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ORIGINAL RESEARCH

Habitation Altitude and Left Ventricular Diastolic Function: A Population-Based Study

Congyi Zheng, PhD; Xin Wang, MD; Haosu Tang, MD; Zuo Chen, PhD; Linfeng Zhang, PhD; Su Wang, PhD; Yuting Kang, PhD; Ying Yang, MD, PhD; Linlin Jiang, MD; Gang Huang, PhD; Zengwu Wang, MD, PhD

BACKGROUND: Although numerous studies have been published evaluating the positive or negative effects of altitude on cardiovascular disease, many of them are conflicting.

METHODS AND RESULTS: Data come from 2 cross-sectional surveys using a similar method in China; and a total of 34 215 residents, aged ≥35 years, were eligible and recruited in the study. Left ventricular diastolic dysfunction (LVDD), according to the 2009 American Society of Echocardiography guidelines, was defined and evaluated. Altitude was divided into low (<1500 m), middle (1500–3500 m), and high (≥3500 m) level groups. Among the 34 215 participants (aged 55.87 years; men, 45.92%; altitude ranging from 3.1 ~ 4507 m), 15 099 (crude prevalence, 44.13%), 517 (crude prevalence, 1.51%), and 272 (crude prevalence, 0.79%) were diagnosed as having grades I, II, and LVDD, respectively. Compared with low-level group, the odds ratios (ORs) (95% CIs) of LVDD for middle- and high-level groups were 1.65 (1.49–1.82) and 1.89 (1.63–2.19), respectively (P_{trend}<0.001). The ORs (95% CI) were 1.43 (1.31–1.56) and 2.03 (1.67–2.47) per 500-m increment for middle- and high-level groups. There was a nonlinear relationship (upward-sloping "W" shape) between altitude and the risk of LVDD, assessed by the restricted cubic spline. For each LVDD grade, ORs (95% CIs) of grade I LVDD for middle- and high-level groups were 1.75 (1.59–1.92) and 1.95 (1.69–2.25), respectively; for grade II, ORs (95% CIs) for middle- and high-level groups were 6.19 (3.67–10.42) and 5.27 (2.18–12.74), respectively. The stratified analyses indicated that LVDD was much more remarkably influenced by elevated altitude in men ($P_{interaction}$=0.0019).

CONCLUSIONS: Higher altitude is associated with increased risk of LVDD among people living over 1500 m, especially for men.

Key Words: cross-sectional study ■ habitation altitude ■ left ventricular diastolic function ■ population ■ risk factor

Left ventricular diastolic dysfunction (LVDD), an early sign of cardiac dysfunction, is a predictor of congestive heart failure, myocardial ischemia, and fatal cardiovascular events.[1–4] Even in asymptomatic patients, grade I (impaired relaxation pattern) diastolic dysfunction was associated with a 5-fold higher 3- to 5-year mortality in comparison with subjects with normal diastolic function.[5] So, the exploration of LVDD and its risk factors will benefit the cardiovascular disease (CVD) early prevention, intervention, and treatment, especially for those who are asymptomatic.

Altitude is the most basic hierarchical classification of geomorphology, and there are >140 million people living at high altitude (>2400 m) in the world.[6] Low air pressure (hypoxic conditions),[7] cold,[8] and large daily temperature variability[9,10] are the typical climate characteristics of plateau regions that affect the cardiovascular system to a certain degree. Although numerous studies have been

Correspondence to: Zengwu Wang, MD, PhD, Division of Prevention and Community Health, National Center for Cardiovascular Disease, Fuwai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 15 (Lin), Fengcunxili, Mentougou District, Beijing 102308, China. E-mail: wangzengwu@foxmail.com

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CLINICAL PERSPECTIVE

What Is New?

- This is the first large-scale, free-living, population-based study to report the association between habitation altitude and left ventricular diastolic dysfunction.

What Are the Clinical Implications?

- The current study found that elevated altitude was significantly associated with a higher risk of left ventricular diastolic dysfunction among people living in ≥1500-m areas, which provided a reference that was necessary to consider the impact of habitation altitude in high-risk individual screening; and for those living in middle or high elevation areas, modifiable cardiovascular disease risk factor intervention and control should be much stricter.

Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
LV	left ventricular
LVDD	left ventricular diastolic dysfunction
OR	odds ratio

published evaluating the positive or negative effects of altitude on CVD, many of them are conflicting on the specific role of altitude on CVD or related conditions.[11] A few studies suggested that living at high altitude or even short-term chronic hypoxia exposure implies functional and morphological changes in the left ventricular (LV) diastolic function; however, a large-sample epidemiological study to confirm such findings is lacking.[7,12,13] Moreover, whether sex and age can modify the association between altitude and LVDD is unclear.

The China Hypertension Survey[14,15] and the chronic cardiopulmonary disease survey in Xinjiang and Tibet were the recent large-scale cross-sectional studies of CVD; meanwhile, China has the complex geomorphic types, varying from hills to plateau.[16] Thus, the 2 studies were pooled to first explore the association between long-term exposure to different altitude habitats and LVDD in a general population. In addition, our research also evaluates the interaction effect between sex or age and altitude on LVDD.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

Data were obtained from 2 cross-sectional studies that were conducted by our group with similar investigation methods and items, including the China Hypertension Survey[15,17] and the chronic cardiopulmonary disease survey in Xinjiang and Tibet area of China.[12] Detailed description of the 2 studies has been published previously. Briefly, the China Hypertension Survey used 4-stage stratified multistage random sampling method to obtain nationwide subjects, aged ≥35 years, from the 14 of provinces (Xinjiang and Tibet area excluded; including 16 cities and 17 counties) in 2012 to 2015. The chronic cardiopulmonary disease survey in Xinjiang and Tibet area of China was conducted during 2014 to 2016 and recruited subjects, aged ≥15 years, from 4 cities and 9 countries by the same sampling method. A total of 34 994 (response rate, 62.5%) and 7593 (response rate, 77.17%) natives or inhabitants who lived in investigation points for >6 months completed the 2 surveys, respectively. The exclusion criteria of this study included the following: history or findings of CVD, including significant valvular heart disease (ie, greater than mild valvular insufficiency or stenosis), and/or hypertrophic cardiomyopathy, and/or congenital heart disease. After exclusion of participants with absence of physician-diagnosed grading LVDD by echocardiography and prior history of significant heart disease (ie, myocardial infarction, atrial fibrillation, chronic heart failure, and valvular heart disease) or major chronic disease (ie, kidney disease, chronic obstructive pulmonary disease, rheumatic immune disease, and tumor), 34 215 participants were eligible for the final analysis. The numbers of participants included and excluded at each stage in the study are shown in a flowchart (Figure S1). Written informed consent was obtained from each participant. The Ethics Committee of Fuwai Hospital (Beijing, China) approved the 2 studies.

