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Glucose intolerance associated with hypoxia in people living at high altitudes in the Tibetan highland

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ABSTRACT

Objectives: To clarify the association between glucose intolerance and high altitudes (2900–4800 m) in a hypoxic environment in Tibetan highlanders and to verify the hypothesis that high altitude dwelling increases vulnerability to diabetes mellitus (DM) accelerated by lifestyle change or ageing.

Design: Cross-sectional epidemiological study on Tibetan highlanders.

Participants: We enrolled 1258 participants aged 40–87 years. The rural population comprised farmers in Domkhar (altitude 2900–3800 m) and nomads in Haiyan (3000–3100 m), Ryuho (4400 m) and Changthang (4300–4800 m). Urban area participants were from Leh (3300 m) and Jiegu (3700 m).

Main outcome measure: Participants were classified into six glucose tolerance-based groups: DM, intermediate hyperglycaemia (IHG), normoglycaemia (NG), fasting DM, fasting IHG and fasting NG. Prevalence of glucose intolerance was compared in farmers, nomads and urban dwellers. Effects of dwelling at high altitude or hypoxia on glucose intolerance were analysed with the confounding factors of age, sex, obesity, lipids, haemoglobin, hypertension and lifestyle, using multiple logistic regression.

Results: The prevalence of DM (fasting DM)/IHG (fasting IHG) was 8.9% (6.5%)/25.1% (12.7%), respectively, in all participants. This prevalence was higher in urban dwellers (9.5% (7.1%)/28.5% (11.7%)) and in farmers (8.5% (6.1%)/28.5% (18.3%)) compared with nomads (8.2% (5.7%)/15.7% (9.7%)) (p=0.0140/0.0001). Dwelling at high altitude was significantly associated with fasting IHG+fasting DM/fasting DM (ORs for >4500 and 3500–4499 m were 3.59/4.36 and 2.07/1.76 vs <3500 m, respectively). After adjusting for lifestyle change, hypoxaemia and polycythaemia were closely associated with glucose intolerance.

Conclusions: Socioeconomic factors, hypoxaemia and the effects of altitudes ≥3500 m play a major role in the high prevalence of glucose intolerance in highlanders. Tibetan highlanders may be vulnerable to glucose intolerance, with polycythaemia as a sign of poor hypoxic adaptation, accelerated by lifestyle change and ageing.

Strengths and limitations of this study

- The study showed the first evidence of a close association of glucose intolerance with dwelling at high altitude over 3500 m or hypoxaemia after adjustment of lifestyle-related factors.
- The study also showed the vulnerability of glucose intolerance in high-altitude people with adaptation to hypoxia accelerated by ageing and lifestyle change. In addition, this study used validated POC (point-of-care) analysers for blood glucose and haemoglobin measurement that were not affected by the high-altitude environment.
- Farmers and nomads could be analysed in different altitudes as almost homogeneous subjects. But urban dwellers, who had changed to a modernised lifestyle, were analysed at different altitudes, which was not homogeneous. Multiple logistic regression analysis was used for adjusting lifestyle and other confounding factors.
- It is a cross-sectional study and, thus, requires a future longitudinal study to disclose any causal relations. Also, the genes involved in adaptation to hypoxia were not examined. The study did not investigate whether nutrition and physical activities were confounding factors to glucose intolerance, but measuring body mass index and dyslipidaemia may reflect those effects.

INTRODUCTION

Over many generations, people living at high altitudes have developed unique practices to survive in challenging environments with

limited ecological resources.[1–3] Traditionally, diabetes mellitus (DM) has been uncommon among highlanders[4 5] compared with lowlanders.[6 7] Lifestyle-related diseases, such as DM and hypertension, are rapidly increasing with an increase in longevity and changes in lifestyle worldwide. A remarkable increase in DM has been reported in lowlander and semi-high altitude (around 1300 m) migrants who moved from traditional lifestyles to Westernised lifestyles.[8–10] Prevention of DM has become an urgent issue among lowlanders, especially in developing countries, where the rate of DM prevalence is much faster than in developed countries.[11 12] Older people with a low economic status in rural areas might be vulnerable to impaired glucose tolerance or DM in developed and developing countries.[13 14] An adverse intrauterine environment is a risk factor of diabetes,[15] and there is an association between low birth weight and type 2 diabetes.[16] These phenomena all show adaptation to a low-caloric intake, and the rapid change to a high intake likely increases the risk of diabetes, possibly through a mechanism related to epigenetics.[17 18]

People living at high altitudes not only have the previously mentioned risk factors, but they are also subject to hypoxia in a severe natural environment.[19] High-altitude dwellers show long-term adaptation to harsh environment-induced hypoxia. Highlanders are biologically adapted to hypoxic environments by various genetic mechanisms, such as an increase in haemoglobin concentrations or increased blood flow without polycythaemia.[20 21] Andean people have increased haemoglobin levels as a result of hypoxic adaptation, but they suffer from chronic mountain sickness with excessive polycythaemia as a maladaptation to hypoxia more often than Tibetan people do.[22] Ageing, menopause, respiratory disorders, obesity and hypertension are risk factors of chronic mountain sickness.[23–26] As a result of rapid lifestyle changes related to urbanisation, highlanders are experiencing an alarming increase in diabetes.[27–30] Tibetan residents, especially those who are obese, may be more vulnerable to glucose intolerance[31] compared with Andean people.[5 32] Whether high-altitude dwellers are more vulnerable to diabetes as a result of lifestyle changes, compared with lowlanders, is unknown, but people living at high altitudes are known to be vulnerable to hypertension.[4 33–36]

A population-based study of the effects of high altitude, between 1200 and 3000 m, on the same ethnic group, showed a low prevalence of impaired glucose regulation at high altitudes.[37] Also, an inverse association has been shown between diabetes and altitudes lower than 3500 m in lowlanders.[38] Additionally, lowland patients with diabetes show better glucose intolerance improvement at a mildly high altitude.[39] However, there are no reports on whether dwelling at altitudes over 3500 m and hypoxaemia increases the risk of diabetes. We previously reported a strong association between glucose intolerance and polycythaemia in elderly Tibetan people living in two highland areas.[40] Because they had adapted to hypoxia by reducing polycythaemia, polycythaemia may be regarded as a sign of maladaptation to hypoxia for Tibetan people.

The aim of this study was to clarify the association of glucose intolerance with hypoxaemia or dwelling at altitudes of 2900–4800 m in Tibetan highlanders, and to verify the hypothesis that high-altitude dwelling in Tibetan highlanders increases their vulnerability to DM when accelerated by lifestyle change or ageing. This hypothesis is based both on the current accelerated and modernised lifestyle change occurring in middle-aged and elderly highlanders coming from a traditional childhood lifestyle, and on the high prevalence of polycythaemia in elderly Tibetan highlanders in contrast with younger Tibetans.

METHODS

Study population

This cross-sectional epidemiological study was carried out from 2008 to 2011. A total of 1258 participants aged 40–87 years (mean age±SD, 58.0±11.5 years) were examined. The study population consisted of consecutive volunteers who attended our medical camps held in three highland communities in China as follows: 86 Tibetan nomads (mean age, 66.7±5.3 years; male/female: 40/46) living in a Tibetan nomadic village in Haiyan County (altitude, 3000–3100 m) in 2008; 324 Tibetan urban residents (59.3±10.6 years; 127/197) in Jiegu Town (3700 m) in 2009; and 41 Tibetan nomads in Ryuho (4200–4400 m) in 2011 in Yushu County, Qinghai (table 1).

Participants in three highland communities in Ladakh, India, were examined as follows: 295 Ladakhi farmers (57.3±12.0 years, 113/182) in Domkhar village (2900–3800 m) in 2009; 308 urban residents (42 Ladakhi/266 Tibetan) (58.1±12.2 years, 126/182) in Leh Town (3300 m) in 2010; and 204 nomads (126 Ladakhi/78 Tibetan) (54.4±10.9 years, 113/91) in six villages in Changthang (4300–4800 m) in 2011. The participants consisted of people aged 40 years or older, except for 86 participants in Haiyan who were elderly people aged 60 years or older. Announcements for recruitment were carried out by health staff of Qinghai University and health centres in a nomadic village in Haiyan, and in two villages in Ryuho and Jiegu Town. Announcements were also made to people aged 40 years or older by health staff from Ladakh Institute of Prevention, from health centres and from village leaders in the three villages in Domkhar, four villages in Changthang and five colonies of migrants in Leh. We carried out health checks of the volunteer participants in health centres or community halls in rural villages or towns.

Haiyan County (population, 38 000) contains a Tibetan nomadic village with 465 people aged 60 years or older,[41 42] who were all invited as volunteer participants for medical check-ups. Eighty-six agreed to take

Table 1 Characteristics of the field sites in high-altitude regions

Rural/urban	Area	Altitude (m above MSL)	n (male/female)	Livelihood
Rural	Domkhar in Ladakh	2900–3800	295 (113/182)	Farmer
	Changthang in Ladakh	4300–4800	204 (113/91)	Livestock-rearing nomads
	Haiyan in Qinghai	3000–3100	86 (40/46)	Livestock-rearing nomads
	Ryuho in Qinghai	4200–4400	41 (22/19)	Livestock-rearing nomads
Urban	Leh Town in Ladakh	3300	308 (126/182)	Urban lifestyle
	Jiegu Town in Yushu, Qinghai	3700	324 (127/197)	Urban lifestyle

MSL, mean sea level.

part. The study site in Haiyan County was located between an agricultural area inhabited by Han Chinese and a pastoral area inhabited by native Tibetans.[43]

Ryuho consists of six villages with a total population of 8700, including 1604 residents aged 40 years or older.[44] People in two representative villages were invited to participate in medical check-ups and 41 Tibetan nomads agreed. Their lifestyle is difficult because of the high altitude and severe cold. They move from one pasture (altitude approximately 4100 m) to another (approximately 5000 m) and back every 6 months, along with their livestock.

Jiegu Town, with a population of 23 000, is the seat of Yushu County (population, 67 000) in a nomadic area of Qinghai on the Tibetan plateau. With socioeconomic globalisation, this town is a rapidly developing area (population in 1996, 6460).[45 46] People aged 40 years or older were randomly invited for medical check-ups and 324 of the urban Tibetan residents agreed to participate. These participants had varied occupations, which included being active or retired nomads, farmers or official workers. They were considered to have a lifestyle similar to city dwellers.

Domkhar in Ladakh is a rural village along the Domkhar valley, which consists of the three communities of Dho, Barma and Gongma, at altitudes of 2900, 3400 and 3800 m, respectively, with a total population of 1269 people, including 449 aged 40 years or older.[47] All were invited for medical check-ups, of whom 295 Ladakhi farmers agreed to volunteer as participants in the survey. The area was not easily accessible and Domkhar has only begun to experience the effects of socioeconomic globalisation in the past few years. Most residents were active farmers with traditional lifestyles, who had experienced changes in their food habits and received access to electricity.

