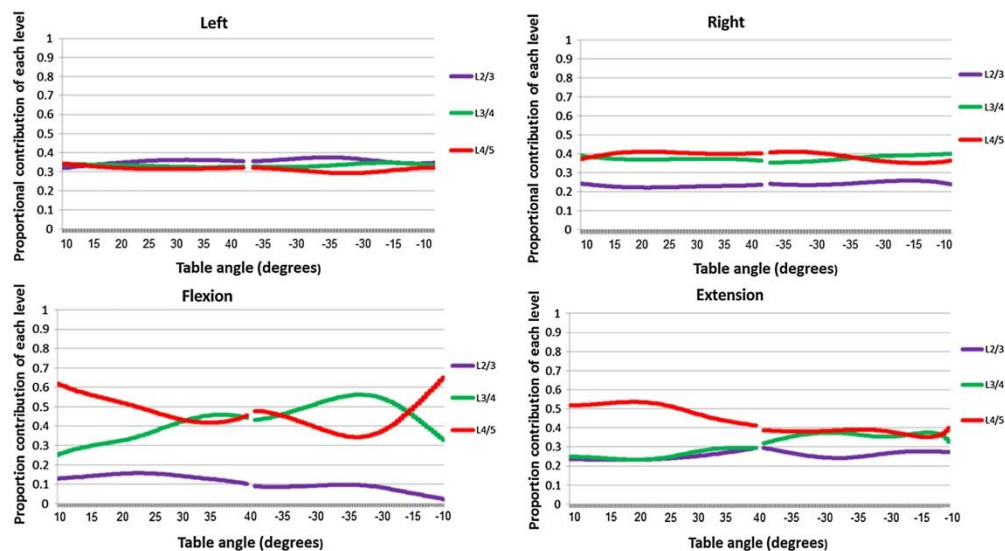
Fig. 1 Examples of mid-range patterns of L2–5 proportional inter-vertebral rotation in left, right, flexion and extension motion

Table 1 Inclusion and exclusion criteria

All participants	Inclusion criteria: male and female. Age 21–51 years (Wong et al. [22]). Able to understand written information. Willing to participate and able to freely give informed consent. Menstruation within last 28 days, or evidence of contraceptive use, or sterility (for females only). Consent to GP being informed of inclusion in study. Able to tolerate 80° of side-bending and flexion–extension passive trunk motion
	Exclusion criteria: pregnancy, mental illness, depression, poor understanding of English. Recent abdominal or pelvic surgery. Previous mid-lumbar spinal surgery. Body mass index (BMI) >31. Medical radiation exposure in the past 2 years with a dose of greater than 8 mSv (defined as CT scan of chest, abdomen or pelvis or interventional procedures under radiological control, i.e. angiography). Current involvement in any other research study. Hyper-mobility syndrome
Patients	Inclusion criteria: back pain of >3 m duration. Von Korff chronic pain grade II or higher (Von Korff et al. [25]) aggravated or relieved by movement or position. Positive prone lumbar spinous pressure test between L2 and L5. Score of 4 or greater on the Roland Morris Disability Questionnaire (Roland and Morris [24])
	Exclusion criteria: pathology such as fracture, infection, neoplasm. Spinal stenosis. Spondyolisthesis. Radicular pain. Litigation or compensation pending
Healthy volunteers	Inclusion criteria: no history of low back pain that ceased normal activity for 1 day in previous year. Negative prone lumbar spinous pressure test L2–L5

Patients completed the Roland and Morris Disability Questionnaire (RMDQ) [24] and the von Korff Chronic Pain Grade [25]. Ethical approval was gained from the UK National Research Ethics Service (Southampton A 09/HO5O2/99) and informed consent was taken by the principal investigator (FM).

Sample size

A sensitivity of 80 % and a specificity of 90 % might be thought of as desirable for identifying biomechanical abnormalities in patients and controls. An observed sensitivity of 80 % with a sample size of 40 would have a lower 95 % confidence limit of 65 % and a specificity of 90 % would have a lower 95 % confidence limit of 77 %. Further, based on the assumption from previous pilot studies that the prevalence of mechanical abnormality in patients and controls might be around 60 and 20 %, respectively, 40 per group would give the study over 90 % power to detect a difference of this magnitude using a 5 % level of significance.

Image acquisition and analysis

The study utilised recumbent passive motion as described in other studies [10, 26]. The table moved the lower trunk to a range of 40° and back over a period of approximately

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286

12 s in each direction (left, right, flexion and extension). Only L2–5 levels were imaged to minimise image registration failures at S1 due to superimposition of the iliac crests.

Participants first lay supine on a bespoke motion table (Atlas Clinical Ltd.) with L3/4 at its fulcrum and the lumbar lordosis flattened by a cushion supporting the knees. Left and right sequences were undertaken separately. Participants then turned onto a left lateral decubitus position and the procedure was repeated for flexion and extension (see Online Resources videos 1 & 2).

A mobile Siemens Arcadis Avantic (VC10A) image intensifier was positioned with its central ray aligned through L3–4 and fluoroscopy at 15 Hz was synchronised with the table motion. Exposure factors were determined by the automatic exposure device (AED) and ranged from 60 to 120 kVp/26.6 to 63.1 mA. Dose was recorded with a dose area product meter and converted to mSv using Monte Carlo simulation software (PCXMC) using the latest tissue weighting factors (ICRP 2007) and an assumed constant field size of 30 cm × 30 cm.

The fluoroscopic sequences were transferred to a desktop computer and Image J (v 1.47 for Windows OS) was used to separate the individual images from the digital sequences. The images underwent user defined edge enhancement, after which templates were manually placed five times around each vertebral body (L2–L5) in the first image. Two trained observers undertook this process on a subset of 10 randomly selected participants to allow calculation of the repeatability of this process. Bespoke software written in Matlab (V R2007b, The Mathworks Inc.) used a cross-correlation method to obtain automated frame to frame image tracking of the vertebral bodies in subsequent images. Co-ordinates were placed on the vertebral body corners in the first image, linked to the tracking templates and used to register the vertebrae in two-dimensional space in each frame. Tracking was verified for

quality assurance by viewing all sequences and repeating any tracking that failed (see Online Resource video 3), Averaged inter-vertebral angles from the five trackings throughout the motion were calculated using the Distortion Compensated Roentgen Analysis method [27]. Previous studies using this method found that translation and up to 10° of out of plane rotation did not materially influence the accuracy of inter-vertebral angle measurement [26]. All patients were recruited and their data acquired, anonymised and analysed by FM.

Repeatability

Table motion was controlled for range. The maximum inter-vertebral range of motion (RoM) for L2–3, L3–4 and L4–5 achieved at any point throughout the 40° range of the table was calculated as the highest y-value per inter-vertebral level (Fig. 2). Observers manually identified the maximum and minimum points of the continuous inter-vertebral motion pattern. Both intra- and inter-observer repeatability were assessed using intraclass correlations (ICC$_{agreement}$ 2, 1) [28] and the standard error of measurement (SEM$_{agreement}$) [29].

Statistical analysis

Continuous rotations were converted to proportional contributions for each inter-vertebral level ($n = 3$) per direction ($n = 4$) (Fig. 1) (see Online Resource 4 for further examples of continuous proportional motion per level and direction). Low overall L2–5 rotation at the initial and final 10° of table motion meant that proportional values were only calculated for the middle 80 %.

