Blood pressure and hypertension in adults permanently living at high altitude : a systematic review and meta-analysis

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Abstract

The objective of this study was to estimate the associations between altitude and mean blood pressure (or prevalence of hypertension) in adults who live permanently at high altitude. A literature search was conducted in December 2014 using PubMed, Scopus and OvidSP (MedLine and EMBASE) databases to identify relevant observational studies. Inclusion criteria were reports of studies in populations permanently living at an altitude of ≥2400 m and in those 18 years or older. Meta-regression was used to estimate the association between average blood pressure and hypertension and altitude. We identified 3375 papers and inclusion criteria were met for 21 reports which included a total of 40854 participants. Random-effects meta-regression estimated that for every 1000 m elevation the average systolic blood pressure (95% CI) increased by 17 mmHg (0.2 to 33.8), P=0.05 and diastolic blood pressure by 9.5 mmHg (0.6 to 18.4), P=0.04 in participants with Tibetan origin. By contrast, in participants with non-Tibetan origin average systolic blood pressure decreased by 5.9 mmHg (-19.1 to 7.3), P=0.38 and diastolic blood pressure by 4 mmHg(-13 to 5), P=0.38. The odds ratios (95% CI) for the proportion of participants with hypertension per 1000 m increment in the altitude were 2.01 (0.37 to 11.02), P=0.446; and 4.05 (0.07 to 244.69), P=0.489 for Tibetan and non-Tibetan participants respectively. Sensitivity analysis excluding two studies with older participants (≥60 years) reversed the direction of this effect in non-Tibetans with OR (95% CI) of 0.10 (0.004 to 2.22) per 1000 m, P=0.143. Overall, this review suggests weak association between blood pressure and altitude in Tibetan origin populations.

Introduction

A significant proportion of the global population lives permanently at high altitude (HA). Over 140 million people, about 2% of the global population, live at an altitude of 2500 m or more (Moore and others 1998). People living in the Ethiopian summits of Africa, the Himalayan mountains of Tibet, and the Andean mountains of South America are the populations with the longest history in HA residency; 70,000 years, 25,000 years, and 11,000 years respectively (Beall 2007). The majority of residents at HA are 80 million in Himalayan mountains of Asia and 35 million in Andean mountains of South America (Moore and others 1998). Although the direct effects of the HA environment on disease and health may be important, those living at HA may also have particular social and cultural practices which also contribute to the differences in health outcomes.

Hypertension (HT) is an important risk factor for adverse health outcomes such as stroke and myocardial infarction (Ezzati and others 2005). Depending on the definition used, HT affects between 20 and 30% of the global population (Asia Pacific Cohort Studies Collaboration 2003; Prospective Studies Collaboration 2002). The world-wide prevalence of HT is likely to rise with time in part because of the ageing of the global population but also related to the increasing prevalence of obesity. One estimate is that the current prevalence will increase from 26.4% currently to reach at 29.2% by 2025 (Kearney and others 2005).

The effect of chronic hypoxic hypobaric conditions, induced by living at HA, on blood pressure (BP) is uncertain and may vary in different populations. Research on this relationship and other cardiopulmonary changes in HA has been ongoing for more than 50 years (Ostadal and Kolar 2007), without a clear cut resolution on whether the relationship between BP and HT and HA is causal or because of coincident lifestyle factors. An inverse association between altitude and systemic BP may be due to, separately or in combination, structural changes in vasculature; and a number of socio-cultural, biological, chemical and physical factors (León-Velarde and others 1993; Ruiz and Penaloza 1977). However, the possible benefit from altitude related hypoxia on systemic BP may diminish when genetic and lifestyle related risk factors become dominant as in Tibetan origin populations(Gesang and others 2002; Mingji and others 2015). An increased amount of smooth muscle cells in the distal pulmonary arteries in those living at HA may directly increase pulmonary BP (Arias-Stella 1966). But this may not hold true for all HA residents such as in Tibetans and Ethiopians possibly due to the higher levels of exhaled nitric oxide than Andeans or low altitude populations (Beall 2007; Beall and others 2001). Thus, empirical data on relationship between HA and BP are not uniformly observed amongst populations living at HA.

This systematic review and meta-analysis aims to estimate the association between BP and HT and altitude in adults permanently living at HA.