Since the 1970s, the residents of Leh Town have had a history of migration from the Changthang area; they comprise Tibetan as well as Ladakhi nomads. From four representative colonies (population 1435), 637 people aged 40 years or older were invited as volunteer participants for medical check-ups, and 308 of these urban residents (266 Tibetans and 42 Ladakhis) agreed to participate in the survey. They were included in the urban population group because they were considered to have adopted a lifestyle similar to that of city dwellers.

Changthang is the highest plateau (altitude 4300–4800 m) among the regions included in this study. From five representative villages (total population 1840), 491 people aged 40 years or older were invited for medical check-ups and 204 nomads (78 Tibetans and 126 Ladakhis) voluntarily agreed to participate. This population is generally made up of nomads who move with their livestock from pasture to pasture every 3 months. Their lifestyle is difficult because of the high altitude and severe cold.

Measurements

Anthropometric measurements, including weight and height, were obtained using standard techniques. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Blood pressure was measured on the arm using an automatic device (HEM 7000; Omron Life Science Co Ltd, Kyoto, Japan) based on the cuff oscillometric principle, and its accuracy has been validated in previous studies.[48] Oxyhaemoglobin saturation (SpO_2) was measured by a pulse oximeter (PULSOX-300; Konica Minolta Co Ltd, Tokyo, Japan). Blood pressure and SpO_2 were measured twice, in the sitting position, after taking a 5 min rest, at least, and the mean systolic blood pressure (SBP), diastolic blood pressure (DBP) and SpO_2 were calculated. Hypertension was defined as SBP ≥140 mm Hg and/or DBP of ≥90 mm Hg and/or taking current antihypertensive medicine.[49]

Overnight fasting venous samples were collected in the morning from all participants. Blood glucose was analysed in venous whole blood by a new-generation StatStrip analyser (Nova Biomedical, Boston, Massachusetts, USA), which has been validated as being affected by neither haematocrit[50–52] nor high altitude.[53] Additionally, the StatStrip is as accurate for measuring plasma glucose as a standard laboratory analyser is,[50–52] although previous analysers were influenced by haematocrit[50–52] and high altitude.[54] Haemoglobin (Hb) was analysed by the Hemocue haemoglobinometer (Hemocue, Angelholm, Sweden).[55 56] Samples were analysed at 15–25°C. Lipids were analysed by either a central laboratory in Qinghai University Hospital, China, or at SRL Inc, India.

Stages of glucose tolerance were classified into either normoglycaemia (NG) or hyperglycaemia (HG) by an oral glucose tolerance test (OGTT) according to WHO

criteria. The presence of HG consisting of DM and intermediate HG (IHG) was defined as follows: DM was fasting blood glucose (FBG) levels ≥7.0 mmol/L or 2 h blood glucose levels of ≥11.1 mmol/L, and IHG was fasting glucose levels ≥6.1 mmol/L and <7.0 mmol/L or 2 h glucose levels ≥7.8 mmol/L and <11.1 mmol/L. Fasting NG and fasting HG were defined using only FBG results. Fasting HG consisted of fasting IHG (FBG levels ≥6.1 and <7.0 mmol/L) and fasting DM (FBG levels ≥7.0 mmol/L).[57]

Overweight was defined as a BMI of 25 or over. Dyslipidaemia was defined as triglycerides ≥150 mg/dL, total cholesterol ≥220 mg/dL and/or high-density lipoprotein (HDL) cholesterol <40 mg/dL. Hypoxaemia was defined as SpO_2 <89 mm Hg. Levels of Hb were classified into four groups: anaemia (Hb <13 g/dL for males and <12 g/dL for females), normal (Hb <18 and ≥13 g/dL for males and Hb <16 and ≥12 g/dL for females), moderate polycythaemia (Hb <21 and ≥18 g/dL for males and Hb <19 and ≥16 g/dL for females) and excessive polycythaemia (Hb ≥21 g/dL for males and ≥19 g/dL for females).

Levels of glycated Hb (HbA1c) based on the National Glycohemoglobin Standardization Program (NGSP) were analysed by Latex agglutination immunoassay (DCA 2000 HbA1c, Siemens Healthcare Co Ltd, Munich, Germany) in 949 participants in all the field sites except for participants in Haiyan. The frequencies of HbA1c levels ≥6.0% and ≥6.5% were compared among the different classifications of glucose intolerance.

The age of the participants was confirmed with reference to carefully prepared cross-tabulation correlating their date of birth with the animal year, which the rural population always remembered, and with historical sentinel events in the case of elderly participants. The interviewers asked participants whether they currently or previously smoked or currently drank alcohol.

Statistics

The χ^2 test, Student t test and one-way analysis of variance (ANOVA) were conducted to analyse: the rate of prevalence of glucose intolerance, hypertension, overweight, hypoxaemia, dyslipidaemia, anaemia and polycythaemia; altitude level, dwelling area and livelihood; mean blood glucose, SBP, DBP, BMI, SpO_2, lipids and Hb levels. The associations of glucose intolerance with the confounding factors, including altitude, hypoxaemia, age, sex, overweight, dyslipidaemia and livelihood, were analysed by multiple logistic regression analysis. Analyses were performed using SPSS V.17.0 (SPSS Inc, Chicago, Illinois, USA). A p value <0.05 was considered statistically significant.

RESULTS

The characteristics of all of the studied variables and the differences by sex are shown in table 2. Male participants were older with a lower prevalence of overweight than female participants. They also had a higher prevalence of IHG/fasting IHG, DM/fasting DM, high triglyceride levels, low HDL levels and dyslipidaemia, excessive polycythaemia and a lower prevalence of anaemia than female participants. In addition, male participants were more prevalent at altitudes over 4500 m and as nomads than female participants, but females were more prevalent as farmers and urban dwellers. The prevalence of current or past smokers was 4.7% (males 9.4% and females 1.1%). The prevalence of current alcohol drinkers was 25.4% (males 35.7% and females 17.6%).

The characteristics of all the studied variables by difference in age are shown in table 3. Male participants were more prevalent at age 70 years or older. The prevalence of dyslipidaemia and hypertension was higher in older participants. Older people were also more prevalent as urban dwellers, but less prevalent in dwelling over 4500 m. Prevalence of hypoxaemia (SpO_2 <89%) was higher in older participants, but not for anaemia and excessive polycythaemia.

Table 4 shows the association of glucose intolerance (fasting IHG/fasting DM or IHG/DM), using the criteria of FBG and OGTT, with all of the studied variables. Glucose intolerance increased with age. Glucose intolerance was also associated with male sex, overweight, dyslipidaemia, hypertension, hypoxaemia, high Hb levels, high HbA1c levels, high altitude and urban dwellers/farmers (vs nomads). Neither smoking nor drinking alcohol was associated with glucose intolerance.

The prevalence of glucose intolerance, overweight, dyslipidaemia, hypertension, hypoxaemia and polycythaemia are shown at different altitude areas in farmers, nomads and urban dwellers (table 5). In farmers, the prevalence of fasting HG using the FBG criterion was significantly increased with elevation of altitude (2900, 3400 and 3800 m) in the three communities of Dho, Barma and Gongma (n=106 (16.0%), 74 (20.3%), 115 (34.8%), respectively, p=0.0033) in Domkhar, Ladakh. The prevalence of HG, using the OGTT criterion in the three communities, was also increased (30.2%, 36.5%, 43.5%, respectively), but not significantly. In comparison, between the two altitude levels of <3500 m (Dho and Barma) and ≥3500 m (Gongma), the prevalence of glucose intolerance using the FBG criterion was significantly increased with elevation of altitude (fasting HG: 17.8% vs 34.8%, fasting DM: 3.3% vs 10.4%, HbA1c >6.0%: 15.5% vs 29.9%) in spite of the low prevalence of overweight people dwelling at a higher altitude compared with those at a lower altitude (table 5).

A comparison of nomad participants was conducted between Haiyan and Ryuho in Qinghai, and the prevalence of fasting HG using the FBG criterion was found to increase, but not significantly (8.1% vs 12.2%) with elevation of altitude (3000–3100 vs 4200–4400 m). In Changthang-1 and Changthang-2 in Ladakh, the

Table 2 Characteristics of the studied variables by sex

	All	Male	Female	p Value
N	1258	541	717	
(%)		43.0 (40.3 to 45.7)	57.0 (54.3 to 59.7)	
Age (years)	58.0±11.5	58.9±11.8	57.3±11.2	0.0120
Height (cm)	157.4±9.4	163.9±8.1	152.4±7.0	<0.0001
Weight (kg)	60.8±13.9	64.8±13.1	57.8±13.7	<0.0001
BMI	24.4±4.5	24.0±4.1	24.7±4.9	0.0064
Overweight (BMI≥25) (%)	40.1 (37.4 to 42.8)	36.6 (32.5 to 40.7)	42.8 (39.2 to 46.4)	0.0259
Blood glucose				
FBG (mg/dL)	101.3±24.5	104.7±29.6	98.7±19.5	<0.0001
2 h-BG (mg/dL)	124.9±50.1	129.3±58.6	121.6±42.3	0.0068
Fasting IHG/Fasting DM (%)	12.7 (10.9 to 14.5)/6.5 (5.1 to 7.9)	15.3 (12.3 to 18.3)/9.6 (7.1 to 12.1)	10.7 (8.4 to 13.0)/4.2 (2.7 to 5.7)	<0.0001
IHG/DM (%)	25.1 (22.7 to 27.5)/8.9 (7.3 to 10.5)	27.5 (23.7 to 31.3)/12.0 (9.3 to 14.7)	23.3 (20.2 to 26.4)/6.6 (4.8 to 8.4)	0.0002
Dyslipidaemia	34.8 (32.2 to 37.4)	38.3 (34.2 to 42.4)	32.2 (28.3 to 36.1)	0.0259
Triglycerides	98.5±58.3	104.8±56.5	93.7±59.3	0.0012
Triglycerides ≥150 mg/dL (%)	12.3 (10.5 to 14.1)	16.0 (12.9 to 19.1)	9.6 (7.1 to 12.1)	0.0011
Total cholesterol	187.3±46.2	185.5±45.2	188.4±47.4	NS
Total cholesterol ≥220 mg/dL (%)	21.9 (19.6 to 24.2)	20.1 (16.7 to 23.5)	23.3 (20.2 to 26.4)	NS
HDL cholesterol	52.6±16.2	50.7±20.2	54.1±12.0	0.0003
HDL cholesterol<40 mg/dL (%)	13.8 (11.9 to 15.7)	19.3 (16.0 to 22.6)	9.6 (7.4 to 11.8)	<0.0001
SBP (mm HG)	134.0±25.1	135.6±23.4	132.8±26.3	0.0507
DBP (mm HG)	85.6±14.4	86.0±14.2	85.2±14.5	NS
Hypertension (%)	40.4 (37.7 to 43.1)	42.7 (38.5 to 46.9)	38.7 (35.1 to 42.3)	NS
Livelihood				
Farmer (%)	23.5 (21.2 to 25.8)	20.9 (17.5 to 24.3)	25.4 (22.2 to 28.6)	0.0001
Nomad (%)	26.3 (23.9 to 28.7)	32.3 (28.4 to 36.2)	21.8 (18.8 to 24.8)	
Urban dweller (%)	50.2 (47.4 to 53.0)	46.8 (42.6 to 51.0)	52.9 (49.2 to 56.6)	
Altitude (m)	3641.7±523.3	3691.7±562.3	3603.9±488.9	0.0032
Altitude level (%)				
2500–3499 m	45.6 (42.8 to 48.4)	44.4 (40.2 to 48.6)	46.6 (42.9 to 50.3	0.0002
3500–4499 m	41.9 (39.2 to 44.6)	38.8 (34.7 to 42.9)	44.2 (40.6 to 47.8)	
4500+ m	12.5 (10.7 to 14.3)	16.8 (13.6 to 20.0)	9.2 (7.1 to 11.3)	
SpO_2 (%)	90.6±4.3	90.8±4.1	90.5±4.4	NS
Hypoxaemia (SpO_2 <89%) (%)	25.2 (22.8 to 27.6)	25.0 (21.4 to 28.6)	25.4 (22.2 to 28.6)	NS
Hb (g/dL)	15.6±2.7	17.1±2.3	14.5±2.4	<0.0001
Group according to Hb (%)				
Anaemia	7.5 (6.0 to 9.0)	2.0 (0.8 to 3.2)	11.6 (9.3 to 13.9)	<0.0001
Normal	56.4 (53.7 to 59.1)	59.3 (55.2 to 63.4)	54.3 (50.7 to 57.9)	
Moderate polycythaemia	27.7 (25.2 to 30.2)	24.8 (21.2 to 28.4)	29.8 (26.5 to 33.1)	
Excessive polycythaemia	8.4 (6.9 to 9.9)	13.9 (11.0 to 16.8)	4.3 (2.8 to 5.8)	