To obtain a numerical expression of the fluctuations of the proportional patterns, the range between the maximum and minimum contribution at each frame was calculated (regardless of which inter-vertebral level contributed to the

Fig. 2 Determination of maximum rotational IV-RoM three adjacent levels in extension. Patterns of continuous raw inter-vertebral rotation range (Y-axis) against motion table angle (X-axis) at three adjacent levels in extension showing maximum ranges. Note that the maxima occur at different points in the motion
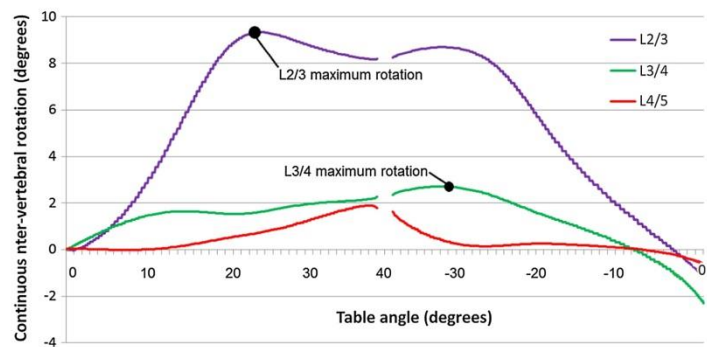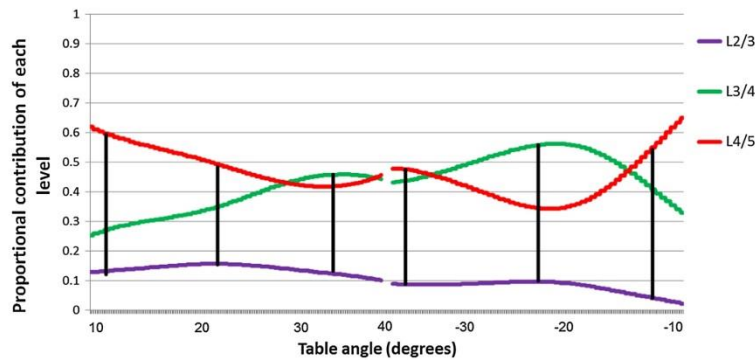
Fig. 3 Measurement of variability of proportional inter-vertebral ranges. Patterns of proportional inter-vertebral rotation from a patient who is flexing passively. The range was calculated for each data point (X-axis) to obtain the variance for that direction (*black lines*). Proportional range variances (*PRV*) for each direction were summed to give the combined proportional range variance (*CPRV*). (CPRV = PRV flexion + PRV extension + PRV left + PRV right)

Table 2 Participant demographics

Variable	Mean (SD)	
	Patients	Controls
N	40	40
Age	35.9 (8.6) (range 21–50)	35.7 (8.4) (range 21–50)
Gender (% M)	55 % (n = 22)	55 % (n = 22)
BMI	24.5 (2.6) (range 19.8–29.3)	24.5 (2.8) (range 19.5–31.5)
Average 6-month intensity (von Korff)/10	5.9 (1.73) (range 3–10)	–
Worst possible pain in the past 6 months (von Korff)/10	8.3 (1.22) (range 5–10)	–
Current pain intensity (von Korff)/10	4.1 (2.05) (range 0–8)	–
Disability (RMDQ)/24	7.8 (4.1) (range 4–19)	–

range). The variance of these ranges was computed and expressed as PRV (Fig. 3). This was used to measure the fluctuations in the proportional contributions between the three levels. The PRVs for all four directions were tested for co-dependency and then summed to obtain a CPRV for each participant.

Statistical analysis of the maximum RoM utilised Stats Direct (V2.7.8) and SPSS (V21 IBM software) to calculate ICC and SEM. Additionally, to find out if the maximum range for any level or direction was different in patients and controls undergoing controlled passive motion, two-way unpaired t tests were used. As the PRV and CPRV data were not normally distributed, their distributions were compared using a two-tailed Mann–Whitney *U*-test. The sensitivity and specificity of the PRVs and CPRV to discriminate cohorts was then determined by receiver operating characteristic (ROC) curve analysis (extended trapezoidal rule method). CPRV was correlated to pain and disability in the patient group.

Results

Participants

Forty-two consenting patients with a diagnosis of chronic non-specific mechanical low back pain were recruited: five were from private chiropractic clinics, one from an outpatient physiotherapy department and 34 from a chiropractic college teaching clinic. Two patients underwent fluoroscopy but had unusable data due to poor image quality. One hundred and forty-six healthy volunteers agreed to submit their personal details to a database. Forty of these were matched for gender, age and BMI.

The mean effective radiation dose for all participants was 0.561 mSv (SD 0.154). Participant demographics are described in Table 2 and the maximum inter-vertebral rotations (SD) achieved from the controlled passive protocol in Table 3. The only significant difference between patients and controls was for maximum IV-RoM in L4/5 left side bending.

Table 3 Maximum IV rotations for patients and controls

Direction and inter-vertebral level	Maximum rotational value (°) mean (SD) patients	Maximum rotational value (°) Mean (SD) controls	$p*$
Left L2/3	6.74 (1.53)	6.80 (1.74)	0.87
Left L3/4	7.13 (2.00)	6.92 (1.51)	0.59
Left L4/5	5.62 (2.63)	6.82 (2.19)	0.03
Right L2/3	5.94 (1.48)	5.72 (1.59)	0.52
Right L3/4	6.68 (2.01)	5.96 (1.32)	0.06
Right L4/5	5.81 (2.80)	6.44 (1.92)	0.25
Flex L2/3	4.23 (1.56)	4.05 (1.54)	0.61
Flex L3/4	5.89 (1.70)	5.49 (1.75)	0.30
Flex L4/5	7.10 (2.46)	6.46 (1.51)	0.17
Ext L2/3	5.04 (1.98)	4.64 (1.90)	0.36
Ext L3/4	4.15 (1.67)	4.11 (1.53)	0.92
Ext L4/5	4.78 (2.43)	5.31 (2.37)	0.32

* Students t test

Repeatability

Inter- and intra-observer reliability and agreement for maximum rotations were high (Table 4). The highest ICC was for right intra observer at L4/5 (ICC = 0.998, 95 % CI 0.992–0.999) and the lowest SEM was 0.081 for right intra observer at L2/3. The lowest ICC was for inter-observer extension at L3/4 (ICC = 0.737, 95 % CI 0.228–0.928) and the highest SEM was for inter-observer extension at L2/3 (SEM = 0.772). Repeatability was excellent for

levels and directions combined, the mean inter- and intra-observer ICCs being 0.956 (95 % CI 0.837–0.989) and 0.990 (0.981–0.999) and the SEM's 0.15° and 0.07°, respectively.

Variance in ranges between proportional motion patterns

The sensitivity and specificity of PRVs and the CPRV for patients are shown in Table 5. There were no significant differences in PRVs, but the median CPRV value for patients (0.011) was significantly higher than for controls (0.008) ($p = 0.008$, two-sided Mann–Whitney).

The number of patients and controls whose CPRV levels fell above the ROC analysis cut-off value in patients and controls were 31/40 (78 %) and 18/40 (45 %), respectively (Yates-corrected $\chi^2 = 7.584$, $p = 0.006$). The sensitivity and specificity of CPRV for discriminating patients from controls were 0.775 (0.615–0.891) and 0.550 (0.385–0.707). This indicates the possibility of a biomechanical subgroup within the patient population.