Methods

This study comprises a systematic review and meta-analysis.

Study inclusion and exclusion criteria

Inclusion criteria for the systematic review were: studies of BP and/or HT in populations living at an altitude of ≥2400 m, with a minimum sample size of 100 permanent residents, and in those aged 18 years or older. Only English language articles available in the full text were included.

Studies on patients, not at population level, and not denoting the specific altitude level, were excluded. The search was completed on 1st December 2014.

Search and selection methods

A search was conducted in three major biomedical databases; PubMed, OvidSP (MedLine and EMBASE) and Scopus. The search terms: 'blood pressure' or 'hypertension', were combined with the words 'altitude' or 'mountain' or 'himalaya' or 'highland'. These combinations were also assessed along with the name of major populations at HA; 'Tibetans' and 'Andeans', and the name of seven South American countries - 'Bolivia', 'Chile', 'Colombia', 'Ecuador', 'Mexico', 'Peru', and 'Venezuela'. Studies were searched by title and/or abstract. In addition, reference lists from identified articles were scrutinized to find relevant published articles. We considered the studies which published data on systolic (SBP) and diastolic blood pressure (DBP) or prevalence of HT. The flow diagram for the article selection process is shown in Figure 1.

Data extraction and quality appraisal

A data extraction table was developed using the Centre for Reviews and Dissemination guidance template (Khan and others 2001). Two authors (NA and MW) assessed the eligibility of identified papers and recorded authors, year of publication, geographical locations, sample size, altitude of the study site, mean BP values and rates of HT. The meta-analysis of observational studies in epidemiology (MOOSE) checklist was followed for reporting (Stroup and others 2000). We present important and relevant risk of bias components separately for each study.

Statistical analysis

Random effects meta-regression was used to evaluate the association between mean BP and HT prevalence by altitude. BP levels were treated as continuous Gaussian variables and a binomial distribution was used for the prevalence of HT. If a study reported an altitude range rather than a specific level, the average of the range was recorded. For the meta-regression the reported mean BP was used as a response variable in a mixed linear model that used the particular study, as a categorical variable, as a random effect, and the inverse variance of the mean BP as a weight. A pooled estimate of mean systolic and diastolic BP was estimated per 1000 m increment in altitude. For the meta-regression of HT prevalence a pooled odds ratio (OR) for HT per 1000 m increment in altitude was estimated using a similar random effects model. Sensitivity testing and sub-group analysis was also performed. Studies which reported data at different levels of HA or from different ethnic populations were treated independently during the analysis if sample size was ≥100 otherwise excluded as per the eligibility criteria. Analysis was performed separately for the studies with participants from Tibetan and non-Tibetan origins due to well-known differences in genetics and physiological responses against environmental hypoxia.

Comprehensive meta-analysis (CMA) version 3.0 was used.

Results

The search identified 3375 papers; 1612 from Scopus, 719 from Embase, 565 from Medline, 479 from PubMed, and ten from reference search. A search of the listed references was performed for 71 articles selected for full text review and the flow of studies is shown in Figure 1.

Twenty one studies were included in this review, including two studies published each in 1970s, 1980s, 1990s, four studies in 2000s and eleven studies after 2010. A total number of participants was 40854; nine studies including less than 500 participants, six studies with 500-1000, five studies with 1000-5000 participants and one with >5000 participants. Six studies were based in China (five in Tibetans), four in India (all in Tibetans), four in Peru, and one each in Colombia & Ecuador, China & India (including Tibetans), Chile, Pakistan, Ethiopia, Nepal (Tibetans) and Saudi Arabia. Ten studies each had Tibetan and non-Tibetan participants and one study had participants from both group. All studies were cross-sectional. The altitude level ranged from 2438 to 4300 m. The key features of the selected studies are shown in Table 1.