Values are mean±SD, or % (95% CI).
Data were analysed using χ^2 test for comparison of the rates of variables, and by the Student t test for comparison of variables between males and females.
2h-BG, 2 h blood glucose following 75 g OGTT; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus by OGTT; fasting DM, fasting diabetes mellitus by FBG; fasting IHG, fasting intermediate hyperglycaemia by FBG; FBG, fasting blood glucose; Hb, haemoglobin; HDL, high-density lipoprotein; NS, not significant; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; SpO_2, oxyhaemoglobin saturation measured by pulse oximeter.

Table 3 Characteristics of the studied variables by age

	Age (years)				p Value
	40–49	50–59	60–69	70+	
N	354	287	384	233	
Male (vs female) (%)	42.1 (37.0 to 47.2)	38.3 (32.7 to 43.9)	41.9 (37.0 to 46.8)	51.9 (45.5 to 58.3)	0.0152
Overweight (BMI≥25) (%)	39.8 (34.7 to 44.9)	38.0 (32.4 to 43.6)	42.7 (37.8 to 47.6)	39.1 (32.8 to 45.4)	NS
Dyslipidaemia (%)	29.1 (24.4 to 33.8)	30.7 (25.4 to 36.0)	42.7 (37.0 to 48.4)	35.6 (30.1 to 41.1)	0.0005
Triglycerides ≥150 mg/dL	10.7 (7.5 to 13.9)	13.3 (9.4 to 17.2)	14.2 (10.7 to 17.7)	10.8 (6.8 to 14.8)	NS
Total cholesterol ≥220 mg/dL	12.4 (9.0 to 15.8)	16.1 (11.8 to 20.4)	34.6 (29.8 to 39.4)	24.1 (18.6 to 29.6)	<0.0001
HDL cholesterol <40 mg/dL	17.9 (13.9 to 21.9)	10.7 (7.1 to 14.3)	11.3 (8.1 to 14.5)	15.1 (10.5 to 19.7)	0.0259
Hypertension (%)	23.4 (19.0 to 27.8)	39.0 (33.4 to 44.6)	44.8 (39.8 to 49.8)	61.0 (54.7 to 67.3)	<0.0001
Livelihood (%)					
Farmer	25.1 (20.6 to 29.6)	28.6 (23.4 to 33.8)	18.8 (14.9 to 22.7)	22.3 (17.0 to 7.6)	0.0125
Nomad	29.4 (24.7 to 34.1)	23.7 (18.8 to 28.6)	28.4 (23.9 to 32.9)	21.5 (16.2 to 26.8)	
Urban dweller	45.5 (40.3 to 50.7)	47.7 (41.9 to 53.5)	52.9 (47.9 to 57.9)	56.2 (49.8 to 62.6)	
Altitude level (%)					
2500–3499 m	41.5 (36.4 to 46.6)	46.3 (40.5 to 52.1)	43.5 (38.5 to 48.5)	54.5 (48.1 to 60.9)	<0.0001
3500–4499 m	42.1 (37.0 to 47.2)	36.9 (31.3 to 42.5)	47.1 (42.1 to 52.1)	39.1 (32.8 to 45.4)	
4500+ m	16.4 (12.5 to 20.3)	16.7 (12.4 to 21.0)	9.4 (6.5 to 12.3)	6.4 (3.3 to 9.5)	
Hypoxaemia					
SpO_2 <89% (%)	20.1 (15.9 to 24.3)	23.7 (18.8 to 28.6)	26.3 (21.9 to 30.7)	33.0 (27.0 to 39.0)	0.0043
Group according to Hb (%)					
Anaemia	13.3 (9.8 to 16.8)	5.2 (2.6 to 7.8)	4.7 (2.6 to 6.8)	6.0 (3.0 to 9.0)	<0.0001
Normal	49.4 (44.2 to 54.6)	54.4 (48.6 to 60.2)	59.9 (55.0 to 64.8)	63.9 (57.7 to 70.1)	
Polycythaemia	24.9 (20.4 to 29.4)	31.0 (25.6 to 36.4)	29.9 (25.3 to 34.5)	24.0 (18.5 to 29.5)	
Excessive polycythaemia	12.4 (9.0 to 15.8)	9.4 (6.0 to 12.8)	5.5 (3.2 to 7.8)	6.0 (3.0 to 9.0)	

Values are % (95% CI).
BMI, body mass index; Hb, haemoglobin; HDL, high-density lipoprotein; SpO_2, oxyhaemoglobin saturation measured by pulse oximeter.

prevalence of fasting HG using FBG criterion increased (12.8% vs 21.0%) with elevation of altitude (4300–4400 vs 4500–4800 m), but not significantly, while the prevalence of fasting DM significantly increased (0.0% vs 8.9%, p=0.0339). Comparing the three altitude levels, <3500 (Haiyan), 3500–4499 (Ryuho and Changthang-1) and ≥4500 m (Changthang-2), the prevalence of glucose intolerance with the FBG criterion was significantly increased with elevation of altitude (fasting HG: 8.1% (Haiyan) vs 12.5% (Ryuho and Changthang-1) vs 21.0% (Changthan-2), fasting DM: 3.5% vs 2.3% vs 8.9%) despite the low prevalence of overweight and dyslipidaemia in people dwelling at a higher altitude than at a lower altitude (table 5).

In urban dwellers, using both criteria to measure fasting HG, fasting DM, HG, DM and HbA1c, showed that the prevalence of glucose intolerance increased significantly with elevation of altitude (table 5). The results also indicated a greater prevalence of overweight and hyperlipidaemia in people dwelling at a higher altitude than in those at a lower altitude. Prevalence of hypertension was not associated with altitude levels in farmers, nomads and urban dwellers.

Prevalence of hypoxaemia and polycythaemia was significantly increased with elevation of altitude in all the groups of farmers, nomads and urban dwellers.

The association of the variables Hb, overweight and glucose intolerance, with hypoxaemia (SpO_2 <89%) as the dependent variable, was separately analysed after adjustment for age, sex and altitude levels, using multiple logistic regression (models 1–3). Polycythaemia (model 1), overweight (models 2 and 3), fasting HG (model 2), fasting DM (OR=1.70, CI 1.02 to 2.85, vs no fasting DM, p=0.0413), HG (model 3) and DM (OR=1.90, CI 1.21 to 2.96, vs no DM, P=0.0049) were associated with hypoxaemia independent of altitude levels (see online supplementary table S1).

The variables that were associated with glucose intolerance and adjusted for age and sex in the four models (for dependent variables of fasting HG, fasting DM, HG and DM) by multiple logistic regression analysis are shown in table 6. Overweight (all models), hypoxaemia (all models), dyslipidaemia (all models), polycythaemia (all models), farmers (models for fasting HG and for HG, vs nomads) and urban dwellers (models for HG vs nomads) were associated with glucose intolerance after adjustment for age and sex. Altitude level of 3500–4499 m was closely associated with all models, while the highest level of ≥4500 m was associated with fasting HG and fasting DM, but not with HG or DM. By classifying the altitude level into two groups of 2500–3499 and ≥3500 m and analysing by multiple logistic regression, the altitude level of ≥3500 m was closely associated with glucose intolerance in all the models compared with 2500–3499 m altitude.