Correlation of CPRV with patient characteristics

There were no significant correlations (Kendall's tau) between CPRV and the patient characteristics: age ($t = 0.215$, $p = 0.0056$), BMI ($t = 0.046$, $p = 0.683$), gender (Fisher exact, two-sided $p = 0.901$), disability scores (RMDQ) ($t = 0.155$, $p = 0.181$) and three

Table 4 Inter- and intra-observer reliability (ICCs 2, 1 absolute) and agreement (SEM agreement) for maximum RoM for each level and direction ($n = 10$ per direction)

	Inter-observer			Intra-observer		
	L2/3	L3/4	L4/5	L2/3	L3/4	L4/5
Left						
SEM (°)	0.459	0.276	0.261	0.172	0.158	0.147
ICC	0.862	0.971	0.990	0.987	0.993	0.997
95 % CI	(0.561–0.963)	(0.895–0.993)	(0.960–0.997)	(0.949–0.997)	(0.971–0.998)	(0.989–0.999)
Right						
SEM (°)	0.553	0.176	0.197	0.081	0.106	0.123
ICC	0.853	0.971	0.992	0.997	0.987	0.998
95 % CI	(0.512–0.961)	(0.892–0.993)	(0.960–0.998)	(0.988–0.999)	(0.945–0.997)	(0.992–0.999)
Flexion						
SEM (°)	0.309	0.165	0.312	0.127	0.125	0.101
ICC	0.912	0.975	0.967	0.975	0.981	0.997
95 % CI	(0.685–0.978)	(0.905–0.994)	(0.877–0.992)	(0.862–0.994)	(0.904–0.996)	(0.987–0.999)
Extension						
SEM (°)	0.772	0.406	0.265	0.347	0.244	0.194
ICC	0.761	0.737	0.988	0.959	0.920	0.993
95 % CI	(0.273–0.935)	(0.228–0.928)	(0.955–0.997)	(0.849–0.990)	(0.719–0.979)	(0.973–0.998)

Table 5 Discrimination between patients and controls by proportional range variance (PRV): sensitivity, specificity and likelihood ratios of PRV for each direction and combined (CPRV) and statistical significance between groups

Variable	Sensitivity	Specificity	AUC	Cutoff	+ve LR	−ve LR	p*
PRV left	0.675 (0.509–0.814)	0.550 (0.385–0.707)	0.579	0.00074	1.500 (1.014–2.297)	0.591 (0.343–0.983)	0.222
PRV right	0.775 (0.615–0.892)	0.500 (0.338–0.662)	0.610	0.00105	1.550 (1.108–2.266)	0.450 (0.231–0.838)	0.090
PRV flexion	0.850 (0.702–0.943)	0.300 (0.166–0.485)	0.568	0.00106	1.214 (0.956–1.591)	0.500 (0.210–1.154)	0.294
PRV extension	0.825 (0.672–0.927)	0.450 (0.293–0.615)	0.623	0.00180	1.500 (1.113–2.118)	0.389 (0.182–0.794)	0.059
Combined (CPRV)[a]	0.775 (0.615–0.892)	0.550 (0.385–0.707)	0.672	0.00865	1.722 (1.203–2.593)	0.409 (0.213–0.749)	0.008

Median CPRV values: patients = 0.011, controls = 0.008 ($p = 0.008$ Mann–Whitney)

* Mann–Whitney, two-sided p

[a] CPRV = PRV left + PRV right + PRV flexion + PRV extension

dimensions from the von Korff Chronic Pain Grade. These were based on ten-point visual analogue scales for current pain intensity ($t = -0.201$, $p = 0.086$), pain intensity over the past 6 months ($t = 0.207$, $p = 0.067$) and worst pain experienced in the past 6 months ($t = -0.045$, $p = 0.706$).

Discussion

Many excellent studies have addressed in vivo spinal kinematic analysis using advanced imaging technologies. Devices such as bi-planar fluoroscopy [30, 31] and upright, kinetic MRI [32–34] have been used to provide 3D information about the relationships between inter-vertebral RoM and structural changes. Such 3-D systems have the added advantage of being able to measure axial rotation as well as rotations and translation in other planes [30]. However, these are mainly research systems whose use is not easily translated into practice and whose results are usually reported as 2-D end-of-range measures. They do not generally analyse continuous motion patterns. QF systems, by contrast, have received US Food and Drug Agency clearance for roles that are traditionally filled by flexion–extension radiographs. They require only motion tables to run with existing hospital C-arm fluoroscopy units to output quantifiable rotation, translation, ICR and attainment rates in two planes and in both active and passive motion. Additionally, the calculated radiation dose is less than standard lumbar spine radiographs [35] which makes it suitable for clinical use.

This study updated the inter- and intra-observer repeatability of maximum inter-vertebral rotation range [26] resulting from improvements in the QF technology and demonstrated a significant difference in maximum rotation between controls and patients for one level and direction only. Additionally, the study used a new measure of combined continuous proportional motion (PRV/CPRV) to compare patients and controls and to determine sensitivity and specificity for mechanical low back pain. The

results suggest that combined variances of proportional patterns in patients were not as regular or evenly proportioned as those in controls, suggesting an association between CPRV and CNSLBP and supporting the conclusions of previous studies [15, 20]. The fact that little difference was found in respect of raw IV-RoM (Table 3), despite standardisation of table range, reflects the variable contributions by the segments from L2–5. In this study, L2–5 absorbed between 35 and 51 % of this motion—a source of extraneous variability that was avoided by calculating proportional motion as recommended by a previous International Forum [18].

Using PRV in continuous sequences and combining them to obtain a summary variable CPRV is a new concept that focuses on fluctuations in motion patterns within and between levels (Fig. 1). This addresses subgrouping in terms of movement dysfunction and may reflect pathoanatomical changes in passive components such as discs and ligaments. Such changes may include scarring, dehydration, glycation, calcification, fissuring and annular tears [11]. However, back pain is unlikely to exist to the exclusion of other biological factors, such as chemical pain stimuli, central sensitisation and abnormal muscle recruitment patterns during active motion.

No significant associations were found between CPRV and the patient characteristics: age, gender, BMI, disability, and pain, which are consistent with Abbott et al. [15]; however, this study examined a primary care population with low levels of pain and disability.

Limitations

The sensitivity and specificity of the CPRV and its AUC supports the existence of a subgroup based on biomechanics, but it is not intended to constitute a diagnostic test. Additionally, proportional ranges cannot be used to determine hyper- or hypo-mobility because they cannot be related back to rotational values.

Finally, our study only analysed patients at the lower end of the pain severity scale. Studies of more disabled patients, such as those with spondylolisthesis, spinal stenosis, instability or electing for, or having had spinal surgery, may show greater differences. Additionally, only rotation was examined; however, the inclusion of other kinematic variables such as translation, instantaneous axis of rotation and attainment rate may also improve discrimination and are suggested for further research in this area. Recording during weight bearing motion would help to give a more complete picture of the relationship between inter-vertebral movement and persistent back pain if the added complexity of loading and muscle contraction can be controlled for.

Conclusion

The variation in proportional motion between lumbar vertebrae during passive, recumbent motion was greater in patients with CNSLPB than in matched healthy controls, indicating that biomechanical factors in passive structures play a part. Additional studies with this method should be useful for improving our understanding of the pathophysiology of non-specific low back pain and the relationship of this to treatment outcomes. These would include replication of the present findings in other participant groups, the incorporation of additional kinematic variables, studies of patient subgroups (e.g. instability, post-surgical disability, etc.) and the possible prediction of future back pain disability, including risk of chronicity and poor outcome.

Conflict of interest None.