Data Collection

A standardized questionnaire was developed by the coordinating center, Fuwai Hospital. Data on demographic characteristics, including education, occupation, and lifestyle, were recorded by interview. Smoking status was classified into 3 categories: nonsmokers, former smokers, and current smokers (over the past 30 days). Family history of CVD was defined as at least one of the subjects' parents or siblings had the history of coronary heart disease or stroke. Blood pressure was measured with the OMRON HBP-1300 Professional Portable Blood Pressure Monitor (OMRON, Kyoto, Japan) 3 times, and the average of the 3 readings was used for analysis. Body weight was obtained using OMRON body fat and weight measurement device (V-body HBF-371). Laboratory analyses were performed by a central core laboratory (Beijing Adicon Clinical Laboratories, Inc, Beijing, China) using standardized techniques. All blood samples were obtained in the morning after at least an 8-hour overnight fast.

The clinical evaluation of LV function based on echocardiography, and the collection data of cardiac ultrasound examination in the questionnaire, included M-mode and 2-dimensional measurements, heart value structure, and Doppler flow parameters. All experienced echocardiographers were trained using the protocol. And the difficult-to-diagnose special cases were discussed with the experts from the coordination center.

Grading LVDD was based on the 2009 American Society of Echocardiography guidelines, recommendations for the evaluation of LV diastolic function by echocardiography.[5] The grading scheme is mild or grade I (impaired relaxation pattern), moderate or grade II (pseudonormal LV filling), and severe or grade III (restrictive filling). Age and heart rate should be considered for assessment: (1) grade I: the mitral E/A (the ratio of the peak early filling velocity [E-wave] and the late diastolic filling velocity [A-wave]) ratio <0.8, deceleration time >200 ms, isovolumetric relaxation time ≥100 ms, predominant systolic flow is seen in pulmonary venous flow (S>D, peak systolic velocity [S] higher than peak anterograde diastolic velocity [D]), annular e' (early diastolic tissue Doppler imaging annular velocity) is <8 cm/s, and the E/e' (the ratio of early diastolic mitral inflow velocity to early diastolic tissue Doppler imaging annular velocity) ratio is <8 (septal and lateral); and (2) grade II: the mitral E/A ratio is 0.8 to 1.5 (pseudonormal) and decreases by ≥50% during the Valsalva maneuver, the E/e' (average) ratio is 9 to 12, and e' is <8 cm/s. Other supporting data include an atrial reversal velocity >30 cm/s and an S/D (the ratio of the peak systolic velocity [S] and the peak anterograde diastolic velocity [D]) ratio <1. In some patients with grade II dysfunction, LV end-diastolic pressure is the only pressure that is increased and is recognized by Ar-A (the time difference between atrial reversal velocity and mitral A-wave duration) duration ≥30 ms. Grade II diastolic dysfunction represents impaired myocardial relaxation with mild to moderate elevation of LV filling pressures. (3) Grade III: restrictive LV filling occurs with an E/A ratio ≥2, deceleration time <160 ms, isovolumetric relaxation time ≤60 ms, systolic filling fraction ≤40%, mitral A flow duration shorter than atrial reversal duration, and average E/e' ratio >13 (or septal E/e' ≥15 and lateral E/e' >12).

For free-living individuals, prevalence of grade II or III diastolic dysfunction was relatively low; furthermore, even grade I dysfunction was associated with higher mortality in comparison with normal individuals. Thus, the participants in this study were divided into 2 groups for analysis, abnormal LV diastolic function group (including grades I–III) and normal group.

Altitudes of each survey site were estimated from 2400 homogenized surface stations.[18]

Statistical Analysis

Characteristics of the study participants were described by altitude, using percentages with the corresponding 95% CI for categorical variables and means (95% CIs) for continuous variables; group differences were assessed by χ^2 test or 1-way ANOVA, respectively. The linear trend between continuous variables and the different level of altitude was evaluated by linear regression analysis. The trend between dichotomous variables' positive rate and altitude was based on Cochran-Armitage trend test in χ^2 test. A given number of participants from each of the sex/age strata (for both men and women; 10-year age group interval) were selected from communities or villages in the final stage of sampling in the protocol, so the participants were divided into 4 groups by their age (35–44, 45–54, 55–64, and ≥65 years). By referring to the related literature,[19,20] we reported the effect estimates by the different altitude levels according to elevation classification from geography[21] and combined with the optimal cutoff value of the smoothing curves of restricted cubic spline regression: low level (<1500 m), middle level (1500–3500 m), and high level (≥3500 m). We also explored the effect estimates for each 500- and 1000-m increase in altitude. Furthermore, we used restricted cubic spline regression to examine the concentration-response relationship between exposure to different altitude and LVDD.

Odds ratios (ORs) and 95% CIs for the associations of habitation altitude with LV diastolic function (abnormal versus normal) in total or different subgroup of sex and age were calculated using multivariate logistic regression analysis. The interaction term was added to estimate the effect on LVDD in stratified analysis. In all statistical models, we adjusted for the following: (1) demographics: age, sex, areas, ethnicity, and education; (2) cardiac risk factors: obesity, hypertension, hyperlipidemia, diabetes mellitus, smoking, alcohol drinking, and family history of CVD; (3) medical therapy: antihypertensive medication, lipid-lowering medicine, and hypoglycemic drug; and (4) the major parameters of LV structure: relative wall thickness and LV mass index. All the covariates were chosen for their established or presumed influence on the LV diastolic function. All the analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). The 2-sided *P*<0.05 was considered statistically significant.