Table 2 shows the risk of bias table of each study including sampling process, HT cut-points, BP measuring devices, number of blood pressure readings, and body position during BP measurements. Briefly, participants were randomly selected in 11 studies, non-randomly in six studies, completely surveyed in two studies, and the sampling process was unclear in two studies. Fourteen studies reported the prevalence of HT, of which eleven used a cut-off point of ≥ 140/90 mmHg, one considered a cut-point of ≥ 130/85 mmHg, while two older studies adopted the cut point of ≥ 160/95 mmHg for HT. With respect to the measurement device for BP this was a standard mercury sphygmomanometer in 10 studies, aneroid sphygmomanometer in one study, automated device in five studies, and the BP measuring device was unclear in five studies. Two readings of BP were taken and averaged in seven studies, three readings were taken in four studies, and number of readings was not mentioned in seven studies. In two studies, a second reading was only considered if HT was observed in first reading and one study repeatedly measured BP until readings were stable within 2 to 3 mmHg. Body position during the BP measurements was sitting in 14 studies, supine in one study, and unclear in six studies.

BP in relation to HA

Seven studies compared the mean BP at HA (≥2400 m) and low altitude (< 2400 m). Of these, five reported higher mean SBP and DBP values in HA for both genders (Clegg and others 1976; Hernandez-Hernandez and others 2010; Khalid and Adzaku 1995; Liu and others 2001; Smith 1999). In one study, average BP values were higher at HA except for DBP in women (Tripathy and Gupta 2007). In a Peruvian study, average SBP was marginally high at HA, but DBP was significantly lower (Lindgärde and others 2004). For individual studies the mean difference was statistically significantly higher at HA for both SBP and DBP in three studies (Hernandez-Hernandez and others 2010; Khalid and Adzaku 1995; Liu and others 2001), in DBP in a Nepalese study (Smith 1999), and in DBP only for young female adults in an Indian study (Tripathy and Gupta 2007). One study reported marginally higher average values for both SBP and DBP at LA (Tripathy and Gupta 2007).

Five studies reported average BP values at different levels of HA (≥2400m). Two each showed decreasing (Makela and others 1978; Negi and others 2012), and increasing BP values (Clegg and others 1976; Okumiya and others 2010) with higher elevation. In one study, SBP increased marginally but DBP decreased with altitude (Hernandez-Hernandez and others 2010). Average SBP levels varied from 97 (Lindgärde and others 2004) to 146.6 mmHg (Zhao and others 2012) and DBP from 59 (Lindgärde and others 2004) to 92 mmHg (Zhao and others 2012) at HA.

Fourteen studies reported the prevalence of HT in HA, in which seven studies showed the prevalence of >30% (Liu and others 2001; Matsubayashi and others 2009; Okumiya and others 2010; Sherpa and others 2013; Tripathy and Gupta 2007; Zhao and others 2012; Zheng and others 2012), including four where the prevalence was >50% (Matsubayashi and others 2009; Okumiya and others 2010; Zhao and others 2012; Zheng and others 2012). Interestingly, all seven of these studies had participants of Tibetan race. Similarly, five studies reported a prevalence of HT between 15 and 30% (Negi and others 2012; Negi and others 2014; Shah and others 2001; Smith 1999; Sun 1986), and two South American studies reported the prevalence of less than 15% (Hernandez-Hernandez and others 2010; Ojeda and others 2014). The prevalence of HT by local definition ranged from 15.2% (Sun 1986) to 71.8% (Okumiya and others 2010) for Tibetan participants and between 1.1% (Ojeda and others 2014) to 57.9% (Matsubayashi and others 2009) in non-Tibetans.

Gender and BP in HA

Among the 10 studies which reported average BP for genders separately, men had a higher value of both systolic and diastolic BP in seven studies (Clegg and others 1976; Gonzales and others 2013; Hernandez-Hernandez and others 2010; Makela and others 1978; Tripathy and Gupta 2007; Zhao and others 2012; Zheng and others 2012). Only one Tibetan study had a high average of both systolic BP and diastolic BP in women (Liu and others 2001). Of eight studies reporting HT for men and women, equal number of studies found high prevalence in men (Negi and others 2014; Tripathy and Gupta 2007; Zhao and others 2012; Zheng and others 2012) and in women (Liu and others 2001; Shah and others 2001; Sherpa and others 2013; Sun 1986).

In four studies the differences were significantly higher in men for at least one of SBP, DBP and HT (Clegg and others 1976; Gonzales and others 2013; Zhao and others 2012; Zheng and others 2012). By contrast, the differences were significantly higher in none of the studies where women had a higher values for average SBP, DBP or HT. Overall, men tended to have a higher average BP than in women but not clear gender-based pattern was observed for HT.