The associations of high altitude, hypoxaemia and polycythaemia with glucose intolerance and adjusted for related variables in the four models were analysed by

Table 4 Variables associated with glucose intolerance

	All	By FBG			p Value	By OGTT			p Value
		Fasting NG	Fasting IHG	Fasting DM		NG	IHG	DM	
N	1258	1016	160	82		830	316	112	
%		80.8 (78.6 to 83.0)	12.7 (10.9 to 14.5)	6.5 (5.1 to 7.9)		66.3 (63.7 to 68.9)	24.9 (22.5 to 27.3)	8.8 (7.2 to 10.4)	
Sex	n	(%)	(%)	(%)		(%)	(%)	(%)	
Male	541	75.0 (71.4 to 78.6)	15.3 (12.3 to 18.3)	9.6 (7.1 to 12.1)	<0.0001	60.4 (56.3 to 64.5)	27.5 (23.7 to 31.1)	12.0 (9.3 to 14.7)	0.0002
Female	717	85.1 (82.5 to 87.7)	10.7 (8.4 to 13.0)	4.2 (2.7 to 5.7)	<0.0001	70.2 (66.9 to 73.5)	23.3 (20.2 to 26.4)	6.6 (4.8 to 8.4)	
Age (years)	n	(%)	(%)	(%)	0.1012	(%)	(%)	(%)	0.0005
40–49	354	84.7 (80.9 to 88.5)	10.5 (7.3 to 13.7)	4.8 (2.6 to 7.0)		72.6 (68.0 to 77.2)	21.8 (17.5 to 26.1)	5.7 (3.3 to 8.1)	
50–59	287	82.2 (77.8 to 86.6)	11.2 (7.6 to 14.8)	6.6 (3.7 to 9.5)		70.7 (65.4 to 76.0)	20.2 (15.6 to 24.8)	9.1 (5.8 to 12.4)	
60–69	384	75.8 (71.5 to 80.1)	15.9 (12.2 to 19.6)	8.3 (5.5 to 11.1)		60.9 (56.0 to 65.8)	27.6 (23.1 to 32.1)	11.5 (8.3 to 14.7)	
70+	233	81.1 (76.1 to 86.1)	12.9 (8.6 to 17.2)	6.0 (3.0 to 9.0)		58.4 (52.1 to 64.7)	32.2 (26.2 to 38.2)	9.4 (5.7 to 13.1)	
BMI	n	(%)	(%)	(%)		(%)	(%)	(%)	
Normal	753	84.1 (81.5 to 86.7)	11.0 (8.8 to 13.2)	4.9 (3.4 to 6.4)	0.0008	72.0 (68.8 to 75.2)	21.4 (18.5 to 24.3)	6.6 (4.8 to 8.4)	<0.0001
Overweight (BMI ≥25%)	505	75.8 (72.1 to 79.5)	15.2 (12.1 to 18.3)	8.9 (6.4 to 11.4)		57.0 (52.7 to 61.3)	30.7 (26.7 to 34.7)	12.3 (9.4 to 15.2)	
Dyslipidaemia	n	(%)	(%)	(%)		(%)	(%)	(%)	
Normal	820	84.1 (81.6 to 86.6)	11.5 (9.3 to 13.7)	4.4 (3.0 to 5.8)	<0.0001	70.0 (66.9 to 73.1)	24.3 (21.4 to 27.2)	5.7 (4.1 to 7.3)	<0.0001
Dyslipidaemia	438	74.4 (70.3 to 78.5)	15.1 (11.7 to 18.5)	10.5 (7.6 to 13.4)		58.4 (53.8 to 63.0)	26.7 (22.6 to 30.8)	14.8 (11.5 to 18.1)	
Blood pressure	n	(%)	(%)	(%)		(%)	(%)	(%)	
Normal	749	83.3 (80.6 to 86.0)	11.5 (9.2 to 13.8)	5.2 (3.6 to 6.8)	0.0220	70.9 (67.6 to 74.2)	22.3 (19.3 to 25.3)	6.8 (5.0 to 8.6)	<0.0001
Hypertension	509	77.4 (73.8 to 81.0)	14.3 (11.3 to 17.3)	8.3 (5.9 to 10.7)		59.1 (54.8 to 63.4)	29.3 (25.3 to 33.3)	11.6 (8.8 to 14.4)	
Livelihood	n	(%)	(%)	(%)		(%)	(%)	(%)	
Farmer	295	75.6 (70.7 to 80.5)	18.3 (13.9 to 22.7)	6.1 (3.4 to 8.8)	0.0140	63.1 (57.6 to 68.6)	28.5 (23.3 to 33.7)	8.5 (5.3 to 11.7)	0.0001
Nomad	331	84.6 (80.7 to 88.5)	9.7 (6.5 to 12.9)	5.7 (3.2 to 8.2)		76.1 (71.5 to 80.7)	15.7 (11.8 to 19.6)	8.2 (5.2 to 11.2)	
Urban dweller	632	81.2 (78.2 to 84.2)	11.7 (9.2 to 14.2)	7.1 (5.1 to 9.1)		62.0 (58.2 to 65.8)	28.5 (25.0 to 32.0)	9.5 (7.2 to 11.8)	
Altitude level (m)	n	(%)	(%)	(%)		(%)	(%)	(%)	
2500–3499	574	88.3 (85.7 to 90.9)	8.5 (6.2 to 10.8)	3.1 (1.7 to 4.5)	<0.0001	70.7 (67.0 to 74.4)	23.2 (19.7 to 26.7)	6.1 (4.1 to 8.1)	<0.0001
3500–4499	527	73.1 (69.5 to 76.7)	17.5 (14.4 to 20.6)	9.5 (7.1 to 11.9)		58.1 (54.1 to 62.1)	30.2 (26.4 to 34.0)	11.8 (9.2 to 14.4)	
4500+	157	79.0 (72.6 to 85.4)	12.1 (7.0 to 17.2)	8.9 (4.4 to 13.4)		75.2 (68.4 to 82.0)	15.3 (9.7 to 20.9)	9.6 (5.0 to 14.2)	
SpO_2	n	(%)	(%)	(%)		(%)	(%)	(%)	
Normal	941	83.2 (80.8 to 85.6)	11.5 (9.5 to 13.5)	5.3 (3.9 to 6.7)	0.0004	68.2 (65.2 to 71.2)	24.4 (21.7 to 27.1)	7.3 (5.6 to 9.0)	0.0010
Hypoxaemia (SpO_2 <89%)	317	73.5 (68.6 to 78.4)	16.4 (12.3 to 20.5)	10.1 (6.8 to 13.4)		59.3 (53.9 to 64.7)	27.1 (22.2 to 32.0)	13.6 (9.8 to 17.4)	
Group according to Hb	n	(%)	(%)	(%)		(%)	(%)	(%)	
Anaemia	94	86.2 (79.2 to 93.2)	11.7 (5.2 to 18.2)	2.1 (0 to 5.0)	<0.0001	73.4 (64.5 to 82.3)	23.4 (14.8 to 32.0)	3.2 (0 to 6.8)	<0.0001
Normal	710	86.3 (83.8 to 88.8)	10.1 (7.9 to 12.3)	3.5 (2.1 to 4.9)		71.3 (68.0 to 74.6)	23.2 (20.1 to 26.3)	5.5 (3.8 to 7.2)	
Polycythaemia	348	73.3 (68.7 to 77.9)	16.4 (12.5 to 20.3)	10.3 (7.1 to 13.5)		57.5 (52.3 to 62.7)	29.0 (24.2 to 33.8)	13.5 (9.9 to 17.1)	
Excessive polycythaemia	106	63.2 (54.0 to 72.4)	18.9 (11.4 to 26.4)	17.9 (10.6 to 25.2)		51.9 (42.4 to 61.4)	26.4 (18.0 to 34.8)	21.7 (13.9 to 29.5)	

Continued

Table 4 Continued

	All	Fasting NG	By FBG Fasting IHG	Fasting DM	p Value	NG	By OGTT IHG	DM	p Value
Blood sugar	n								
FBG (mg/dL)	1258	93.9±9.6	115.2±4.2***	166.0±53.3***,†	<0.0001	93.3±9.3	105.3±12.2***	148.8±54.4***,†	<0.0001
2 h-BG (mg/dL)	1258	116.4±31.1	130.7±41.2***	224.5±114.3***,†	<0.0001	105.5±19.2	141.3±29.4***	226.2±98.1***,†	<0.0001
N	949	769	123	57		619	253	77	
HbA1c (%)		5.7±0.5	5.9±0.6**	7.2±2.4***,†	<0.0001	5.7±0.5	5.8±0.4*	7.0±2.2***,†	<0.0001
≥6.0% (%)		22.4 (19.5 to 25.3)	36.6 (28.1 to 45.1)	59.6 (46.9 to 72.3)	<0.0001	18.9 (15.8 to 22.0)	34.4 (28.5 to 40.3)	61.0 (50.1 to 71.9)	<0.0001
≥6.5% (%)		2.3 (1.2 to 3.4)	14.6 (8.4 to 20.8)	35.1 (22.7 to 47.5)	<0.0001	1.8 (0.8 to 2.8)	7.1 (3.9 to 10.3)	35.1 (24.4 to 45.8)	<0.0001

Values are % (95% CI) or mean±SD.
Fasting NG, fasting normoglycaemia (FBG levels <110 mg/dL) by FBG; NG, normoglycaemia (fasting glucose levels <110 mg/dL and 2 h glucose levels <140 mg/dL) by OGTT.
Data were analysed by the χ^2 test for comparison of the rate of variables, or by ANOVA and Fisher's PLSD for the comparison of mean of variables among fasting NG, fasting IHG and fasting DM by FBG, and among NG, IHG and DM, by the OGTT.
*p<0.05, **p<0.01, ***p<0.0001 vs FNG or NG by ANOVA (Fisher's PLSD).
†p<0.0001 vs FIHG or IHG by ANOVA (Fisher's PLSD).
2h-BG, 2 h blood glucose following 75 g OGTT; ANOVA, analysis of variance; BMI, body mass index; DM, diabetes mellitus by OGTT; fasting DM, fasting diabetes mellitus by FBG; fasting IHG, fasting intermediate hyperglycaemia by FBG; FBG, fasting blood glucose; Hb, haemoglobin; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; SpO_2, oxyhaemoglobin saturation measured by pulse oximeter.

multiple logistic regression (table 7). For the dependent variables of glucose intolerance (fasting HG/fasting DM) as measured using the FBG criterion, the results showed that dwelling at high altitudes was a closely associated factor (ORs of fasting HG/fasting DM for >4500 and 3500–3999 m were 3.59/4.36 and 2.07/1.76 vs <3500 m) independent of hypoxaemia and the lifestyle-related factors of overweight and livelihood. Classifying the altitude levels into two groups, 2500–3499 and ≥3500 m, and using multiple logistic regression analysis, the ≥3500 m altitude level was also closely associated with fasting HG (OR=2.19, CI 1.53 to 3.12, p<0.0001) and fasting DM (OR=1.94, CI 1.06 to 3.55, p=0.0305), but not with HG and not with DM. For the dependent variables of glucose intolerance (HG and DM), using the OGTT criterion, there was no association with dwelling at a high altitude, but hypoxaemia was a closely associated factor. Polycythaemia, overweight, dyslipidaemia, farmers and urban dwellers were also closely associated with glucose intolerance according to both criteria. Hypertension was not associated with glucose intolerance by multivariate analysis.

The effect of livelihood or ethnicity on the association between altitudes and fasting HG was analysed and is shown in online supplementary table S2. In models 1–3, multivariate analyses were carried out separately in each livelihood of farmer, nomad and urban dweller. In farmers and nomads, higher altitude had significantly higher OR for fasting HG compared with lower altitude, but not in urban dwellers after adjustment with other confounding factors. In models 4 and 5, multivariate analysis was carried out separately in each ethnic group, Tibetan and Ladakhi. Higher altitude had significantly greater OR compared with lower altitude in both groups. The OR was higher in the Ladakhi (2.53 vs 1.69) than in the Tibetan group. In models 6 and 7, multivariate analysis was carried out in all participants, and higher altitude had significantly greater OR compared with lower altitude independently of livelihood and ethnicity (see online supplementary table S2).