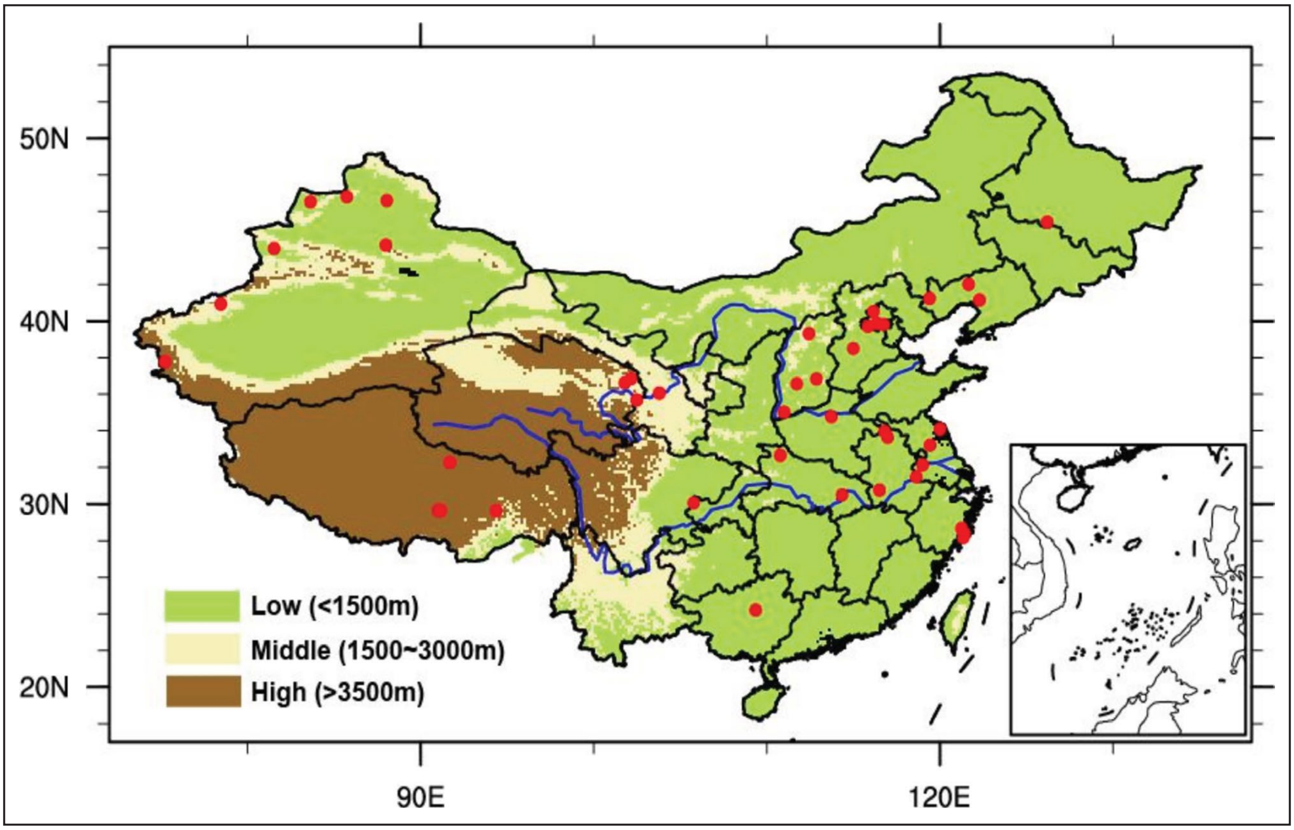

Figure 1. Elevation classification in China.
The red dots are the survey sites of this study. E indicates east–west; and N, south–north.

RESULTS

Characteristics of the Study Population

There were a total of 34 215 participants (mean age, 55.87 years; men, 45.92%), and their average habitation altitude was 758.6 m, ranging from 3.1 to 4507 m (Figure 1). The demographic characteristics of the participants are presented in Table 1. Participants exposed to lower altitude levels were more likely to be men, were more likely to be higher educated, and had elevated systolic blood pressure, fasting plasma glucose, and triglycerides (*P* for trend <0.05). Of the participants, 15 099 (crude prevalence, 44.13%), 517 (crude prevalence, 1.51%), and 272 (crude prevalence, 0.79%) were diagnosed as having grade Ⅰ, Ⅱ, and Ⅲ LVDD, respectively. The crude prevalence of each LVDD category (I–III) in 3-level altitude group is presented in Table S1.

Echocardiographic Parameter of LV and Altitude

Table 2 showed the collected echocardiographic parameters of LV structure and function among the 3-level categorical altitude groups. There were remarkable negative linear associations between altitude and LV end-systolic diameter, left atrial diameter, interventricular septum thickness, LV posterior wall thickness, and LV ejection fraction. However, the increasing E-wave and E/A ratio were found with higher altitude level (*P* for trend <0.05). Compared with the low altitude level group, the ORs (95% CIs) of left atrial enlargement for middle- and high-level groups were 1.77 (1.49–2.11) and 0.14 (0.07–0.29), respectively (Table S2).

Multivariable Analysis of the Association Between Altitude and LVDD

The association between altitude and LVDD is detailed in Table 3. Using the 3 levels of altitude, the multivariable analysis demonstrates increasing risks with higher exposure altitude level after adjusting for confounding factors (*P* for trend <0.001); compared with the low level, the OR of LVDD for high-level group was 1.89 (95% CI, 1.63–2.19). For each 1000-m increase, the OR was 1.16 (95% CI, 1.12–1.20) among the total participants. The ORs (95% CIs) per 500-m increment were 1.43 (1.31–1.56) and 2.03 (1.67–2.47) for middle- and high-level groups, respectively; and the ORs (95% CIs) per 1000-m increment were 2.05 (1.73–2.42) and 4.41(2.80–6.11) for middle- and