Age and BP in HA

Thirteen studies reported an analysis of any relationship between BP at HA and age (Clegg and others 1976; Dasgupta and others 1982; Hernandez-Hernandez and others 2010; Khalid and Adzaku 1995; Makela and others 1978; Negi and others 2012; Shah and others 2001; Sherpa and others 2013; Smith 1999; Sun 1986; Tripathy and Gupta 2007; Zhao and others 2012; Zheng and others 2012). Among these only three did not show an impact of age on BP (Clegg and others 1976; Dasgupta and others 1982; Makela and others 1978). An Indian study showed a rise of BP at a younger age in women (Dasgupta and others 1982), while a Pakistani study showed a more gradual increment between age and DBP (Shah and others 2001). An Ethiopian study showed no impact of age at HA except in high socio-economic status population (Clegg and others 1976).

Predictors of high BP in HA

Among the ten studies which reported statistical analysis of predictors of BP in HA, six found Body Mass Index (BMI) as a best predictor (Negi and others 2012; Shah and others 2001; Smith 1999; Tripathy and Gupta 2007; Zhao and others 2012; Zheng and others 2012). Likewise, body weight better explained the rise of BP levels in two studies (Khalid and Adzaku 1995; Makela and others 1978). Other predictors were family history of HT (Shah and others 2001), higher socio-economic group (Clegg and others 1976), alcohol intake (Smith 1999), and packed cell volumes (Khalid and Adzaku 1995).

Results from the closely relevant but excluded studies

There were six studies which would have met the criteria for this review, but included data from participants <18 years (Baker 1969; Beall and others 1997; He and others 1991; Murillo and others 1980; Otsuka and others 2005; Ruiz and Penaloza 1977). Of these, three studies from South America (Baker 1969; Murillo and others 1980; Ruiz and Penaloza 1977), one study from

Ethopia (Beall and others 1997), and one study from China (He and others 1991) showed low levels of BP in HA, whereas an Indian study found high levels (Otsuka and others 2005).

Association of mean BP with altitude

Twenty population samples from 17 studies were included in the meta-regression of BP. Eleven samples were from non-Tibetan and 9 from Tibetan origin participants. Mean SBP (95% CI) increased by 17 mmHg (0.2 to 33.8), P=0.05 in Tibetans per 1000 m; but decreased by 5.9 mmHg (-19.1 to 7.3), P=0.38 in non-Tibetans. The mean DBP (95% CI) also increased by 9.5 mmHg (0.6 to 18.4), P=0.04 in Tibetans but decreased by 4 mmHg (-13 to 5), P=0.38 in non-Tibetans per 1000 m higher altitude. Compared to women both Tibetan and non-Tibetan men had higher average values for both SBP and DBP. However, this difference was statistically significant for non-Tibetan participants only; with an average SBP difference (95% CI) of 2.5 mmHg (0.78 to 4.15), P=0.004 and DBP difference (95% CI) of 2.5 (1.78 to 3.19), P<0.001.

There were six studies which collected the BP values in both high (≥2400 m) (N=7) and low (<2400 m) (N=10) levels of altitude. In random-effects meta-regression including the data observed in high and low altitude both average SBP and DBP decreased with similar magnitudes with 1000 m higher altitude; SBP (95% CI) by 1.1 mmHg (-5.1 to 2.9), P=0.58; and DBP (95% CI) by 1.3 mmHg (-3.6 to 1), P=0.27. The point estimates suggested that SBP decreased more rapidly below 2400 m, -4 mmHg compared to -1.2 mmHg per 1000 m elevation, whereas DBP fell steeply above 2400 m (-3.7 mmHg vs. -2.5 mmHg per 1000 m elevation). However, no definite inflection points were noted (Appendix 1).

Association of HT prevalence with altitude

Random-effects meta-regression of HT by altitude was performed in 18 population samples (from 14 studies); 11 had Tibetan and seven had non-Tibetan origin. The estimated OR (95% CI) of HT in participants of Tibetan origin was 2.01 (0.37 to 11.0) per 1000 m, P=0.446. For those of non-Tibetan origin the association was 4.05 (0.07 to 244.7) per 1000 m, P=0.489. The point estimates reflect the gradient seen for the prevalence of HT by altitude of: 16.5% (2000 m), 28.5% (3000 m), and 44.6% (4000 m) for Tibetans; and 4.1% (2000 m), 14.9% (3000 m), and 41.4% (4000 m) for non-Tibetans. Sensitivity analysis excluding two studies with older populations (≥60 years) (Matsubayashi and others 2009; Okumiya and others 2010) showed a similar result for Tibetans but for non-Tibetans the direction of the effect was reversed with OR (95% CI) of 0.10 (0.004 to 2.22) per 1000 m, P=0.143. The estimated effect sizes were similar after excluding six studies which presented an altitude range, rather than an exact altitude.