DISCUSSION

Association of hypoxaemia with glucose intolerance

The association of glucose intolerance with lifestyle-related health factors and hypoxaemia was studied in 1258 residents dwelling at a wide range of altitudes from 2900 to 4800 m in the Tibetan highland. Previous studies have reported a negative association between glucose intolerance and altitudes below 3500 m in Tibetans[37] and lowlanders.[38] To the best of our knowledge, we showed, for the first time, epidemiological evidence of a positive association between the prevalence of fasting glucose intolerance at high altitudes over 3500 m and independently of hypoxaemia. These positive effects of dwelling at high altitudes were more distinct when glucose intolerance was defined by FBG. The association of high altitude ≥3500 m with fasting HG was

Table 5 Prevalence of glucose intolerance and other variables at different altitudes, in farmers, nomads and urban dwellers

	Altitude (m above MSL)			
	2500–3499 m	3500–4499 m	4500+ m	p Value
Farmer				
	Dho and Barma (2900–3400 m) n=180	Gongma (3800 m) n=115		
Age	56.7±12.7	58.0±11.5		NS
Male (%)	41.3 (34.1 to 48.5)	33.9 (25.2 to 42.6)		NS
Fasting hyperglycaemia (%)	17.8 (12.2 to 23.4)	34.8 (26.1 to 43.5)		0.0009
Fasting DM (%)	3.3 (0.7 to 5.9)	10.4 (4.8 to 16.0)		0.0129
Hyperglycaemia (%)	32.8 (25.9 to 39.7)	43.5 (34.4 to 52.6)		0.0633
DM (%)	7.2 (3.4 to 11.0)	10.4 (4.8 to 16.0)		NS
Overweight (%)	21.7 (15.7 to 27.7)	11.3 (5.5 to 17.1)		0.0227
Dyslipidaemia (%)	16.7 (11.3 to 22.1)	17.4 (10.5 to 24.3)		NS
Hypertension (%)	34.4 (27.5 to 41.3)	41.7 (32.7 to 50.7)		NS
Hypoxaemia (%)	13.3 (8.3 to 18.3)	30.4 (22.0 to 38.8)		0.0004
Polycythaemia (moderate and excessive) (%)	18.4 (12.7 to 24.1) n=161	35.6 (26.8 to 44.4) n=107		0.0014
HbA1c ≥6.0% (%)	15.5 (9.9 to 21.1)	29.9 (21.2 to 38.6)		0.0048
Nomad				
	Haiyan (3000–3100 m) n=86	Ryuho and Chngthang-1 (4100–4400 m) n=88	Changthang-2 (4500–4800 m) n=157	
Age	66.7±5.3	52.6±10.8	54.5±10.5	<0.0001
Male (%)	46.5 (36.0 to 57.0)	50.0 (39.6 to 60.4)	58.0 (50.3 to 65.7)	NS
Fasting hyperglycaemia (%)	8.1 (2.3 to 13.8)	12.5 (5.6 to 19.4)	21.0 (14.6 to 27.4)	0.0197
Fasting DM (%)	3.5 (0 to 7.4)	2.3 (0 to 5.4)	8.9 (4.4 to 13.4)	0.0581
Hyperglycaemia (%)	20.9 (12.3 to 29.5)	25.0 (16.0 to 34.0)	24.8 (18.0 to 31.6)	NS
DM (%)	8.1 (2.3 to 13.9)	5.7 (0.9 to 10.5)	9.6 (5.0 to 14.2)	NS
Overweight (%)	40.7 (30.3 to 51.1)	40.9 (30.6 to 51.2)	19.7 (13.5 to 25.9)	0.0002
Dyslipidaemia (%)	59.3 (48.9 to 69.7)	45.5 (35.1 to 55.9)	26.1 (19.2 to 33.0)	<0.0001
Hypertension (%)	34.9 (24.8 to 45.0)	23.9 (15.0 to 32.8)	24.8 (18.0 to 31.6)	NS
Hypoxaemia (%)	25.6 (16.4 to 34.8)	36.2 (26.2 to 46.2)	63.7 (56.2 to 71.2)	<0.0001
Polycythaemia (moderate and excessive) (%)	36.1 (25.9 to 46.3)	64.7 (54.7 to 74.7) n=73	64.3 (56.8 to 71.8) n=118	0.0016
HbA1c ≥6.0% (%)	–	24.7 (14.8 to 34.6)	26.3 (18.4 to 34.2)	NS
Urban dweller				
	Leh Town, Ladakh (3300 m) n=308	Yushu, Qinghai (3700 m) n=324		
Age	58.1±12.2	59.3±10.6		NS
Male (%)	40.9	39.2		NS
Fasting hyperglycaemia (%)	9.1 (5.9 to 12.3)	28.1 (23.2 to 33.0)		<0.0001
Fasting DM (%)	2.9 (1.0 to 4.8)	11.1 (7.7 to 14.5)		<0.0001
Hyperglycaemia (%)	29.5 (24.4 to 34.6)	46.0 (40.6 to 51.4)		<0.0001
DM (%)	4.9 (2.5 to 7.3)	13.9 (10.1 to 17.7)		0.0001
Overweight (%)	42.9 (37.4 to 48.4)	67.6 (62.5 to 72.7)		<0.0001
Dyslipidaemia (%)	24.0 (19.2 to 28.8)	56.2 (50.8 to 61.6)		<0.0001
Hypertension (%)	48.1 (42.5 to 53.7)	49.4 (44.0 to 54.8)		NS
Hypoxaemia (%)	8.4 (5.3 to 11.5)	27.8 (22.9 to 32.7)		<0.0001
Polycythaemia (moderate and excessive) (%)	10.1 (6.7 to 13.5) n=305	49.4 (44.0 to 54.8) n=185		<0.0001
HbA1c ≥6.0% (%)	22.3 (17.6 to 27.0)	41.6 (34.5 to 48.7)		<0.0001

Values are mean±SD, n, or % (95% CI).
Data were analysed by the χ^2 test for comparison of the rate of variables, or by the ANOVA for age among the different altitude groups.
ANOVA, analysis of variance; DM, diabetes mellitus; HbA1c, glycated haemoglobin; MSL, mean sea level; NS, not significant.

Table 6 Variables associated with glucose intolerance adjusted for age and sex by multiple logistic regression analysis

	Fasting hyperglycaemia			Fasting DM			Hyperglycaemia (OGTT)			DM (OGTT)		
	OR	CI	p Value	OR	CI	p Value	OR	CI	p Value	OR	CI	p Value
Age (years)												
40–49	Reference			Reference			Reference			Reference		
50–59	1.20	(0.79 to 1.83)	NS	1.41	(0.72 to 2.76)	NS	1.10	(0.78 to 1.55)	NS	1.66	(0.91 to 3.05)	0.0992
60–69	1.78	(1.22 to 2.58)	0.0025	1.80	(0.98 to 3.31)	0.0572	1.70	(1.25 to 2.32)	0.0008	2.16	(1.25 to 3.75)	0.006
70+	1.29	(0.84 to 2.00)	NS	1.27	(0.61 to 2.62)	NS	1.89	(1.33 to 2.68)	0.0004	1.74	(0.93 to 3.27)	0.0843
Male (vs female)	1.90	(1.43 to 2.52)	<0.0001	2.44	(1.54 to 3.89)	0.0002	1.54	(1.22 to 1.95)	0.0003	1.95	(1.31 to 2.89)	0.0009
Overweight (BMI ≥25)	1.77	(1.33 to 2.36)	<0.0001	2.05	(1.30 to 3.23)	0.0022	2.02	(1.58 to 2.57)	<0.0001	2.10	(1.41 to 3.12)	0.0003
Dyslipidaemia	1.70	(1.27 to 2.27)	0.0003	2.38	(1.50 to 3.76)	0.0002	1.56	(1.22 to 1.99)	0.0004	2.69	(1.80 to 4.01)	<0.0001
Triglycerides ≥150	3.28	(2.26 to 4.77)	<0.0001	3.25	(1.93 to 5.48)	<0.0001	2.79	(1.95 to 3.99)	<0.0001	3.7	(2.33 to 5.89)	<0.0001
Total cholesterol ≥220	1.71	(1.22 to 2.38)	0.0018	2.49	(1.52 to 4.08)	0.0003	1.6	(1.19 to 2.14)	0.0017	2.88	(1.88 to 4.43)	<0.0001
HDL cholesterol <40	1.50	(1.01 to 2.23)	0.0441	1.70	(0.95 to 3.03)	0.0736	1.4	(0.99 to 1.98)	0.0579	1.39	(0.81 to 2.39)	NS
Hypertension	1.40	(1.04 to 1.87)	0.0272	1.58	(0.99 to 2.52)	0.0544	1.53	(1.20 to 1.96)	0.0007	1.68	(1.12 to 2.52)	0.0128
Livelihood												
Farmer	2.06	(1.37 to 3.11)	0.0005	1.24	(0.63 to 2.43)	NS	2.10	(1.47 to 2.99)	<0.0001	1.17	(0.66 to 2.07)	NS
Nomad	Reference			Reference			Reference			Reference		
Urban dweller	1.38	(0.96 to 2.00)	0.0817	1.40	(0.80 to 2.45)	NS	2.06	(1.52 to 2.80)	<0.0001	1.26	(0.78 to 2.03)	NS
Altitude level (n=1275)												
2500–3499 m	Reference			Reference			Reference			Reference		
3500–4499 m	2.87	(2.07 to 3.97)	<0.0001	3.31	(1.90 to 5.79)	<0.0001	1.80	(1.40 to 2.33)	<0.0001	2.10	(1.36 to 3.26)	0.0009
4500+ m	1.95	(1.22 to 3.13)	0.0055	2.81	(1.35 to 5.88)	0.006	0.82	(0.54 to 1.24)	NS	1.60	(0.84 to 3.05)	NS
Hypoxaemia												
SpO_2 <89%	1.81	(1.33 to 2.46)	0.0002	2.06	(1.29 to 3.29)	0.0027	1.42	(1.09 to 1.86)	0.0098	1.99	(1.32 to 2.99)	0.0010
Group according to Hb												
Anaemia	1.44	(0.76 to 2.75)	NS	0.92	(0.21 to 4.01)	NS	1.17	(0.70 to 1.93)	NS	0.83	(0.25 to 2.78)	NS
Normal	Reference			Reference			Reference			Reference		
Moderate polycythaemia	2.50	(1.80 to 3.46)	<0.0001	3.48	(2.03 to 5.95)	<0.0001	1.98	(1.50 to 2.60)	<0.0001	2.92	(1.86 to 4.60)	<0.0001
Excessive polycythaemia	3.67	(2.30 to 5.86)	<0.0001	5.75	(2.97 to 11.14)	<0.0001	2.44	(1.59 to 3.74)	<0.0001	4.97	(2.77 to 8.94)	<0.0001

DM, diabetes mellitus; BMI, body mass index; Hb, haemoglobin; HDL, high-density lipoprotein; NS, not significant; OGTT, oral glucose tolerance test; SpO_2, oxyhaemoglobin saturation measured by pulse oximeter.