Table 1. Characteristics of Participants

Characteristic	Total (n=34 215)	3-Level Categorical Altitude, m <1500 (n=27 241)	1500–3500 (n=5201)	≥3500 (n=1773)	*P* Value	*P* for Trend
Age, y	55.87 (55.73–56.01)	56.37 (56.21–56.53)	54.74 (54.39–55.1)	51.42 (50.9–51.94)	<0.0001	<0.0001*
Men, n (%)	15 711 (45.92)	12 638 (46.39)	2401 (46.16)	672 (37.9)	<0.0001	<0.0001†
Rural, n (%)	19 672 (57.50)	14 898 (54.69)	3660 (70.37)	1114 (62.83)	<0.0001	<0.0001†
Education (middle school or higher), n (%)	15 669 (45.8)	13 778 (50.58)	1593 (30.63)	298 (16.81)	<0.0001	<0.0001†
Smoking, n (%)						
Current	8178 (23.9)	6801 (24.97)	1152 (22.15)	225 (12.69)	<0.0001	
Former	2082 (6.09)	1578 (5.79)	335 (6.44)	169 (9.53)		
Never	23 955 (70.01)	18 862 (69.24)	3714 (71.41)	1379 (77.78)		
Alcohol drinking, n (%)	9260 (27.06)	7626 (27.99)	1277 (24.55)	357 (20.14)	<0.0001	<0.0001
Family history of CVD, n (%)	3728 (10.9)	3334 (12.24)	288 (5.54)	106 (5.98)	<0.0001	<0.0001
SBP, mm Hg	132.0 (131.79–132.23)	132.52 (132.28–132.77)	129.74 (129.15–130.32)	130.76 (129.7–131.82)	<0.0001	<0.0001*
DBP, mm Hg	77.4 (77.32–77.57)	77.26 (77.13–77.39)	77.4 (77.07–77.72)	80.41 (79.76–81.05)	<0.0001	<0.0001*
BMI, kg/m^2	24.8 (24.76–24.83)	24.84 (24.8–24.88)	24.22 (24.12–24.32)	25.76 (25.57–25.95)	<0.0001	0.6612
WC, cm						
Men	86.2 (86.03–86.35)	86.25 (86.08–86.43)	84.83 (84.38–85.29)	89.87 (89.09–90.66)	<0.0001	0.4308
Women	83.4 (83.24–83.55)	83.49 (83.32–83.66)	80.8 (80.4–81.21)	88.79 (88.13–89.46)	<0.0001	0.0008*
Total cholesterol, mmol/L	4.77 (4.76–4.78)	4.83 (4.82–4.84)	4.45 (4.42–4.47)	4.8 (4.75–4.85)	<0.0001	<0.0001*
HDL cholesterol, mmol/L	1.37 (1.37–1.38)	1.39 (1.38–1.39)	1.27 (1.27–1.28)	1.46 (1.44–1.47)	<0.0001	<0.0001*
LDL cholesterol, mmol/L	2.8 (2.79–2.81)	2.83 (2.82–2.84)	2.61 (2.59–2.63)	2.88 (2.84–2.92)	<0.0001	<0.0001*
Triglycerides, mmol/L	1.41 (1.4–1.42)	1.44 (1.43–1.45)	1.33 (1.31–1.36)	1.08 (1.05–1.11)	<0.0001	<0.0001*
FPG, mmol/L	5.54 (5.52–5.55)	5.62 (5.6–5.64)	4.45 (4.42–4.47)	4.85 (4.77–4.93)	<0.0001	<0.0001*
Medical therapy, n (%)						
Antihypertensive drug	6417 (18.75)	5332 (19.57)	806 (15.5)	279 (15.74)	<0.0001	<0.0001†
Hypoglycemic drug	1521 (4.45)	1358 (4.99)	140 (2.69)	23 (1.3)	<0.0001	<0.0001†
Statin	1282 (3.75)	959 (3.52)	143 (2.75)	180 (10.15)	<0.0001	<0.0001†
LVDD, n (%)	15 888 (46.44)	12 895 (47.34)	2350 (45.18)	643 (36.27)	<0.0001†	<0.0001†

Data are means (95% CIs), and the categorical variables are presented as absolute numbers (percentages). $P < 0.05$: The group difference assessed by χ^2 test or 1-way ANOVA was significant. BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVDD, left ventricular diastolic dysfunction (included impaired relaxation pattern, pseudonormal, and restrictive filling); SBP, systolic blood pressure; and WC, waist circumference.

**P* for trend <0.05: There was a significant positive or negative linear association between continuous variables, and the elevated altitude level was evaluated by linear regression analysis.

†*P* for trend <0.05: The trend between dichotomous variables' positive or negative rate and the elevated altitude level based on Cochran-Armitage trend test in χ^2 test was statistically significant.

high-level groups, respectively. There was a nonlinear relationship (upward-sloping "W" shape) between altitude and the risk of LVDD, assessed by the restricted cubic spline in Figure 2. The plot showed a substantial reduction of the LVDD risk with the increase of altitude in low-level group, which reached the lowest risk around 1000 m; thereafter, the risk increased, and the increasing trend was generally rapid, although it was relatively flat around 2500 to 3500 m.

Compared with the low level, ORs (95% CIs) of grade I LVDD for middle- and high-level groups were 1.75 (1.59–1.92) and 1.95 (1.69–2.25), respectively (*P* for trend <0.001); and ORs (95% CIs) of Grade II for middle- and high-level groups were 6.19 (3.67–10.42) and 5.27 (2.18–12.74), respectively (*P* for trend <0.001) (Table 4).

Among 42 576 participants before exclusion, the crude prevalences of self-reported chronic heart failure, stratified by 3-level altitude, were 1.01%, 1.18%, and 0.99%, respectively (*P* for trend=0.0228). Compared with the low level, the fully adjusted ORs (95% CIs) of chronic heart failure for middle- and high-level groups were 1.98 (1.34–2.94) and 0.61 (0.21–1.77), respectively (Table S3).

Table 2. Echocardiographic Parameters of LV Structure and Function by Altitude

Parameter	Total (n=34 215)	3-Level Categorical Altitude, m			*P* Value	*P* for Trend
		<1500 (n=27 241)	1500–3500 (n=5201)	≥3500 (n=1773)		
LV structure						
LVEDD, mm	45.94 (45.49–46.4)	45.82 (45.73–45.91)	48.06 (45.12–51)	41.6 (41.15–42.04)	<0.0001	0.6173
LVESD, mm	29.99 (29.79–30.2)	29.65 (29.58–29.71)	31.97 (31.82–32.13)	29.45 (25.68–33.23)	<0.0001	0.0002
LA diameter, mm	31.3 (31.17–31.42)	31.61 (31.45–31.77)	31.11 (30.96–31.27)	26.99 (26.79–27.18)	<0.0001	<0.0001
IVSD, mm	9.49 (9.43–9.56)	9.57 (9.49–9.65)	9.18 (9.08–9.28)	9.16 (9–9.33)	<0.0001	<0.0001
LVPWD, mm	9.16 (9.13–9.19)	9.2 (9.17–9.23)	9.01 (8.93–9.09)	8.98 (8.88–9.08)	<0.0001	0.0025
RWT	0.43 (0.42–0.43)	0.43 (0.42–0.44)	0.41 (0.4–0.41)	0.44 (0.44–0.45)	0.0009	0.9359
LV mass index, g/m^2	98.24 (72.36–124.13)	103.02 (70.61–135.42)	82.34 (79.68–85)	70.64 (65.48–75.79)	0.7602	0.3238
LV systolic function						
LVEF, %	64.2 (64.12–64.28)	64.48 (64.4–64.56)	63.06 (62.87–63.24)	63.29 (62.64–63.95)	<0.0001	<0.0001
LV diastolic function						
E-wave, m/s	0.83 (0.54–1.12)	0.71 (0.7–0.71)	0.68 (0.67–0.69)	1.18 (0.13–2.23)	<0.0001	<0.0001
A-wave, m/s	0.73 (0.7–0.76)	0.76 (0.75–0.76)	0.66 (0.65–0.67)	0.73 (0.63–0.83)	0.0298	0.0769
E/A ratio	1.04 (1.03–1.05)	1.01 (1–1.03)	1.08 (1.06–1.1)	1.04 (1.02–1.07)	<0.0001	<0.0001