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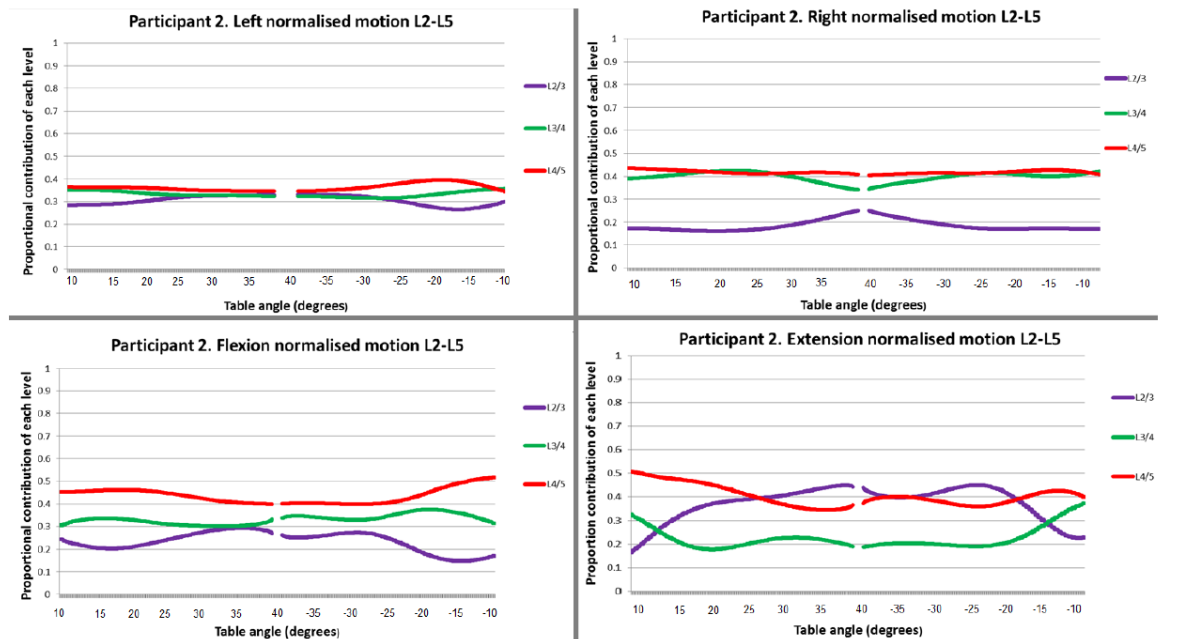19. Ahmadi A, Maroufi N, Behtash H, Zekavat H, Parnianpour M (2009) Kinematic analysis of dynamic lumbar motion in patients with lumbar segmental instability using digital videofluoroscopy. Eur Spine J 18:1677–1685
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Figure 13-15 Mellor et al (2014b)

292

Example 1

Participant 1. Left normalised motion L2-L5

Participant 1. Right normalised motion L2-L5

Participant 1. Flexion normalised motion L2-L5

Participant 1. Extension normalised motion L2-L5

Example 2

Participant 2. Left normalised motion L2-L5

Participant 2. Right normalised motion L2-L5

Participant 2. Flexion normalised motion L2-L5

Participant 2. Extension normalised motion L2-L5

293

Example 3

Example 4

Figure 13-16 Four examples of continuous proportional motion for each level and direction

	Differences in mean values of PRV (Mann Whitney U test)
Left	0.22
Right	0.09
Flexion	0.29
Extension	0.06
All directions combined	0.008

Table 13-33 Difference in mean PRV values for each direction and combined

Appendices for Chapter 10 The radiation dose received from lumbar spine quantitative fluoroscopy compared to lumbar spine radiographs with suggestions for dose reduction, and diagnostic reference levels (DRL's)

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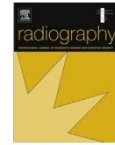
Moving back: The radiation dose received from lumbar spine quantitative fluoroscopy compared to lumbar spine radiographs with suggestions for dose reduction

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ABSTRACT

Purpose: Quantitative fluoroscopy is an emerging technology for assessing continuous inter-vertebral motion in the lumbar spine, but information on radiation dose is not yet available. The purposes of this study were to compare the radiation dose from quantitative fluoroscopy of the lumbar spine with lumbar spine radiographs, and identify opportunities for dose reduction in quantitative fluoroscopy.
Methods: Internationally reported dose area product (DAP) and effective dose data for lumbar spine radiographs were compared with the same for quantitative fluoroscopy and with data from a local hospital for functional radiographs (weight bearing AP, lateral, and/or flexion and extension) ($n = 27$). The effects of procedure time, age, weight, height and body mass index on the fluoroscopy dose were determined by multiple linear regression using SPSS v19 software (IBM Corp., Armonck, NY, USA).
Results and conclusion: The effective dose (and therefore the estimated risk) for quantitative fluoroscopy is 0.561 mSv which is lower than in most published data for lumbar spine radiography.
The dose area product (DAP) for sagittal (flexion + extension) quantitative fluoroscopy is 3.94 Gy cm^2 which is lower than local data for two view (flexion and extension) functional radiographs (4.25 Gy cm^2), and combined coronal and sagittal dose from quantitative fluoroscopy (6.13 Gy cm^2) is lower than for four view functional radiography (7.34 Gy cm^2).
Conversely DAP for coronal and sagittal quantitative fluoroscopy combined (6.13 Gy cm^2) is higher than that published for both lumbar AP or lateral radiographs, with the exception of Nordic countries combined data.
Weight, procedure time and age were independently positively associated with total dose, and height (after adjusting for weight) was negatively associated, thus as height increased, the DAP decreased.
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Introduction

Quantitative fluoroscopy (QF) of the lumbar spine allows inter-vertebral motion to be measured from fluoroscopic sequences where trunk motion is standardised for velocity and range. Sequences can be recorded using passive recumbent (i.e. no muscle or

motor control) or active weight-bearing protocols in both the coronal and sagittal planes. Automated frame-to-frame image registration relies upon good digital image quality and provides continuous inter-vertebral rotational and translational data, giving more information about the function of the spine than AP, lateral, or flexion-extension (functional) radiographs.[1,2]

Functional radiographs have long been used for measuring spinal movement and for diagnosing instability.[3] However, such measurements are unreliable due to errors from positioning, distortion and magnification, with mean test-retest errors of up to 4.9° [4] By contrast, QF is reported to be accurate to 0.32° for coronal, and 0.52° for sagittal plane inter-vertebral rotation[5] with inter-observer errors below 1.5° for rotation and 1.5 mm for translation.[6–9]

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QF technology is mainly limited to research, although a new system for clinical use has recently gained 510(K) clearance from the United States Food and Drug Administration (KineGraph VMA, Ortho Kinematics, Austin, Texas, USA).[10] However, few authors have published radiation dose data and none have compared these to published data from radiographic images. The present study sought to provide this, with suggestions for further optimising radiation doses by analysis of the characteristics which contribute to dose.

The aim was to determine if quantitative fluoroscopic investigation of the lumbar spine imparts a similar dose-area product (DAP) and effective dose (ED) to lumbar spine radiographs .To determine this, published data for AP and lateral radiographs were interrogated. Because no published data exists for functional radiographs, local hospital data were used to represent this dose for comparison. A secondary aim was to determine which factors may contribute to a reduction of the dose from quantitative fluoroscopy.

Methods and materials

This was a retrospective study comparing the radiation dose from an on-going QF study with AP and lateral lumbar spine radiographs, functional radiographs, and other QF studies. The comparisons were Dose Area Product (DAP) measured in Gray multiplied by area (Gy cm^2) and the estimated effective dose (ED) measured in miliSievert (mSv).

Published dose data

National and international surveys,[11–15] and peer reviewed scientific literature reporting radiation doses of lumbar spine radiographs and quantitative fluoroscopy/cineradiography/video-fluoroscopy were examined.[5,9,16–20] Literature was excluded if only entrance skin doses (ESD's) were reported leaving six references reporting DAP values and eight reporting effective dose. DAP and ED were extracted and compared to the dose from QF in this study.

Quantitative fluoroscopy

Ethical approval was obtained from the UK National Research Ethics Committee Southampton A (09/H0502/99). Recruitment of all participants and their written informed consent were carried out by the principal researcher prior to screening. QF was undertaken in the recumbent coronal and sagittal planes, in a cross-sectional mixed gender study ($n = 74$) of in vivo lumbar spine biomechanics, and movement was controlled by a specially designed motorised motion table (Fig. 1). Data collection was undertaken by the principal researcher using a portable digital C-arm fluoroscope with a 30 cm Image Intensifier (Siemens Avantic, Germany), and a pulse rate of fifteen frames per second was selected to minimise movement blurring.