Table 7 Associations of high-altitude, hypoxaemia and polycythaemia with glucose intolerance adjusted for all other confounders by multiple logistic regression analysis

	Fasting hyperglycaemia			Fasting DM			Hyperglycaemia (OGTT)			DM (OGTT)		
	OR	CI	p Value	OR	CI	p Value	OR	CI	p Value	OR	CI	p Value
Age (years)												
40–49	Reference			Reference			Reference			Reference		
50–59	1.21	(0.77 to 1.91)	NS	1.49	(0.73 to 3.06)	NS	1.05	(0.73 to 1.52)	NS	1.73	(0.91 to 3.30)	0.0951
60–69	2.03	(1.34 to 3.07)	0.0008	2.06	(1.06 to 4.02)	0.0336	1.73	(1.23 to 2.43)	0.0016	2.34	(1.28 to 4.27)	0.0057
70+	1.36	(0.83 to 2.22)	NS	1.38	(0.62 to 3.06)	NS	1.79	(1.21 to 2.65)	0.0035	1.77	(0.89 to 3.54)	NS
Male (vs female)	2.17	(1.57 to 2.99)	<0.0001	2.5	(1.50 to 4.18)	0.0004	1.68	(1.29 to 2.18)	0.0001	1.95	(1.26 to 3.01)	0.0026
Overweight	1.68	(1.18 to 2.40)	0.0041	1.43	(0.82 to 2.52)	NS	1.66	(1.25 to 2.21)	0.0004	1.46	(0.91 to 2.35)	NS
Dyslipidaemia	1.59	(1.14 to 2.22)	0.0058	2.11	(1.26 to 3.54)	0.0048	1.38	(1.05 to 1.81)	0.023	2.51	(1.60 to 3.92)	<0.0001
Hypertension	1.09	(0.78 to 1.50)	NS	1.18	(0.71 to 1.96)	NS	1.16	(0.88 to 1.51)	NS	1.26	(0.82 to 1.95)	NS
Livelihood												
Farmer	6.62	(3.56 to 12.32)	<0.0001	5.61	(1.90 to 16.55)	0.0018	3.83	(2.38 to 6.15)	<0.0001	3.10	(1.40 to 6.86)	0.0051
Nomad	Reference			Reference			Reference			Reference		
Urban dweller	2.53	(1.42 to 4.49)	0.0015	3.47	(1.28 to 9.42)	0.0145	2.66	(1.74 to 4.07)	<0.0001	1.96	(0.96 to 3.99)	0.0641
Altitude level												
2500–3499 m	Reference			Reference			Reference			Reference	1	
3500–4499 m	2.07	(1.44 to 2.98)	<0.0001	1.76	(0.94 to 3.28)	0.0767	1.23	(0.92 to 1.64)	NS	1.08	(0.65 to 1.78)	NS
4500+ m	3.59	(1.75 to 7.37)	0.0005	4.36	(1.33 to 14.31)	0.0150	1.25	(0.70 to 2.23)	NS	1.46	(0.59 to 3.65)	NS
Hypoxaemia												
SpO_2 <89%	1.48	(1.04 to 2.10)	0.0305	1.56	(0.92 to 2.65)	0.099	1.45	(1.07 to 1.97)	0.0183	1.72	(1.09 to 2.73)	0.0202
Group according to Hb												
Anaemia	1.47	(0.75 to 2.89)	NS	0.95	(0.21 to 4.24)	NS	1.24	(0.74 to 2.08)	NS	0.84	(0.25 to 2.89)	NS
Normal	Reference			Reference			Reference			Reference		
Moderate polycythaemia	2.00	(1.39 to 2.87)	0.0002	2.57	(1.44 to 4.60)	0.0014	1.90	(1.40 to 2.58)	<0.0001	2.34	(1.42 to 3.84)	0.0008
Excessive polycythaemia	3.58	(2.11 to 6.06)	<0.0001	5.46	(2.62 to 11.38)	<0.0001	3.16	(1.94 to 5.15)	<0.0001	5.35	(2.76 to 10.34)	<0.0001

DM, diabetes mellitus; Hb, haemoglobin; NS, not significant; OGTT, oral glucose tolerance test; SpO_2, oxyhaemoglobin saturation measured by pulse oximeter.

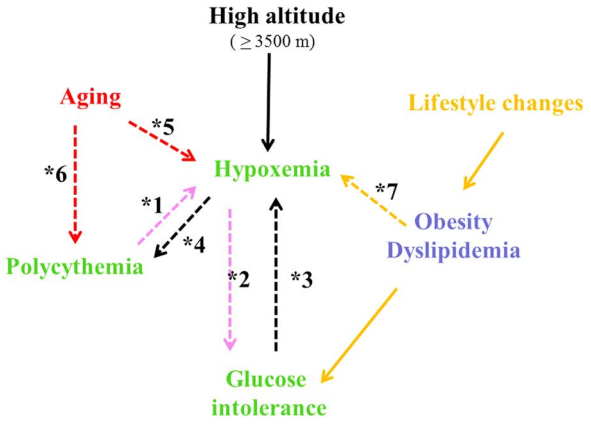

Figure 1 Hypothesised associations of hypoxaemia, polycythaemia and glucose intolerance with the influence of ageing and lifestyle change. Hypothesis 1 (*1 and *2) and hypothesis 2 (*3 and *4) in the association of hypoxia, polycythaemia and glucose intolerance. Ageing and lifestyle change accelerate the association, 'Diabetes acceleration hypothesis'. *1 or 4: Proposed according to online supplementary table S1 and table 5. *2 or 3: Proposed according to data in tables 6 and 7, online supplementary table S1, and previous studies.[58–64] *1 and *2: Proposed according to a previous study.[66] *3 and *4: Proposed according to previous studies.[76 77] *5: Proposed according to table 3. *6: Proposed according to our data compared with a previous study.[74] *7: Proposed according to online supplementary table S1.

shown even after adjustment of the effects of both lifestyle and ethnicity in all participants, and also in a separate analysis of farmers and nomads, but not in urban dwellers. Analysis of hypoxaemia, using SpO_2, was closely associated with a high prevalence of glucose intolerance as measured by FBG and OGTT after adjustment for both dwelling at high altitude and all lifestyle-related health factors (figure 1).

Comparison with other studies on the association between hypoxaemia and glucose intolerance

No previous reports have shown an association between hypoxia and glucose intolerance in high-altitude dwellers. However, there are some reports on the association of hypoxaemia with glucose intolerance in lowlanders[58–63] and in animals.[64] People with respiratory diseases,[58] sleep apnoea syndrome[60 61] and insomnia,[62 63] have a high prevalence of glucose intolerance. An isolated high fasting glucose pattern in a glucose tolerance test was dominant and insulin resistance increased in these people.[60–63] High-altitude dwellers have more severe hypoxaemia during sleep than during waking hours, and the prevalence of insomnia was higher in people dwelling at higher altitudes. Aggravation of insulin resistance in an acute hypoxic environment has also been reported to be caused not only by an increase in stress hormones, including epinephrine and corticosteroid, but also by the direct effect of hypoxia.[59] Although there are no reports on humans showing vulnerability to glucose intolerance in newborns from mothers who have hypoxaemia, this has been reported in calves (figure 1).[64]

In our previous study on lowlanders aged 40 years or older in Tosa, Japan, the prevalence of HG (fasting HG) and DM (fasting DM) was 46.2% (22.7%) and 16.7% (6.8%), respectively.[65] In that study, the percentages of 'fasting HG in HG' ('fasting DM in DM') were 49.1% (40.7%). Those percentages were calculated using the same data as in table 5 and they increased parallel with altitude (2500–3499 vs 3500–4499 vs 4500 m). In farmers, the percentages of 'fasting HG in HG' ('fasting DM in DM') increased with elevation of altitude from 54.3% (45.8%) to 80.0% (100%), in nomads these percentages also increased from 38.8% (43.2%) to 50.0% (40.4%) to 84.7% (92.7%), and in urban dwellers, these percentages increased from 30.8% (59.2%) to 61.1% (79.9%). The percentage of 'fasting HG in HG' in farmers and urban dwellers exceeded 60–80% above 3500 m, and in nomads, exceeded 80% above 4500 m. The 2 h-BG levels in our result in fasting IHG/fasting DM were much lower (130.7/224.5 mg/dL) compared with those in Tosa Town (172.4/ 262.6 mg/dL), though FBG levels in our study of fasting IHG/fasting DM (115.2/166.0 mg/dL) were not lower compared with those in Tosa Town (115.8/146.2 mg/dL). These results are compatible with the isolated high fasting glucose pattern and increased insulin resistance in people who have hypoxaemia and stress while sleeping.[60–63]

Our results and previous reports suggest that mild hypoxia and a higher metabolic rate in participants living at an altitude lower than 3500 m may be preventive for glucose intolerance. However, moderate hypoxia and dwelling at higher altitudes over 3500 m may increase the risk of fasting glucose intolerance (figure 1).

Hypothesis of associations of polycythaemia, hypoxaemia and glucose intolerance in high-altitude dwellers

An association between polycythaemia and glucose intolerance in a small sample population has been previously reported.[40] In our study of a large high-altitude population, using multivariate analysis, after adjustment for lifestyle-related factors and hypoxaemia, this association was strong. As a result, we propose the following two hypotheses to explain the mechanism of the strong associations among polycythaemia, hypoxaemia and glucose intolerance. The first hypothesis is that polycythaemia aggravates hypoxaemia and leads to glucose intolerance (*1 and *2 in figure 1). This hypothesis was based on the association of polycythaemia with hypoxaemia (table 5 and online supplementary table S1) and the association of hypoxaemia with glucose intolerance (tables 6 and 7).