Data are means (95% CIs). *P* value <0.05: The group difference assessed by 1-way ANOVA was significant. *P* for trend <0.05: There was a significant positive or negative linear association between parameter value and altitude, assessed by linear regression analysis. E/A indicates the ratio of the peak early filling velocity (E-wave) and the late diastolic filling velocity (A-wave); IVSD, interventricular septum thickness; LA, left atrial; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVPWD, LV posterior wall thickness; and RWT, relative wall thickness.

Stratified Analyses for LVDD Associated With Altitude

The stratified analyses suggested that LV diastolic function was much more remarkably influenced by elevated altitude in male participants; ORs (95% CIs) of LVDD for 1500 to 3500 m and ≥3500 m were 1.92 (1.68–2.2) and 2.46 (1.98–3.07) among men, respectively, and 1.59 (1.4–1.8) and 1.67 (1.38–2.02) among women, respectively ($P_{interaction}$=0.0019). However, no significant interaction was observed when data were stratified in terms of age (Table 5).

Table 3. Crude Prevalence of LVDD and Adjusted ORs for LVDD Associated With Altitude

Variable	No. (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
3-Level categorical altitude, m			
<1500 (Reference)	12 895 (47.34)	1.00	1.00
1500–3500	2350 (45.18)	1.59 (1.45–1.74)	1.65 (1.49–1.82)
≥3500	463 (36.27)	1.38 (1.21–1.56)	1.89 (1.63–2.19)
P for trend		0.228	<0.001
Altitude as continuous variable			
Total	15 888 (46.44)		
Per 500-m increase		1.03 (1.02–1.05)	1.08(1.06–1.10)
Per 1000-m increase		1.07 (1.03–1.10)	1.16(1.12–1.20)
<1500-m Group			
Per 500-m increase		0.57 (0.54–0.60)	0.71 (0.66–0.75)
Per 1000-m increase		0.32 (0.29–0.36)	0.50 (0.44–0.56)
1500- to 3500-m group			
Per 500-m increase		1.11 (1.05–1.18)	1.43 (1.31–1.56)
Per 1000-m increase		1.24 (1.10–1.40)	2.05 (1.73–2.42)
≥3500-m Group			
Per 500-m increase		1.60 (1.38–1.87)	2.03 (1.67–2.47)
Per 1000-m increase		2.57 (1.90–3.50)	4.41 (2.80–6.11)

In model 1, all estimates are adjusted for age and sex; in model 2, all estimates are adjusted for age, sex, region, areas, ethnicity, education, smoking, alcohol drinking, family history of stroke and coronary heart disease, obesity, hypertension, hyperlipidemia, diabetes mellitus, medical therapy, relative wall thickness, and left ventricular mass index. LVDD indicates left ventricular diastolic dysfunction; and OR, odds ratio.

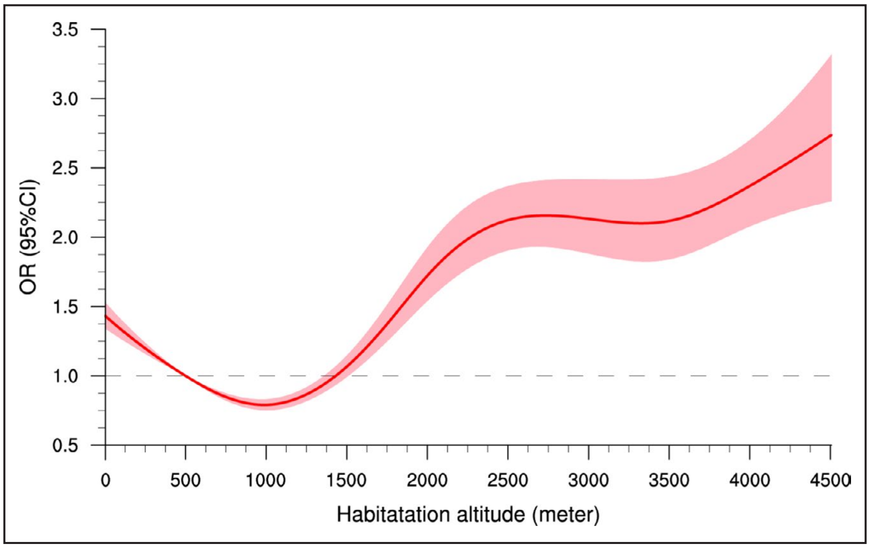

Figure 2. Nonlinear concentration-response relationship between habitation altitude and the risk of left ventricular diastolic dysfunction.
The red curve represents estimates of odds ratios (ORs), and the light red shaded area represent 95% CIs. All estimates are adjusted for age, sex, region, areas, ethnicity, education, smoking, alcohol drinking, family history of stroke and coronary heart disease, obesity, hypertension, hyperlipidemia, diabetes mellitus, medical therapy, relative wall thickness, and left ventricular mass index.

DISCUSSION

This study showed a significant positive association between habitation altitude and the risk of LVDD in China, especially for people living higher than 1500 m, as well as in male subjects.