The point estimates from the individual studies were not combined for both BP and HT analysis because the heterogeneity statistics examined by tau, I^2, and the Q statistics showed a considerable degree of variances across the studies.

Discussion

In this systematic review and meta-analysis of adult populations living at HA we identified weak evidence of positive association between SBP and DBP and altitude in participants with Tibetan origin. In studies of non-Tibetan origin participants, both average SBP and DBP tended to decrease with elevation but the associations were not statistically significant. For HT, both Tibetan and non-Tibetan populations showed increasing prevalence with increasing altitudes. However, sensitivity analysis by excluding two studies with older participants gave a point estimate consistent with a reduction in HT prevalence in non-Tibetan participants. Based on our models we estimated that more than a quarter of the Tibetan origin populations and less than 15% of the non-Tibetan origin populations had HT (by local definition) at 3000 m. The estimated rate of HT for Tibetan populations at 3000 m is consistent with the estimated global rate of HT in the general population (Kearney and others 2005). However, we have shown that the prevalence rate increases at further higher altitudes, e.g. 44.6% for Tibetans at 4000 m. We were able to demonstrate the known association that men have a higher value of SBP and DBP than women. BMI and body weight were the best predictors of higher BP in HA residents.

Tibetan and non-Tibetan (mainly Andeans) origin populations demonstrate contrasting physiological changes in response to environmental hypoxia and might have developed different genetic variants for better adaptation (Huerta-Sánchez and others 2013). Usually, Tibetan HA populations have a better levels of hypoxic ventilation response, blood oxygen saturation, lung function, maximum cardiac output, sleep quality and a lower levels of pulmonary vasoconstriction and hemoglobin concentration when compared with Andean HA dwellers(Wu and Kayser 2006). Tibetans have also longer generational history at HA and lesser degree of genetic admixture than the Andeans which could have advanced their degree of adaptation (Moore and others 1998).

The discrepancies in BP and HT between Tibetan and non-Tibetan HA populations in the present study may be due to the differences in genetic and lifestyle related risk. Physiological studies show a reduction of systemic BP under hypoxic hypobaric conditions due to the relaxation of smooth muscles, increase in collateral circulation and vascularization (León-Velarde and others 1993; Ostadal and Kolar 2007). However, lifestyle and genetic factors as opposed to direct environmental effects of HA may be more strongly related to BP in Tibetans. The diet of Tibetans traditionally consists of high levels of salt, a minimum 20 to 30 gram per day (Sehgal and others 1968; Sun 1986), which is five times more than the WHO recommendation. Traditional food consumption also comprises high amounts of meat and fat, high alcohol drinking, with low consumption of potassium, fruits and vegetables (Luobu 2012; Zhao and others 2012). These factors are highly associated with the prevalence of HT (Furberg and others 2010). Evidence from genetic studies in Tibetans also suggested associations between the D allele of the angiotensin-converting enzyme gene and HT and higher frequency of the G allele in hypertensive Tibetans (Gesang and others 2002; Kumar and others 2003). On the other hand, in addition to the benefit from hypoxia induced physiological changes, lower mean BP in Andes HA population has also been suggested due to low socio-cultural status, increased intake of minerals such as zinc, healthier diets, lesser thickness of aorta and probable elasticity, and lower cardiac output (Ruiz & Penaloza 1977). Earlier study reported that they had a low prevalence of risk factors for HT such as obesity and smoking (Ruiz and others 1969).

A recent systematic review has suggested the prevalence of HT ranged between 23% to 56% in HA populations of Tibet and estimated a 2% increment in the HT prevalence with every 100 m increment of altitude (Mingji and others 2015). This systematic review suggests that rates of HT may be increasing in some populations living at HA over time. For example, the prevalence of stage II HT has increased by two to three times in Tibet between the period of 1979 (Sun 1986) and 2009 (Zhao and others 2012). This is consistent with lifestyle factors affecting the rising prevalence.