DAP, procedure time, age, gender, height and weight of the participants was obtained. DAP was then converted to ED using PCXMC v2 software(stuk.fi) and 2007 ICRP 103 tissue weighting factors.[21] For QF, The mean kVp was 67 for coronal and 79 for sagittal plane, and the mean focus skin distances (FSD) were 75 cm and 60 cm respectively.

Hospital radiographs

A local hospital database of referrals by spinal surgeons for functional radiographs was inspected. The search covered the previous 12-month period and the cumulative DAP was recorded for patients who had a four series examination (weight-bearing AP, lateral, flexion and extension) or a two series examination (weight-
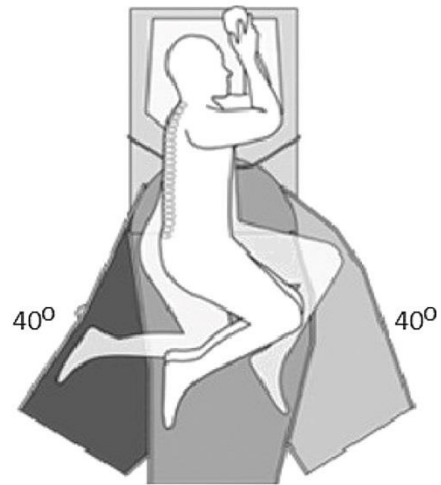
Figure 1. Diagram of the passive motion table for QF of the lumbar spine. Patients lie in either a supine or lateral decubitus position with L3 centred to the fulcrum with knees bent to flatten the lumbar lordosis. The table swings through an arc of 40° each way.

bearing flexion and extension). The collection of retrospective hospital dose data did not require ethical review; however hospital and radiology department R&D approvals were gained.

No identifying details were recorded and patients who had images that were repeated were excluded, as were those who only had supine AP and lateral lumbar radiographs. Examinations were undertaken by different practitioners using the same room equipped with a GE Medical Systems DEFINIUM 8000 System. ED was estimated using generalised conversion coefficients from the NRPB-R262 report[22] (see Table 2).

Statistical analysis

For QF, the relationships between DAP (outcome variable) and procedure time, age, gender, height, weight and body mass index (BMI) (predictor variables) were examined. A 2-sided 5% significance level was used. Initially, a least squares linear regression (IBM SPSS Statistics Version 19) of total dose was conducted to calculate unadjusted regression and correlation coefficients. Next, a multiple linear regression model including only height, weight and BMI determined whether all 3 variables independently predicted dose. Large changes in the standard errors of the regression coefficients

Table 1
Demographics of participants imaged with QF versus local hospital data of weight-bearing lumbar radiographs (2 or 4 series) for instability.

	This QF study	Local hospital
	N = 74	N = 27
Gender (%)	Male = 42 (57%)	Male = 11 (41%)
	Female = 32 (43%)	Female = 16 (59%)
Age years. Mean (SD)	36.9 (8.49)	63.2 (17.2)
Weight Kg. Mean (SD)	74.97 (12.73)	–
Height m. mean (SD)	1.716 (0.127)	–
BMI mean (SD)	24.77 (2.57)	–

253

Table 2
DAP and effective (ED) radiation dose data for QF recumbent sagittal and coronal plane sequences and weight bearing AP, lateral, flexion and extension radiographs from a local hospital database.

	Coronal QF ($n = 74$)	Sagittal QF ($n = 74$)	Total QF ($n = 74$)	Radiographic views 4 series (weight-bearing AP, lateral, flexion and extension) ($n = 15$)	Radiographic views 2 series (weight-bearing flexion and extension) ($n = 12$)
kVp Mean(SD)	66.99 (4.25)	79.09 (8.95)	73.04 (9.26)	90	90
DAP Gy cm^2 Mean (SD)	2.19 (0.78)	3.94 (0.86)	6.13 (1.5)	7.34 (4.4)	4.25 (1.98)
ED mSv Mean (SD)	0.321 (0.115)	0.24 (0.529)	0.561 (0.154)	—	2.2 (2.1)
Procedure time (seconds). Mean (SD)	36.08 (3.52)	39.27 (4.55)	75.35 (6.11)	—	—

from values seen in the unadjusted analyses were used to identify collinearity.

A variety of different models containing different combinations of these three predictor variables were also run, using adjusted R-squared values to help choose the best. From this, the best anthropometric variables were chosen and included with all the other remaining predictor variables in a single regression model. Variables that were not statistically significant were dropped from the analysis in order to obtain a parsimonious model. Adjusted regression (95% CI) and partial correlation coefficients of all statistically significant variables in the resultant model are presented.

Results

Demographics

Table 1 summarises the participant demographics for QF ($n = 74$) and functional radiographic studies ($n = 27$).

QF and lumbar spine radiation doses

Data from the functional radiographs were separated into 2 view ($n = 12$) and 4-view series ($n = 15$). The mean kVp, DAP and effective doses, along with the same from QF, are summarised in Table 2. The mean age at which patients had functional radiography (63 years) was much higher than the participants in this study (37 years). The age of the functional radiographic sample is indicative of the population in the local area, whereas the QF study participants were limited to an age range of 20–51 years.

Dose Area Product (DAP)

Fig. 2 shows the internationally published DAPs for lumbar spine radiographs compared to two series functional radiography, one previous QF lumbar spine study, and the mean DAP for coronal and sagittal QF in this study.

DAP data for separate coronal or sagittal QF studies (2.19 Gy cm^2 (SD 0.78) 3.94 Gy cm^2 (SD 0.86) respectively) were higher than UK dose reference levels AP (1.6 Gy cm^2) and lateral (3 Gy cm^2) lumbar radiographs, whereas sagittal QF was lower than local data for functional radiographs two view series (4.25 Gy cm^2) and lower than data reported from Sweden (6.5 Gy cm^2).

When combined (coronal and sagittal, Fig. 3), DAP for QF (6.13 Gy cm^2) was smaller than combined Nordic countries (9.15 Gy cm^2) and the Nordic guidance level (10 Gy cm^2). Conversely DAP for QF was higher than individual Nordic countries data; however data for the latter were reported 10 years later than the combined data, which may reflect updates in practice and equipment. Combined QF is lower than four view functional radiography (7.34 Gy cm^2) which is the examination it is comparable with in the USA.[23]

Comparison of effective dose (ED)

Fig. 4 shows that the effective doses for QF coronal (0.32 mSv) or sagittal (0.24 mSv) were less than the estimated ED for 2 view functional radiographs (2.2 mSv) and the weighted average for AP and lateral lumbar spine radiographs across 18 countries (1.2 mSv and 1 mSv respectively)[13]. In comparison with individual countries, ED for coronal QF was less than that reported for AP lumbar spine
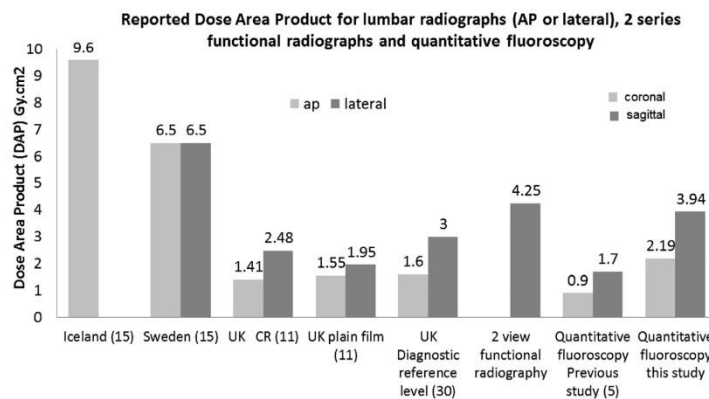
Figure 2. The reported DAP of AP and lateral lumbar spine radiographs compared to quantitative fluoroscopy and local data for 2 view (flexion and extension) functional radiographs.