Although a few previous studies have identified that long-term, even short-term, exposure to high altitude was the independent risk factor for LVDD, this is the first large-scale, free-living, population-based study to report the association between habitation altitude and LV function in a population free from preexisting significant heart disease and/or major chronic disease. Maufrais and colleagues[7] found that even 6 days on the top of Europe (4350 m) could impair the LV diastolic function, with the greatest effect observed at the second day for 11 male subjects (age, 28±8 years) at sea level concomitantly with the occurrence of acute mountain sickness. Sareban et al showed that rapid and active ascent of healthy individuals to 4559 m impairs passive filling and stroke volume of the LV; however, these alterations were not related to changes in LV and left atrium mechanics.[22] A prior study[13] identified high altitude was the independent risk factor for LVDD among Sherpa adolescents (3840 m; n=26) compared with age-matched lowland Sherpa (1400 m; n=10) and lowland White controls (sea level; n=30). And, for the children without heart disease in Tibet, compared with those born and living at sea level, lower systolic and diastolic function of both ventricles has been revealed after the age of 14 years.[23] The possible potential contributing mechanisms of LVDD caused by high altitude include the following: (1) hypoxic condition; altered cardiac energy supply in hypoxia caused an increased right ventricular afterload, a decrease in LV filling pressure, and a delayed LV untwist[7]; responsiveness of the pulmonary circle to

Table 4. Adjusted ORs of Each Category of LVDD Associated With Altitude

LVDD Grade	No. (%)	3-Level Categorical Altitude, m <1500 (Reference) (n=27 241)	1500–3500 (n=5201)	≥3500 (n=1773)	*P* for Trend
I	15 099 (44.13)	1.00	1.75 (1.59–1.92)	1.95 (1.69–2.25)	<0.001
II	517 (1.51)	1.00	6.19 (3.67–10.42)	5.27 (2.18–12.74)	<0.001
III	272 (0.79)	1.00	0.10 (0.03–0.31)	3.09 (0.97–9.83)	0.015

Values are OR (95% CI), unless otherwise indicated. All ORs are adjusted for age, sex, region, areas, ethnicity, education, smoking, alcohol drinking, family history of stroke and coronary heart disease, obesity, hypertension, hyperlipidemia, diabetes mellitus, medical therapy, relative wall thickness, and left ventricular mass index. LVDD indicates left ventricular diastolic dysfunction; and OR, odds ratio.

Table 5. Crude Prevalence of LVDD and Adjusted ORs in Stratified Analyses for LVDD Associated With Altitude

Category	No. of LVDDs (Crude Prevalence, %)	3-Level Categorical Altitude, m			*P* for Trend
		<1500 (Reference)	1500–3500	≥3500	
Sex					
Men	7785 (49.55)	1.00	1.92 (1.68–2.2)	2.46 (1.98–3.07)	<0.0001
Women	8103 (43.79)	1.00	1.59 (1.4–1.8)	1.67 (1.38–2.02)	<0.0001
$P_{interaction}$=0.0019					
Age group, y					
35–45	1389 (16.28)	1.00	1.89 (1.52–2.35)	1.69 (1.23–2.32)	<0.0001
45–55	2985 (33.94)	1.00	1.22 (1.03–1.45)	1.58 (1.24–2.01)	0.0001
55–65	4065 (57.22)	1.00	1.66 (1.39–1.99)	2.06 (1.57–2.7)	<0.0001
≥65	7449 (76.13)	1.00	2.69 (2.13–3.38)	2.24 (1.51–3.33)	<0.0001
$P_{interaction}$=0.3493					

Values are OR (95% CI), unless otherwise indicated. All estimates are adjusted for age (excluded in age-stratified model), sex (excluded in sex-stratified model), region, areas, ethnicity, education, smoking, alcohol drinking, family history of stroke and coronary heart disease, obesity, hypertension, hyperlipidemia, diabetes mellitus, medical therapy, relative wall thickness, and left ventricular mass index. LVDD indicates left ventricular diastolic dysfunction; and OR, odds ratio.

the acute or chronic hypoxic condition, its possible progression to the high-altitude pulmonary hypertension,[24] and pulmonary hypertension related to left heart disease by far represent the most common form of pulmonary hypertension, accounting for 65% to 80% of cases[25]; and (2) large daily temperature variability and cold weather: the cardiovascular system plays a crucial role in human thermoregulation, and cause-specific study of CVD morbidity/mortality indicated that the sensitivity to temperature was disease specific, with different patterns for acute and chronic heart disease.[9,10] In addition, it has been well documented that cold temperatures were associated with increased risk of CVD.[8]

A few studies have evaluated the association of long-term high altitude with CVD; however, this association is uncertain.[11] Inconsistent with the current study, many studies have suggested a protective effect of living at high altitudes for morbidity and mortality of CVD in Swiss,[26] Greek,[27] and US[28] populations. But, a few of the participants from the prior studies were living above 1500 m; however, the habitation altitude of the current study ranged from 3.1 to 4507 m. Meanwhile, Faeh and colleagues found that mortality from coronary heart disease (22% per 1000 m) and stroke (12% per 1000 m) significantly decreased with increasing altitude, which was similar with our findings about the <1500-m group (50% decrease per 1000 m). Other studies were in accord with the current study, which suggested that residence at high altitude comes at the trade-off of developing diseases, such as chronic mountain sickness and high-altitude pulmonary hypertension, and worsens outcomes for diseases, such as chronic obstructive pulmonary disease.[29] However, in the current study, it cannot be ignored that, although there was a small but significant increase in the crude prevalence of self-reported heart failure with altitude, the significant increasing trend has disappeared in the fully adjusted model among participants before exclusion. Thus, the findings of our study still need to be proved by further investigations.

In addition, we observed that LV diastolic function was remarkable influenced by elevated altitude in male participants. The probable explanation is that the potential CVD risk factors (eg, unhealthy diet, smoking, and drinking) are more popular in middle-aged men than women, which might have significant effect on the association between LV diastolic dysfunction and elevated altitude. The strengths of this study include a large-scale investigation about Chinese echocardiography condition, which also adjusted for known and potential confounding factors; and the data of participants' living altitude were from the reliable and homogenized surface stations. However, our work has some potential limitations. First, as a cross-sectional study, a causal relationship cannot be established. Second, we did not have data on some important covariates, such as eating habits, physical activity, biomarkers of CVD, or oxidative damage, which might prevent us from validating our findings accurately and mechanistically. Third, some diastolic function assessment related echocardiographic parameters, such as left atrial volume and lateral annular e', were not collected by our questionnaire in the field. Finally, we defined and evaluated the LV diastolic function according to the 2009 American Society of Echocardiography guidelines, not the latest 2016 version, because the protocol was developed in 2012 to 2014, which may decrease the specificity to assess the association with altitude, especially for elderly individuals.

CONCLUSIONS

In this large China-wide middle-aged population, we found a significant positive association between higher habitation altitude and LVDD (especially grade I/II) among people living in middle or high elevation areas (≥1500 m). LV diastolic function is much more remarkably influenced by elevated altitude in male participants. The current study provided a reference that for modifiable CVD risk factors, control should be much stricter among those living in middle/high altitude areas. Further confirmatory investigations among populations from multilevel habitation altitude and randomized clinical trials would further strengthen our findings.