Population origin rather than the country of residence seems to be an important factor for BP variation in those living at HA. Populations with Tibetan ancestry living at HA in China, India, and Nepal, but following their traditional cultural practices, have elevated BP (Matsubayashi and others 2009; Okumiya and others 2010; Sherpa and others 2013; Smith 1999; Tripathy and

Gupta 2007; Zhao and others 2012; Zheng and others 2012). One large Tibetan study of 25,000 adults reported stage II HT (≥160/95mmHg) among 15% of the participants (Sun 1986). Conversely, studies based on populations from South America suggested low BP values (Hernandez-Hernandez and others 2010; Lindgärde and others 2004; Makela and others 1978). In Nepal, highland residents from Tibetan origin had a HT prevalence of 25%, as opposed to just 3.7% in other HA population group (Shrestha and others 2012; Smith 1999). Ethnicity may of course confer a risk of cardiovascular problems both by way of lifestyle and genetic influences.

It has been speculated that systemic BP varies with the time of residence at HA, which gradually becomes lower after years of residence at HA than levels observed among sea level residents (Hanna 1999). Our analysis does not support this because Tibetans from Asia are one of the oldest HA populations dating back to some 25,000 years ago (Beall 2007).

HA is associated with cold temperature which may in turn influence BP. A large British study showed that the higher exposure to the colder climate, combined with poor house quality, is associated with diastolic HT (Mitchell and others 2002). By contrast, hot and humid conditions may cause vasodilation and lower BP (Ladell 1964).

Obesity is an important risk factor for HT (Furberg and others 2010). This was also found in the studies identified in this systematic review. The mechanism by which obesity is linked with HT is not properly understood. However, an increase in sympathetic activity, sodium retention, insulin resistance, hyperleptinemia, and renal abnormalities are thought to be the likely underlying pathways (Hall 2000; Mark and others 1999). Among the studies included in this review which compared mean value of BMI in high and low altitude level; BMI was similar in four studies (Khalid and Adzaku 1995; Lindgärde and others 2004; Negi and others 2012; Smith

1999), lower in HA in one study(Hernandez-Hernandez and others 2010), and no specific trend was observed by altitude levels in one study (Okumiya and others 2010).

Limitations of this review were that it was limited to published and electronically available studies written in English. The “grey literature” and in particular theses, conference papers and government reports were not sought. Publication bias may be present, specifically with regards to Chinese language papers and studies from Andean countries published in Spanish.

Implications for clinical practice, policy and research

The major implications of our findings for clinical practice, policy and research are that clinicians give attention on HT risk in HA populations from Tibetan origin, whatever their current living situation. Culturally driven excessive consumption of salt, alcohol and dietary fats may be the key reasons behind the increased levels of BP among HA Tibetans. Thus, health education and lifestyle modification interventions may be particularly important in this population rather than developing different HT cut-off points. For example, strategies to reduce sodium and increase potassium (e.g. with salt substitutes) might be appropriate (Zhao and others 2014). In light of the relatively poor availability of health care services at HA, we recommend that health policy planners consider strategies (for example health camps) to raise awareness and management of cardiovascular risk factors and disease.

Conclusions and unanswered questions

In this study we presented the evidence of positive association of BP and altitude in adult HA populations from Tibetan origin. This could be due to the additive effects of hypoxia, lifestyle habits (particularly diet), and genetic predisposition. Non-Tibetan HA populations generally found to have a low risk of raised BP. In both population groups, men were more likely than women to have increased BP. Regions with HA countries particularly South Asia, Central Asia, and Africa do not have enough epidemiological data on blood pressure and other cardiovascular risk factors in their HA residents. More population-specific prevalence studies are needed to estimate the comprehensive risk of CVD in these regions.

Figure legends:

Figure 1 : Flow diagram for identification and selection of articles

Figure 2: The relationship between altitude and mean systolic blood pressure in Tibetan (above) and non-Tibetan (below) participants in meta-regression analysis with 95% confidence interval.

Appendix 1: The relationship between altitude and mean systolic (above) and diastolic (below) blood pressure in meta-regression analysis of the studies which have data for both low and high altitudes.

We declare no conflict of interest.

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