F.E. Mellor et al. / Radiography 20 (2014) 251–257
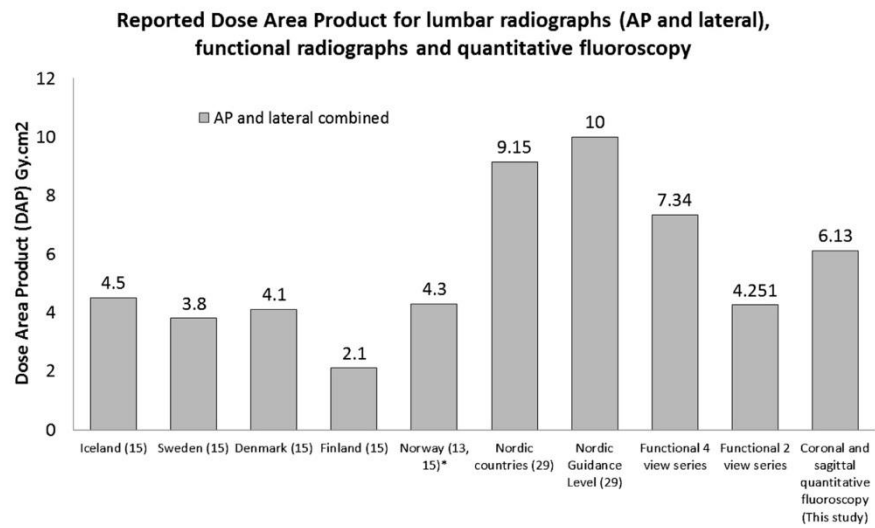
Figure 3. The reported DAP of combined lumbar spine radiographs (AP + lateral) compared to quantitative fluoroscopy and local data for functional radiographs. *Data for Norway has been reported as 4.2 Gy cm² and 4.4 Gy cm² in two separate references. The average of 4.3 Gy cm² is shown here.

radiographs in 9/12 regions, and for sagittal QF the ED was less in 5/12 regions.

ED data for lumbar radiographs (Figs. 4 and 5) comes from international sources where there is greater variation in the number of radiographs that make up the series. Additionally these studies did not quote their conversion coefficients which may have influenced the resultant estimation; hence a margin of error is expected when interpreting these comparisons.

One previous QF study undertaken in Hong Kong[9] reported an ED of 1.5 mSv for males and 2.3 mSv for females. No other exposure factors were reported but these estimates are between 1 and 2 mSv higher than the EDs in this study.

Fig. 5 shows the reported EDs for AP and lateral radiographs combined, a previous report from QF in 2011,[2] and QF in this study. The EDs from this study are lower than the QF data reported in 2011 where the imaging technique was similar but the sample size was
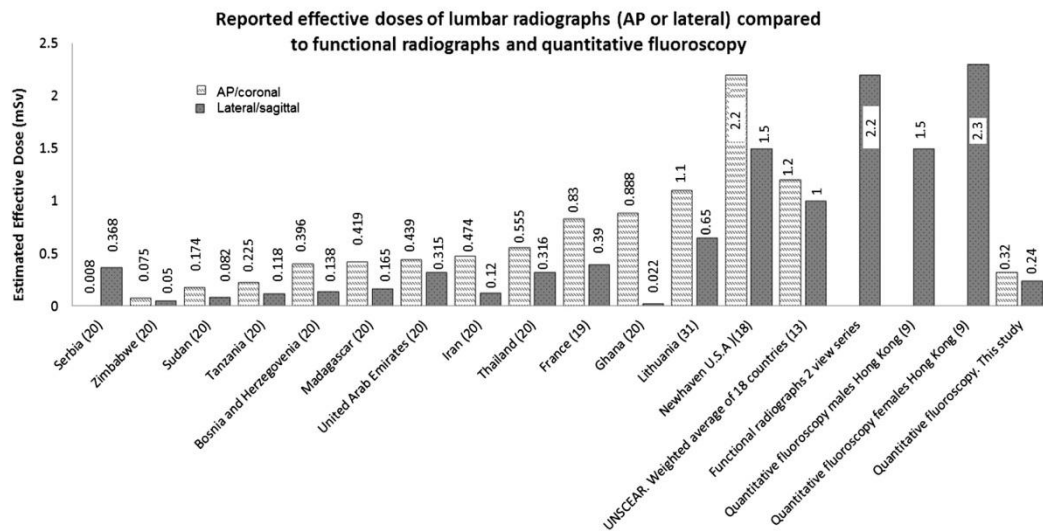
Figure 4. Reported effective dose for lumbar spine radiographs (AP or lateral) compared to quantitative fluoroscopy.
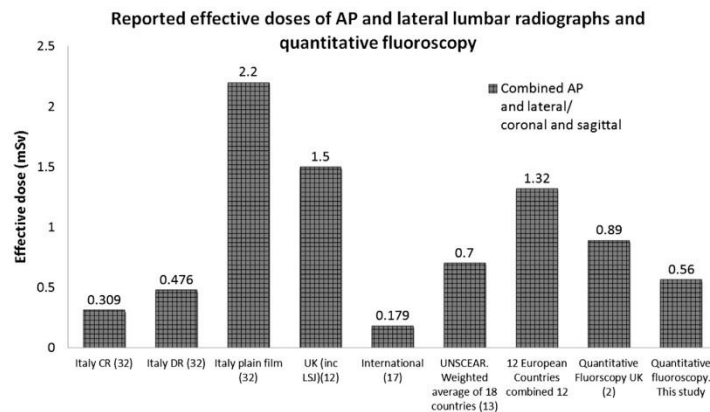
Figure 5. The effective dose of combined lumbar spine radiographic series compared to quantitative fluoroscopy and local data for functional radiographs.

smaller. When combined the ED for QF is again lower than the averages of 18 countries.[13]

Relationship of patient characteristics to QF dose

Inspection of the histogram and the result from the Kolmogorov–Smirnov test ($p = 0.30$) suggested that it was reasonable to assume that total dose was normally distributed. Unadjusted regression and correlation coefficients relating potential predictors to DAP are shown in Table 3. All variables were significantly associated with total dose. The regression model of total dose against height, weight and BMI displayed substantial collinearity so not all could be included. A model containing weight and height together had a larger adjusted R squared (69%) than BMI alone (56%), and slightly larger adjusted R squared than BMI and height together (67%) and BMI and weight together (68%). Thus BMI was dropped from subsequent models. The effect of gender on total dose appears to be explained by height and weight differences. The remaining statistically significant variables are shown in Table 3. Increased average total dose was associated with greater age, longer procedure time, increased weight and smaller height (after weight is taken into account). The partial correlation coefficients suggest that, of the predictors of total dose, the association is greatest for weight. The adjusted R squared for this final model was 82%.

Discussion

There is large variation in methods and reporting of dosage data in existing literature which is reflected in the conflicting results presented here. However we can confidently say that the mean effective dose for QF in this study was less than 1 mSv. When undertaking research involving ionising radiation the risk to the individual versus societal benefit must be considered. A dose of less than 1 mSv places this research in the International Commission for Radiological Protections (ICRP) category of 'IIa Intermediate' which means the risk to the individual is minor and the benefit to society is intermediate to moderate.[24] Alternatively stated, the risk of inducing cancer from 1 mSv is 1:20 000[25] which is in addition to the lifetime risk of 1:3 .[26] The mean background radiation dose received annually in the UK is 2.7 mSv[27] thus the mean effective

dose of 0.561 mSv from QF is equivalent to approximately 11 weeks' background radiation.