The cross-sectional design of our study is a limitation to the causal relation. Additionally, there are no longitudinal studies on highlanders. However, a previous longitudinal report on lowlanders in a large 9-year follow-up study supports our hypothesis in which the highest haematocrit group (>44.3%) has a higher risk (OR=1.6)

of diabetes onset compared with the lowest group (<39.0%).[66] The mechanism of this association is speculated as follows: lower blood circulation caused by the high viscosity of polycythaemia is considered to disrupt the transport of insulin, glucose and oxygen to tissue cells, resulting in low cellular intake of glucose and lower activity of respiration, which requires oxygen and glucose in cells.[66] Our study showed an association of anaemia with HG.[67] This supports our first hypothesis because anaemia results in low activity of O_2 transport and subsequent hypoxaemia in tissue, which is aggravated at high altitude. Almost all study participants with anaemia had iron deficiency.[67] Also, Ladakhi farmers eat less meat than Tibetan nomads do,[33 68] and are vulnerable to suffering from iron deficiency anaemia.

Polycythaemia may be a sign of maladaptation to hypoxia, which leads to glucose intolerance, because Tibetan people have acquired a hypoxic adaptation by preventing polycythaemia through a genetic response to hypoxia.[20 21 69–73] Tibetans (mean age 34–35 years, BMI 18.4–18.5) compared with Andean highlanders (mean age 37–38 years, BMI 22.3–23.4) living at similar altitudes (4000 m) have lower Hb levels (male/female: 15.6/14.2 vs 19.1/17.8 g/dL, respectively), though participants with anaemia were excluded from this study.[74] The genes responsible for lower Hb are *PPARA*, *EGLN1* and *EPAS1*, and the mean Hb of both sexes is decreased by these advantageous haplotypes.[70] The frequency of the adaptive haplotype of *EPAS1* is reported to be 87% in Tibetans and 9% in Han Chinese.[71] The sex-adjusted Hb level is 0.8 g/dL lower in homozygotes compared with heterozygotes of *EPAS1*.[69]

Mean Hb in our older participants (mean 58.3 years, BMI 24.0–25.1, altitude 2900–4800 m, anaemia was excluded) was 16.1 g/dL (male/female: 17.2/15.1), which was 1.6/0.9 g/dL higher compared with the younger Tibetans (34–35 years).[74] Excluding overweight participants from the older group, the mean Hb of these older participants was 1.4/0.6 g/dL (male/female) higher compared with that of the younger participants.[74] Another report showed the associations between age, polycythaemia and the genes that have adapted to hypoxia. Older Tibetan chronic mountain sickness patients (mean age 54 years, n=45) have as much as 96% of the adaptive haplotype *EPAS1* compared with 72% in younger people without polycythaemia (mean age: 30 years, n=34).[75] Ageing may aggravate not only hypoxaemia (table 3) but also polycythaemia in Tibetan people (*5 and *6 in figure 1), even in those with adaptive haplotypes.[75]

Hypothesis of associations of glucose intolerance, hypoxaemia and polycythaemia in high-altitude dwellers

Our second hypothesis is that glucose intolerance leads to microvascular complications and aggravation of tissue hypoxaemia. Polycythaemia is enhanced with compensation for this hypoxaemia (*3 and *4 in figure 1). The basis of our results for this hypothesis is the same as in the first hypothesis because it was a cross-sectional study without causal relation. However, there are observational studies in lowlanders supporting this hypothesis.[76 77] Infants have complications of polycythaemia from mothers with diabetes. Chronic intrauterine hypoxaemia intermediates this association.[76 77]

The advantageous homozygotes of the genes that are involved in adaptation to hypoxia (*EGLN1* and *PPARA*) have stronger metabolic effects to facilitate anaerobic glycolysis and regression of lipid catabolism, resulting in higher serum concentrations of lipids by adaptation to hypoxia.[70 78 79] This effect may prevent the development of diabetes in younger people with a traditional lifestyle. However, sedentary workers and elderly people with advantageous genetic adaptations to hypoxia may be vulnerable to obesity, hyperlipidaemia and increased insulin resistance by lifestyle changes compared with people without these advantageous genes. Obesity and dyslipidaemia lead not only to increased insulin resistance (tables 6 and 7), but also to hypoxaemia (see online supplementary table S1 and *7 in figure 1).

Higher Hb was found in participants in Jiegu Town who were overweight compared with those not overweight. This difference in Hb (male/female 1.3/0.9 g/dL) was higher than the difference of the sex-adjusted Hb (0.8 g/dL) in homozygotes compared with heterozygotes of *EPAS1*.[69] The effect of lifestyle changes on polycythaemia in our study overcame the acquired hypoxic adaptation for prevention of polycythaemia. People in Jiegu Town (3700 m) with a high prevalence of overweight also had the highest prevalence of HG and fasting HG. Those parameters were accelerated both by lifestyle changes and by hypoxaemia, with an extremely high frequency of polycythaemia. While people in the higher altitude community of Domkhar (3800 m) had a low prevalence of overweight, they had a high prevalence of HG with an especially high fasting HG and polycythaemia, which may be accelerated mainly by hypoxia.

Our first hypothesis mainly explains our result of the association of dwelling at high altitude or hypoxaemia with an increase in glucose intolerance as seen in Domkhar. The second hypothesis is mainly associated with our result of lifestyle-related factors leading to an increase in glucose intolerance. According to our results and previous reports, these two hypotheses may be acting simultaneously with each other, considering the close associations among hypoxaemia, polycythaemia and glucose intolerance as seen in Jiegu Town. The association of glucose intolerance with polycythaemia and hypoxaemia is accelerated by ageing and lifestyle changes, and there may be the vulnerability of the hypoxia adaptive genes for glucose intolerance as the background, called the 'Diabetes acceleration hypothesis' (figure 1).

Conclusions, unanswered questions and policy implications

Socioeconomic factors and hypoxia—the effect of altitudes over 3500 m—play major roles in the prevalence

of glucose intolerance in highlanders. Hypoxaemia and polycythaemia were closely associated with glucose intolerance after adjustment for the effects of lifestyle changes in our study. Tibetan people may be vulnerable to glucose intolerance, with polycythaemia as a sign of poor hypoxic adaptation. However, the mechanism of the onset of glucose intolerance by hypoxaemia in high-altitude dwellers is unknown. A previous report showed higher oxidative stress in Tibetan people compared with in Han people, and higher oxidative stress was associated with glucose intolerance and arteriosclerosis.[80 81] Further examination of the metabolic mechanism and oxidative stress in association with the effects of genes involved in hypoxia adaptation in high-altitude dwellers is needed. Because the matter of whether the WHO criteria of glucose intolerance can be applicable in high-altitude people has not been established, the prognosis of fasting HG and HG associated with high-altitude should be examined longitudinally. Prevention of lifestyle-related diseases and health education should be advocated, especially in high altitude dwellers, with rapidly prevailing socioeconomic globalisation.

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REFERENCES

1. Aldenderfer MS. Moving up in the world. Archaeologists seek to understand how and when people came to occupy the Andean and Tibetan plateaus. *Am Sci* 2003;91:542–9.
2. Pawson IG, Jest C. The high-altitude areas of the world and their cultures. In: Baker PT, ed. *The biology of high altitude peoples*. New York, NY: Cambridge University Press, 1978:17–45.
3. West JB, Schoene RB, Luks AM, Milledge JS (eds). Geography and the human response to altitude. In: *High altitude medicine and physiology*. New York, NY: CRC Press, 2013:28–39.
4. Chen W, Liu Q, Wang H, *et al*. Prevalence and risk factors of chronic kidney disease: a population study in the Tibetan population. *Nephrol Transplant* 2011;26:1592–9.
5. Santos JL, Pérez-Bravo F, Carrasco E, *et al*. Low prevalence of type 2 diabetes despite a high average body mass index in the Aymara natives from Chile. *Nutrition* 2001;17:305–9.
6. Chen F, Yang W, Weng J, *et al*. Albuminuria: prevalence, associated risk factors and relationship with cardiovascular disease. *J Diabetes Invest* 2014;5:464–71.
7. Jia W, Gao X, Pang C, *et al*. Prevalence and risk factors of albuminuria and chronic kidney disease in Chinese population with type 2 diabetes and impaired glucose regulation: Shanghai diabetic complications study (SHDCS). *Nephrol Dial Transplant* 2009;24:3724–31.
8. Schulz LO, Bennett PH, Ravussin E, *et al*. Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. *Diabetes Care* 2006;29:1866–71.
9. Centers for Disease Control and Prevention (CDC). Prevalence of diagnosed diabetes among American Indians/Alaskan Natives—United States, 1996. *MMWR Morb Mortal Wkly Rep* 1998;47:901–4.
10. IDF Diabetes atlas. http://www.diabetesatlas.org/ (accessed 20 May 2015).
11. Wild S, Roglic G, Green A, *et al*. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047–53.
12. Lefe'bvre P, Silink M. Diabetes fights for recognition. *Lancet* 2006;368:1625–6.
13. Okumiya K, Ishine M, Wada T, *et al*. The close association between low economic status and glucose intolerance in the elderly in a rural area in Laos. *J Am Geriatr Soc* 2007;55:2101–2.
14. Okumiya K, Sakamoto R, Kimura Y, *et al*. J curve association between economic status and diabetes independently of functional disability in Japanese elderly. *Geriatr Gerontol Int* 2012;12:755–6.
15. Ravelli AC, van der Meulen JH, Michels RP, *et al*. Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998;351:173–7.