ARTICLE INFORMATION

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Affiliations

From the Division of Prevention and Community Health, National Center for Cardiovascular Disease, National Clinical Research Center of Cardiovascular Disease, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China (C.Z., X.W., Z.C., L.Z., Y.K., Y.Y., L.J., Z.W.); State Key Laboratory of Numerical Modeling for Atmospheric Sciences and Geophysical Fluid Dynamics, Institute of Atmospheric Physics, Chinese Academy of Sciences, Beijing, China (H.T., S.W., G.H.); and University of Chinese Academy of Sciences, Beijing, China (H.T., S.W., G.H.).

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Author contributions: Dr. Z. Wang designed the study. Dr Zheng wrote the first draft of the report. Drs Z. Wang and Huang critically reviewed the manuscript. Drs Zheng, X. Wang, Chen, Zhang, Kang, Yang, Jiang, and Z. Wang took part in the field investigation and collected the data. Drs Zheng, Tang, and S. Wang conducted analysis and interpretation of data.

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1.

List of the China Hypertension Survey Investigators

This study was accomplished through the fine work of the staff at the national level. For a partial listing of colleagues see the follows (provinces sorted as alphabetical order):

Anhui: Liqun Hu, Hongqi Li, Qi Zhang, Guang Yan, Anhui Provincial Hospital, Hefei, Anhui, China; Fangfang Zhu, Anhui Institute of Cardiovascular Disease, Hefei, Anhui, China.

Beijing: Xianghua Fang, Chunxiu Wang, Shaochen Guan, Xiaoguang Wu, Hongjun Liu, Chengbei Hou, Xuanwu Hospital, Capital Medical University, Beijing, China.

Chongqing: Han Lei, Wei Huang, Nan Zhang, First Affiliated Hospital of Chongqing Medical University, Chongqing, China; Ge Li, Lihong Mu, Xiaojun Tang, Chongqing Medical University, Chongqing, China.

Fujian: Ying Han, Huajun Wang, Dongjie Lin Liangdi Xie, First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China; Daixi Lin, Fujian medical university, Fuzhou, Fujian, China.

Gansu: Jing Yu, Xiaowei Zhang, Wei Liang, Heng Yu, Qiongying Wang, Lanzhou University Second Hospital, Lanzhou, Gansu, China; Lan Yang, Maternal and Child Care Service Centre, Lanzhou, Gansu, China.

Guangdong: Yingqing Feng, Yuqing Huang, Guangdong General Hospital, Guangzhou, Guangdong, China; Peixi Wang, Jiaji Wang, Guangzhou Medical University, Guangzhou, Guangdong, China; Harry HX Wang, Sun Yat-Sen University, Guangzhou, Guangdong, China; Songtao Tang, Community Health Services Center of Liaobu, Dongguan, Guangdong, China.

Guangxi: Tangwei Liu, Rongjie Huang, Zhiyuan Jiang, Haichan Qin, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.

Guizhou: Guoqin Liu, Zhijun Liu, Wenbo Rao, Zhen Chen, Yalin Chu, Fang Wu, Zunyi Medical University, Zunyi, Gouzhou, China.

Hainan: Haitao Li, Jianlin Ma, Tao Chen, Hainan General Hospital, Haikou, Hainan, China; Ming Wu, Health and Family Planning Commission of Hainan, Haikou, Hainan, China.

Hebei: Jixin Sun, Yajing Cao, Yuhuan Liu, Center for Disease Prevention and Control of Hebei, Shijiazhuang, Hebei, China; Zhikun Zhang, Center for Disease Prevention and Control of Tangshan, Tangshan, Hebei, China; Yanmei Liu, Center for Disease Prevention and Control of Langfang, Langfang, Hebei, China; Dejin Dong, Center for Disease Prevention and Control of Xingtai, Xingtai, Hebei, China; Guangrong Li, Center for Disease Prevention and Control of Dingzhou, Dingzhou, Hebei, China.

Heilongjiang: Hong Guo, Lihang Dong, Haiyu Zhang, Fengyu Sun, Xingbo Gu, Ye Tian, First Affiliated Hospital of Harbin Medical University, Haerbin, Heilongjiang, China.

Henan: Kaijuan Wang, Chunhua Song, Peng Wang, Hua Ye, Zhengzhou University, Zhengzhou, Henan, China; Wei Nie, Shuying Liang, Henan Academy of Medical Sciences, Zhengzhou, Henan, China.

Hubei: Congxin Huang, Fang Chen, Yan Zhang, Heng Zhou, Jing Xie, Jianfang Liu, Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China.

Hunan: Hong Yuan, Chengxian Guo, Third Xiangya Hospital, Central South University, Changsha, Hunan, China; Yuelong Huang, Biyun Chen, Center for Disease Control and Prevention of Hunan, Changsha, Hunan, China.

Inner Mongolia: Xingsheng Zhao, Wenshuai He, Xia Wen, Yanan Lu, Inner Mongolia people's hospital, Hohhot, Inner Mongolia, China.

Jiangsu: Xiangqing Kong, Ming Gui, Wenhua Xu, Yan Lu, Jun Huang, First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; Min Pan, Affiliated Hospital of Nantong University, Nanjing, Jiangsu, China; Jinyi Zhou, Ming Wu, Center for Disease Control and Prevention of Jiangsu, Nanjing, Jiangsu, China.

Jiangxi: Xiaoshu Cheng, Huihui Bao, Xiao Huang, Kui Hong, Juxiang Li, Ping Li, Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China.

Jilin: Bin Liu, Junduo Wu, Longbo Li, Yunpeng Yu, Yihang Liu, Chao Qi, Second Hospital of Jilin University, Changchun, Jilin, China.

Liaoning: Jun Na, Li Liu, Yanxia Li, Guowei Pan, Center for Disease Prevention and Control of Liaoning, Shenyang, Liaoning, China; Degang Dong, Peng Qu, Health and Family Planning Commission of Liaoning, Shenyang, Liaoning, China.

Ningxia: Jinbao Ma, Health and Family Planning Commission of Ning Xia Hui Autonomous Region, Yinchuan, Ningxia, China; Juan Hui, Center for Disease Control and Prevention of Ning Xia Hui Autonomous Region, Yinchuan, Ningxia, China; Fu Zhao, Health Supervision Institute of Xixia District in Yinchuan, Ning Xia Hui Autonomous Region, Yinchuan, Ningxia, China.