When considering risks to health from radiation, epidemiological evidence currently states that there is insufficient statistical power to detect excess carcinomas for doses below 100 mSv,[28] although a more recent editorial summarised the evidence on the health effects of low level radiation[29] and agreed that it remains prudent to stay within the linear no threshold (LNT) model and adhere to the ALARA principle because it is possible for a single radiation track to cause significant DNA changes.[30]

Considering dose reduction strategies for QF, patient weight appears to be the strongest predictor, followed by procedure time. It is interesting to note the statistically significant correlation between age and dose which cannot be explained by other factors in the model. The negative association between height and total dose after adjusting for weight can be explained by the fixed field of radiation exposure during the procedure. That is, people of the same weight but greater height will have less of their bodies within the field.

Implications for clinical practice

Quantitative fluoroscopy has advanced our understanding of the biomechanics of the spine and it can be used with any portable image intensifier, a motion platform, and bespoke tracking software. This technique is currently being adopted in some centres in the USA[23] and could be used to replace functional radiographs without adding to the medical radiation burden. However QF has an examination time of 15 min for one plane of motion which is longer than functional radiographs. Hence departments would need to consider the extra information gained in light of the increased examination time.

Quantitative fluoroscopy ensures that trunk movement is highly standardised to reduce inter and intra subject variation, hence all participants were bent to 40°, rather than their maximum voluntary trunk bend. Adopting the standardisation of trunk movement in functional radiography would advance upon the current technique by reducing inter and intra subject variation. However not bending to the maximum may not stress inter-vertebral segments sufficiently to establish a diagnosis of radiological instability, thus if standardisation of trunk motion was to be adopted, revised normative values would also be required.

Table 3
Linear regression analyses of total absorbed dose on potential predictor.

Predictor	Unadjusted regression coefficient (95% CI) p-value	Correlation	Adjusted regression coefficient for parsimonious model (95% CI) p-value	Partial correlation
Age (years)	6.03 (2.14, 9.92) $p = 0.003$	0.34	3.64 (1.79, 5.49) $p < 0.001$	0.43
Procedure time (min)	9.30 (3.98, 14.62) $p < 0.001$	0.38	8.47 (5.96, 10.97) $p < 0.001$	0.63
Weight (kgs)	9.56 (7.90, 11.22) $p < 0.001$	0.80	11.83 (9.77, 13.90) $p < 0.001$	0.81
BMI (Kgs/m2)	43.62 (34.67, 52.57) $p < 0.001$	0.75	A	
Height (m)	829.46 (508.06, 1150.87) $p < 0.001$	0.52	−543.24 (−814.5, −271.97) $p < 0.001$	−0.43
Sex (M relative to F)	149.15 (87.98, 210.32) $p < 0.001$	NA	B	

Regression coefficients represent mean change in total dose (cGy cm^2) per unit increase in predictor.
NA — sex is a nominal variable so Pearson's correlation not presented.
A — BMI excluded because of collinearity with weight and height.
B — Effect of sex explained by height, weight and other variables when added to the model ($p = 0.87$).

Limitations

Studies reporting effective dose did not give details of their standard radiographic series or conversion coefficients so these comparisons are provided as an overview. The ED for 2 series functional radiographs was estimated using generalised co-efficients[22] because of the limited retrospective data available, however it is acknowledged that they are less accurate than those used for QF. Additionally the sample size for functional radiography is small and limited to one site; hence it is unlikely to be representative of the dose received from functional radiographs, it is presented here as an introduction and a suggestion that further research could examine radiation doses received from functional radiographs.

It is acknowledged that comparing QF (dynamic) with published AP and lateral (static) lumbar radiographs is not ideal, as the image quality and clinical indications differ. However it is necessary to show that new and emerging medical technologies are at least equal to, if not superior to, existing examinations and thus the nearest proxy data for radiation dosage was used.

The effective doses for QF in this study were calculated using Monte Carlo simulation software (PCXMC) and used the latest tissue weighting factors[21] with an assumed constant field size of 30 cm × 30 cm. In practice, collimation was used throughout ensuring the field size was smaller than this and thus the EDs reported here are likely to be overestimated.

Options for further dose reduction

QF reduces the intra- and inter-subject variation in lumbar spine kinematics which allows for better comparisons of populations. Linear regression/correlation showed that QF procedure time had a significant correlation with DAP. Therefore, since range and velocity are controlled, increasing the velocity of the trunk motion should lead to a reduction in procedure time and thus a reduction in dose. However this needs to be carefully balanced against motion blurring which would render the objective automated tracking templates ineffective.

Another way to reduce dose from QF would be to reduce the pulse rate. The method currently in use employs a rate of 15 fps however the system in use in the USA employs a pulse rate of 8 fps. If the motion output is equally accurate and reproducible with the pulse rate halved, then it could be safely reduced.

As patients' weight increases so too does the amount of scatter which degrades the image quality upon which the QF tracking algorithms depend. One way of reducing the collective dose to patients undergoing QF would be to impose a maximum weight limit. In some diagnostic centres maximum weight limits are already imposed for CT and MRI although this is mainly for logistical reasons. However when undertaking QF, tracking algorithms are likely to fail if image quality is poor hence in larger participants there would be no benefit to those who exceed a certain weight limit if the tracking algorithms fail. However, further analysis would be needed to determine what that weight limit may be. In the present study a BMI limit of 30 was imposed due to the maximum output capacity of the mobile C arm.

Conclusion

Quantitative fluoroscopy of the lumbar spine has a similar radiation dose to AP, lateral and functional radiographs. Because QF can provide more reliable and comprehensive information about inter-vertebral motion, which improves the clinical decisions about the functional integrity of the spine, this technique could be used as a replacement for functional radiographs without an increase in radiation dose.

However QF requires careful standardisation of patient movement and bespoke tracking algorithms which are essential for accuracy and reliability. Hence its wider adoption within clinical departments will require careful management. However this technique has already been adopted in the U.S.A. and work is underway to improve its accessibility in the U.K.

Finally, caution is advised when referring to published studies comparing radiation dose because of the variation in methods used to both obtain the image, and calculate effective dose. It is therefore recommended that this paper should only be used to compare the order of magnitude of the radiation dose between QF and other lumbar spine radiography.

Conflict of interest

None.

257

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Figure 13-17 Mellor et al (2014a)

Appendices for Chapter 11 General discussion

Appendices for Chapter 11 General discussion

Kinematic parameter		Differences in mean values between patients and controls (student's independent t test or Mann Whitney U test)			
		Maximum intervertebral rotation	Initial intervertebral attainment rate	Continuous intervertebral rotation	Continuous proportional motion
Left	L2/3	0.87	0.29		-
	L3/4	0.59	0.12		-
	L4/5	0.03	0.003		-
	Combined	0.22	-		0.22
Right	L2/3	0.52	0.14	A single variable was not created for cIVR so it was not possible to examine differences in mean values	-
	L3/4	0.06	0.16		-
	L4/5	0.25	0.09		-
	Combined	0.72	-		0.09
Flexion	L2/3	0.61	0.90		-
	L3/4	0.30	0.92		-
	L4/5	0.16	0.40		-
	Combined	0.17	-		0.29
Extension	L2/3	0.36	0.56		-
	L3/4	0.92	0.15		-
	L4/5	0.32	0.96		-
	Combined	0.92	-		0.06
All directions		-	-		0.008

Table 13-34 statistically significant differences in means of the kinematic parameters in this thesis (highlighted values are significant at the 5% level)