16. Whincup PH, Kaye SJ, Owen CG, *et al*. Birth weight and risk of type 2 diabetes: a systemic review. *JAMA* 2008;300:2886–97.
17. Gillberg L, Ling C. The potential use of DNA methylation biomarkers to identify risk and progression of type 2 diabetes. *Front Endocrinol (Lausanne)* 2015;6:43.
18. Ling C, Groop L. Epigenetics: a molecular link between environmental factors and type 2 diabetes. *Diabetes* 2009;58:2718–25.
19. Peacock AJ. ABC of oxygen: oxygen at high altitude. *BMJ* 1998;317:1063–6.
20. Beall CM. Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia. *Integr Comp Biol* 2006;46:18–24.
21. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. *Proc Natl Acad Sci USA* 2007;104(Suppl 1):8655–60.
22. Sahota IS, Panwar NS. Prevalence of chronic mountain sickness in high altitude districts of Himachal Pradesh. *Indian J Occup Environ Med* 2013;17:94–100.
23. León-Velarde F, Arregui A, Monge CC, *et al*. Ageing at high altitude and the risk of chronic mountain sickness. *J Wilderness Med* 1993;4:183–8.
24. León-Velarde F, Arregui A, Vargas M, *et al*. Chronic mountain sickness and chronic lower respiratory tract disorders. *Chest* 1994;106:151–5.
25. León-Velarde F, Ramos MA, Hernández JA, *et al*. The role of menopause in the development of chronic mountain sickness. *Am J Physiol* 1997;272:R90–4.
26. Rivera Ch M, León-Velarde F, Huicho L. Treatment of chronic mountain sickness: critical reappraisal of an old problem. *Respir Physiol Neurobiol* 2007;158:251–65.
27. Singh DL, Bhattarai MD. High prevalence of diabetes and impaired fasting glycaemia in urban Nepal. *Diabet Med* 2003;20:170–1.
28. Sasaki H, Kawasaki T, Ogaki T, *et al*. The prevalence of diabetes mellitus and impaired fasting glucose/glycaemia (IFG) in suburban and rural Nepal—the communities-based cross-sectional study during the democratic movements in 1990. *Diabetes Res Clin Pract* 2005;67:167–74.
29. Carrasco EP, Pérez FB, Angel BB, *et al*. [Prevalence of type 2 diabetes and obesity in two Chilean aboriginal populations living in urban zones]. *Rev Med Chil* 2004;132:1189–97.
30. Okumiya K, Sakamoto R, Kimura Y, *et al*. Diabetes mellitus and hypertension in elderly highlanders in Asia. *J Am Geriatr Soc* 2010;58:1193–5.
31. Sherpa LY, Deji Stigum H, Chongsuvivatwong V, *et al*. Prevalence of metabolic syndrome and common metabolic components in high altitude farmers and herdsmen at 3700 m in Tibet. *High Alt Med Biol* 2013;14:37–44.
32. Baracco R, Mohanna S, Seclén S. A comparison of the prevalence of metabolic syndrome and its components in high and low altitude populations in Peru. *Metab Syndr Relat Disord* 2007;5:55–62.
33. Norboo T, Stobdan T, Tsering N, *et al*. Prevalence of hypertension at high altitude: cross-sectional survey in Ladakh, Northern India 2007–2011. *BMJ Open* 2015;5:e007026..
34. Sun SF. Epidemiology of hypertension on the Tibetan Plateua. *Hum Biol* 1986;58:507–15.
35. Hu YS, Yao CH, Wang WZ, *et al*. [Survey on the prevalence of hypertension in different ethnic groups in China in 2002]. *Wei Sheng Yan Jiu* 2006;35:573–5.
36. Tripathy V, Gupta R. Blood pressure variation among Tibetans at different altitudes. *Ann Hum Biol* 2007;34:470–83.
37. Lhamo SY, Supamai S, Virasakdi C. Impaired glucose regulation in a Sherpa indigenous population living in the Everest region of Nepal and in Kathmandu Valley. *High Alt Med Biol* 2008;9:217–22.
38. Woolcott OO, Castillo OA, Gutierrez C, *et al*. Inverse association between diabetes and altitude: a cross-sectional study in the adult population of the United States. *Obesity (Silver Spring)* 2014;22:2080–90.
39. Hessien M. Improved glycemic control in moderate altitude type II diabetic residents. *High Alt Med Biol* 2013;14:27–30.
40. Okumiya K, Sakamoto R, Kimura Y, *et al*. Strong association between polycythemia and glucose intolerance in elderly high-altitude dwellers in Asia. *J Am Geriatr Soc* 2010;58:609–11.
41. Popular Government of Haibei Province. Annual report of Health Office in Haibei Province in China, 2008.
42. Popular Government of Haiyan county. Homepage of introduction of Haiyan county. 2008. http://www.qh.xinhuanet.com/haiyan/index.htm (accessed 7 Nov 2008).
43. Editorial committee of History of Haiyan County. *History of Haiyan County (Hai An Xian Zhi)*. Shanghai: Shanghai Academy of Social Sciences Publisher, 1997.
44. Popular Government of Yushu Province. Annual report of Health Office in Yushu Province in China, 2011.
45. Popular Government of Yushu County. Homepage of introduction of Haiyan county. 2009. http://www.qh.xinhuanet.com/yushu/index.htm (accessed 4 Oct 2009).
46. Zang YS, Zhi ZZ, Zhi Z. *History of Yushu Tibetan Autonomous Prefecture*. Xian, China: Three Qin Publisher, 2005.
47. Yamaguchi T, Ngodup S, Nose M, *et al*. Land use and its transition in an agro-silvo-pastoral system of a Ladkhi Village, Jammu & Kashmir, India. Himalayan study monographs. 2014 (in Japanese). http://www.kyoto-bhutan.org/pdf/Himalayan/014/Himalayan-14-102.pdf14 1-2-113 (accessed 7 May 2015).
48. Okumiya K, Matsubayashi K, Wada T, *et al*. A U-shaped association between home systolic blood pressure and four-year mortality in community-dwelling older men. *J Am Geriatr Soc* 1999;47:1415–121.
49. Chobanian AV, Bakris GL, Black HR, *et al*. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–52.
50. Karon BS, Griesmann L, Scott R, *et al*. Evaluation of the impact of hematocrit and other interference on the accuracy of hospital-based glucose meters. *Diabetes Technol Ther* 2008;10:111–20.
51. Karon BS, Blanshan CT, Deobald GR, *et al*. Retrospective evaluation of the accuracy of Roche AccuChek Inform and Nova StatStrip glucose meters when used on critically ill patients. *Diabetes Technol Ther* 2014;16:828–32.
52. Lockyer MG, Fu K, Edwards RM, *et al*. Evaluation of the Nova StatStrip glucometer in a pediatric hospital setting. *Clin Biochem* 2014;47:840–3.
53. de Mol P, Krabbe HG, de Vries ST, *et al*. Accuracy of handheld blood glucose meters at high altitude. *PLoS ONE* 2010;5:e15485.
54. Olateju T, Begley J, Flanagan D, *et al*. Effects of simulated altitude on blood glucose meter performance: implications for in-flight blood glucose monitoring. *J Diabetes Sci Technol* 2012;6:867–74.
55. van Schenck H, Falkensson M, Lundberg B. Evaluation of "HemoCue", a new device for determining haemoglobin. *Clin Chem* 1986;32:526–9.
56. WHO: *Hemoglobin concentrations for the diagnosis of anemia and assessment of severity. Vitamin and mineral nutrition information system*. Geneva: World Health Organization (WHO/NMH/NHD/MNM/11.1), 2011. http://www.who.int/vmnis/indicators/haemoglobin.pdf (accessed 7 May 2015).
57. WHO. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia*. Report of a WHO/IDF consultation. http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf (accessed 7 May 2015).
58. Klein OL, Krishnan JA, Glick S, *et al*. Systemic review of the association between lung function and type 2 diabetes mellitus. *Diabet Med* 2010;27:977–87.
59. Oltmanns KM, Gehring H, Rudolf S, *et al*. Hypoxia causes glucose intolerance in humans. *Am J Respir Crit Care Med* 2004;169:1231–7.
60. Punjabi NM, Shahar E, Redline S, *et al*, Sleep Heart Health Study Investigators. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 2004;160:521–30.
61. Rasche K, Keller T, Tautz B, *et al*. Obstructive sleep apnea and type 2 diabetes. *Eur J Med Res* 2010;15(Suppl 2):152–6.
62. Yamamoto N, Yamanaka G, Ishizawa K, *et al*. Insomnia increases insulin resistance and insulin secretion in elderly people. *J Am Geriatr Soc* 2010;58:801–4.
63. Spiegel K, Knutson K, Leproult R, *et al*. Sleep loss: a novel risk factor for insulin resistance and type 2 diabetes. *J Appl Physiol* 2005;99:2008–19.
64. Cheng N, Cai W, Jiang M, *et al*. Effect of hypoxia on blood glucose, hormones, and insulin receptor functions in newborn calves. *Pediatr Res* 1997;41:852–6.
65. Fujisawa M, Ishine M, Okumiya K, *et al*. Trends in diabetes. *Lancet* 2007;369:1257.
66. Tamariz LJ, Young JH, Pankow JS, *et al*. Blood viscosity and hematocrit as risk factor for type 2 diabetes mellitus: the atherosclerosis risk in communities (ARIC) study. *Am J Epidemiol* 2008;168:1153–60.
67. Okumiya K, Sakamoto R, Ishikawa M, *et al*. The J-curve association between glucose intolerance with hemoglobin and ferritin levels at high-altitude. *J Am Geriatr Soc* 2016;64:207–10.
68. Kimura Y, Matsubayashi K, Sakamoto R, *et al*. Food diversity and its relation to health of highlanders–comparison of urban and rural settings in Qinghai and Ladakh. *Himalayan Study Monograph* 2012;13:86–93. http://www.kyoto-bhutan.org/pdf/Himalayan/013/Himalayan-13-086.pdf (in Japanese).
69. Beall CM, Cavalleri GL, Deng L, *et al*. Natural selection on EPAS1 (HIF2alpha) associated with low hemoglobin concentration in Tibetan highlanders. *Proc Natl Acad Sci USA* 2010;107:11459–64.

70. Simonson TS, Yang Y, Huff CD, *et al*. Genetic evidence for high-altitude adaptation in Tibet. *Science* 2010;329:72–5.
71. Yi X, Liang Y, Huerta-Sanchez E, *et al*. Sequencing of 50 human exomes reveals adaptation to high altitude. *Science* 2010;329:75–8.
72. Beall CM. Genetic changes in Tibet. *High Alt Med Biol* 2012;12:101–2.
73. Simonson TS, McClain DA, Jorde LB. Genetic determinants of Tibetan high-altitude adaptation. *Hum Genet* 2012;131:527–33.
74. Beall CM, Brittenham GM, Strohl KP. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. *Am J Phys Anthropol* 1998;106:385–400.
75. Buroker NE, Ning XH, Zhou ZN, *et al*. EPAS1 and EGLN1 association with high altitude sickness in Han and Tibetan Chinese at the Qinghai-Tibetan Plateau. *Blood Cells Mol Dis* 2012;49:67–73.
76. Weintrob N, Karp M, Hod M. Short- and long-range complications in offspring of diabetic mothers. *J Diabetes Complications* 1996;10:294–301.
77. Cetin H, Yalaz M, Akisu M, *et al*. Polycythaemia in infants of diabetic mothers: β-hydroxybutyrate stimulates erythropoietic activity. *J Int Med Res* 2011;39:815–21.
78. Ge RL, Simonson TS, Cooksey RC, *et al*. Metabolic insight into mechanisms of high-altitude adaptation in Tibetans. *Mol Genet Metab* 2012;106:244–7.
79. McClain DA, Simonson TS, Cooksey RC, *et al*. Metabolic consequences of genetic adaptation to high altitude in Tibetans. *2nd Congress of Asia-Pacific Society for Mountain Medicine (APSMM) [abstract]*; 2011:11.
80. Sakamoto R, Matsubayashi K, Kimura Y, *et al*. Comprehensive geriatric assessment of elderly highlanders in Qinghai, China, III: oxidative stress and aging in Tibetan and Han elderly highlanders. *Geriatr Gerontol Int* 2009;9:352–8.
81. Sakamoto R, Okumiya K, Wang H, *et al*. Oxidized low density lipoprotein among the elderly in Qinghai-Tibet Plateau. *Wilderness Environ Med* 2015;26:343–9.

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