		Diagnostic accuracy									
		Maximum intervertebral rotation		Initial segmental attainment rate		Continuous intervertebral rotation (above upper reference limits)		Continuous intervertebral rotation (below lower reference intervals)		Continuous proportional motion	
		Sensitivity (95% C.I.)	Specificity (95% C.I.)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Sensitivity (95% C.I.)	Specificity (95% C.I.)
Left	L2/3	0.775 (0.615 to 0.892)	0.375 (0.227 to 0.542)	0.825 (0.672 to 0.927)	0.375 (0.228 to 0.542)	0.200 (0.090 to 0.357)	0.800 (0.644 to 0.909)	0.150 (0.057 to 0.298)	0.925 (0.796 to 0.984)	-	-
	L3/4	0.375 (0.227 to 0.542)	0.825 (0.671 to 0.927)	0.550 (0.385 to 0.707)	0.700 (0.535- 0.834)	0.225 (0.868 to 0.994)	0.975 (0.868 to 0.999)	0.325 (0.186 to 0.491)	0.925 (0.796 to 0.984)	-	-
	L4/5	0.400 (0.249 to 0.567)	0.900 (0.763 to 0.975)	0.750 (0.588 to 0.873)	0.600 (0.433 to 0.751)	0.175 (0.073 to 0.328)	0.875 (0.732 to 0.958)	0.275 (0.146 to 0.439)	0.975 (0.868 to 0.994)	-	-
	Combined	0.300 (0.166 to 0.465)	0.875 (0.731 to 0.958)	-	-	0.425 (0.270 to 0.591)	0.725 (0.561 to 0.851)	0.525 (0.361 to 0.649)	0.825 (0.672 to 0.927)	0.675 (0.509 to 0.814)	0.550 (0.385 to 0.707)
Right	L2/3	0.650 (0.483 to 0.793)	0.475 (0.315 to 0.639)	0.825 (0.672 to 0.927)	0.425 (0.27 to 0.591)	0.200 (0.090 to 0.357)	0.850 (0.702 to 0.943)	0.075 (0.016 to 0.204)	0.925 (0.796 to 0.984)	-	-

References

	L3/4	0.475 (0.315 to 0.638)	0.875 (0.732 to 0.958)	0.425 (0.27 to 0.591)	0.800 (0.644 to 0.909)	0.325 (0.186 to 0.491)	0.850 (0.702 to 0.943)	0.200 (0.091 to 0.972)	0.900 (0.763 to 0.972)	-	-
	L4/5	0.325 (0.186 to 0.491)	0.900 (0.763 to 0.972)	0.300 (0.166 to 0.465)	0.950 (0.83 to 0.994)	0.150 (0.056 to 0.298)	0.825 (0.672 to 0.927)	0.350 (0.206 to 0.517)	0.925 (0.796 to 0.984)	-	-
	Combined	0.425 (0.27 to 0.591)	0.750 (0.588 to 0.873)	-	-	0.450 (0.296 to 0.615)	0.650 (0.482 to 0.794)	0.425 (0.270 to 0.591)	0.750 (0.588 to 0.873)	0.775 (0.615 to 0.892)	0.500 (0.338 to 0.662)
Flexion	L2/3	0.900 (0.763 to 0.972)	0.250 (0.123 to 0.412)	0.775 (0.615 to 0.892)	0.375 (0.227 to 0.542)	0.175 (0.073 to 0.328)	0.875 (0.732 to 0.958)	0.150 (0.057 to 0.299)	0.900 (0.763 to 0.972)	n/a	n/a
	L3/4	0.400 (0.249 to 0.567)	0.775 (0.615 to 0.891)	0.725 (0.561 to 0.854)	0.450 (0.293 to 0.615))	0.200 (0.090 to 0.356)	0.900 (0.763 to 0.972)	0.250 (0.127 to 0.412)	0.925 (0.796 to 0.984)	n/a	n/a
	L4/5	0.725 (0.561 to 0.854)	0.475 (0.315 to 0.639)	0.325 (0.186 to 0.413)	0.850 (0.702 to 0.943)	0.225 (0.108 to 0.385)	0.925 (0.796 to 0.984)	0.200 (0.091 to 0.357)	0.925 (0.796 to 0.984)	n/a	n/a
	Combined	0.275 (0.146 to 0.439)	0.925 (0.796 to 0.984)	n/a	n/a	0.425 (0.270 to 0.591)	0.725 (0.561 to 0.851)	0.425 (0.270 to 0.591)	0.800 (0.641 to 0.910)	0.850 (0.702 to 0.943)	0.300 (0.166 to 0.485)
Extension	L2/3	0.900 (0.763 to 0.972)	0.275 (0.146 to 0.439)	0.600 (0.434 to 0.751)	0.625 (0.458 to 0.773)	0.125 (0.419 to 0.268)	0.950 (0.831 to 0.994)	0.175 (0.073 to 0.328)	0.875 (0.732 to 0.958)	n/a	n/a

	L3/4	0.650 (0.48 to 0.794)	0.475 (0.315 to 0.639)	0.600 (0.434 to 0.751)	0.650 (0.483 to 0.793)	0.100 (0.028 to 0.237)	0.900 (0.763 to 0.972)	0.300 (0.166 to 0.465)	0.825 (0.672 to 0.927)	n/a	n/a
	L4/5	0.325 (0.186 to 0.491)	0.850 (0.702 to 0.943)	0.350 (0.206 to 0.517))	0.825 (0.672 to 0.927)	0.300 (0.166 to 0.465)	0.850 (0.702 to 0.943)	0.200 (0.091 to 0.357)	0.925 (0.796 to 0.984)	n/a	n/a
	Combined	0.100 (0.028 to 0.237)	0.975 (0.864 to 0.999)	n/a	n/a	0.450 (0.483 to0.615)	0.650 (0.483 to 0.794)	0.350 (0.206 to 0.517)	0.775 (0.615 to 0.892)	0.825 (0.672 to 0.927)	0.450 (0.293 to 0.615)
All directions		n/a	n/a	n/a	n/a		0.750 (0.588 to 0.873)	0.275 (0.146 to 0.439)	0.850 (0.702 to 0.943)	0.400 (249 to 0.567)	0.550 (0.385 to 0.707)

Table 13-35 Diagnostic accuracy of the kinematic parameters in this thesis

		Proportion of patients and healthy volunteers below lower reference limit. P=0.05 Fishers Exact test			
		Maximum intervertebral rotation	Initial segmental attainment rate	Continuous intervertebral rotation	Continuous proportional motion
Left	L2/3	>0.99		0.48	
	L3/4	0.12		0.01	
	L4/5	0.20		0.003	
	Combined	0.01		0.001	
Right	L2/3	-		n/a	
	L3/4	0.62		0.35	
	L4/5	0.11	The lower reference limit for initial intervertebral attainment rate is clinically meaningless because it reflects an increase in the proxy neutral zone	0.01	Reference intervals for CPM were created but nor pursued (see Chapter 9 Introduction p159)
	Combined	0.05		0.15	
Flexion	L2/3	-		0.73	
	L3/4	>0.99		0.07	
	L4/5	0.36		0.19	
	Combined	0.20		0.05	
Extension	L2/3	>0.99		0.76	
	L3/4	-		0.29	
	L4/5	-		0.19	
	Combined	>0.99		0.32	
All directions		0.04		0.02	

Table 13-36 Significant proportions of patients with hypo mobility (mIVR, cIVR)

		Upper reference values. Fishers exact two tailed test p values for proportion of patients and healthy volunteers below lower reference limit			
		Maximum intervertebral rotation	Initial segmental attainment rate	Continuous intervertebral rotation	Continuous proportional motion
Left	L2/3	>0.99	>0.99	n/a	n/a
	L3/4	-	0.36	0.01	
	L4/5	-	0.2	0.76	
	Combined	-		0.24	
Right	L2/3	-	0.24	0.77	
	L3/4	0.06	-	0.11	
	L4/5	>0.99	>0.99	>0.99	
	Combined	-	-	0.49	
Flexion	L2/3	0.49	0.62	0.76	
	L3/4	-	>0.99	0.35	
	L4/5	0.03	-	0.05	
	Combined	-	-	0.24	
Extension	L2/3	0.65	0.68	0.43	
	L3/4	-	>0.99	n/a	
	L4/5	0.49	>0.99	0.18	
	Combined	-	-	0.50	
All directions		-	-	>0.99	

Table 13-37 Significant proportions of patients exceeding upper reference limit for three kinematic parameters

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