Qing Hai: Jianning Yue, Minru Zhou, Zhihua Xu, Xiaoping Li, Qiongyue Sha, Fuchang Ma, Qing Hai Center for Disease Control and Prevention, Xining, Qinghai, China; Qiuhong Chen, Huiping Bian, Qinghai Cardio-Cerebrovascular Disease Special Hospital, Xining, Qinghai, China.

Shaanxi: Jianjun Mu, Tongshuai Guo, Keyu Ren, Chao Chu, First Affiliated Hospital of Xi’an Jiaotong University, Xian, Shaanxi, China.

Shandong: Zhendong Liu, Hua Zhang, Yutao Diao, Shangwen Sun, Yingxin Zhao, Institute of Basic Medicine, Shandong Academy of Medical Sciences, Jinan, Shandong, China.

Shanghai: Junbo Ge, Jingmin Zhou, Xuejuan Jin, Jun Zhou, Zhongshan Hospital, Fudan University, Shanghai, China.

Shanxi: Bao Li, Lijun Zhu, Yuean Zhang, Gang Wang, Shanxi Cardiovascular Hospital, Taiyuan, Shanxi, China; Zhihan Hao, Wuxiang County People's Hospital, Wuxiang, Shanxi, China.

Sichuan: Li Cai, Zhou Liu, Zhengping Yong, Jianhong Tao, Yijia Tang, Sichuan Provincial People's Hospital, Chengdu, Sichuan, China; Shaoping Wan, Sichuan Cancer Hospital, Chengdu, Sichuan, China.

Tianjin: Zhenshan Jiao, Yuqiang Fan, Tianjin Academy of Traditional Chinese Medicine, Tianjin, China; Hui Gao, Wei Wang, Tianjin Municipal Commission of Health and Family Planning, Tianjin, China; Qingkui Li, Xiaomei Zhou, Tianjin Medical University, Tianjin, China.

Tibet: Yundai Chen, Bin Feng, Qinglei Zhu, Sansan Zhou, Chinese People’s Liberation Army General Hospital, Lasha, Tibet, China.

Xinjiang: Nanfang Li, Lin Zhou, Delian Zhang, Jing Hong, People's Hospital of Xinjiang Uygur Autonomous Region, Urumuqi, Xinjiang, China.

Yunnan: Tao Guo, Min Zhang, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, China; Yize Xiao, Center for Disease Prevention and Control of Yunnan, Kunming, Yunnan, China; Xuefeng Guang, Affiliated Yan'an Hospital of Kunming Medical University, Kunming, Yunnan, China.

Zhejiang: Xinhua Tang, Jing Yan, Xiaoling Xu, Li Yang, Aimin Jiang, Wei Yu, Zhejiang Hospital, Hangzhou, Zhejiang, China.

List of the Study on prevalence of chronic cardiopulmonary disease in Tibet and Xinjiang area

Investigators

National Center for Cardiovascular Diseases, Fuwai Hospital: Lan Shao, Ye Tian, Tianming Zhao, Guohui Fan, Ying Dong, Jingyu Nie, Pei Chen, Jiali Wang, Xiuyun Jia, Manlu Zhu, Wen Wang, Weiwei Chen, Runlin Gao.

Beijing Hospital: Yanfei Guo, Tieying Sun, Yuxia Wang, Di Chai, Yali Ma, Yaqi Tong.

Chinese PLA General Hospital: Yundai Chen, Bin Feng, Qinglei Zhu, Shanshan Zhou, Jie Liu, Jing Wang, Lina Yang, Ying Yang, Peng Duan.

People's Hospital of Xinjiang Uygur Autonomous Region: Nanfang Li, Ling Zhou, Delian Zhang, Xiaoguang Yao, Jing Hong, FeiyaSuo, Mei Cao.

Chinese Center For Disease Control And Prevention：Jing Wu, Wenhui Shi, Yi Zhai, Liu He.

Table S1. Participants distribution of each LVDD category (0 to III) by three-level altitude group.

LVDD grade	Total (n=34,215)	Three-level categorical altitude		
		＜1,500m (n=27,241)	1,500-3,500m (n=5,201)	≥3,500m (n=1,773)
0	18,327 (53.56)	14,346 (52.66)	2,851 (54.82)	1,130 (63.73)
I	15,099 (44.13)	12,163 (44.65)	2,308 (44.38)	628 (35.42)
II	517 (1.51)	470 (1.73)	39 (0.75)	8 (0.45)
III	272 (0.79)	262 (0.96)	3 (0.06)	7 (0.39)

Data are presented as absolute numbers and crude prevalence, n (%). M, meter; Ref, reference. LVDD, left ventricular diastolic dysfunction.

Table S2. Adjusted odds ratios for left atrial enlargement associated with altitude.

	n (%)	Model 1	Model 2
＜1500m （Ref）	1,565 (5.75)	1.00	1.00
1500-3500m	365 (6.84)	1.31 (1.16-1.48)	1.77 (1.49-2.11)
≥3500m	11 (0.62)	0.14 (0.08-0.25)	0.14 (0.07-0.29)
P for trend	--	<0.001	0.9372

Values are odds ratio (95% confidence interval). M, meter; Ref, reference. In model 1, all estimates are adjusted for age, sex; In model 2, all estimates are adjusted for age, sex, region, areas, ethnicity, education, smoking, alcohol drinking, family history of stroke and coronary heart disease, obesity, hypertension, hyperlipidemia, diabetes, medical therapy, relative wall thickness and left ventricular mass index.

Table S3. Crude prevalence of self-reported chronic heart failure and adjusted odds ratios associated with altitude among 42,576 participants prior to exclusion.

	Crude prevalence (n/N)	Model 1	Model 2
＜1500m （Ref）	1.01% (351/34,806)	1.00	1.00
1500-3500m	1.18% (68/5,741)	1.25 (0.96-1.63)	1.98 (1.34-2.94)
≥3500m	0.99% (4/2,029)	0.25 (0.10-0.68)	0.61 (0.21-1.77)
P for trend	--	0.316	0.103

Values are odds ratio (95% confidence interval). M, meter; Ref, reference. In model 1, all estimates are adjusted for age, sex; In model 2, all estimates are adjusted for age, sex, region, areas, ethnicity, education, smoking, alcohol drinking, family history of stroke and coronary heart disease, obesity, hypertension, hyperlipidemia, diabetes, medical therapy, relative wall thickness and left ventricular mass index.

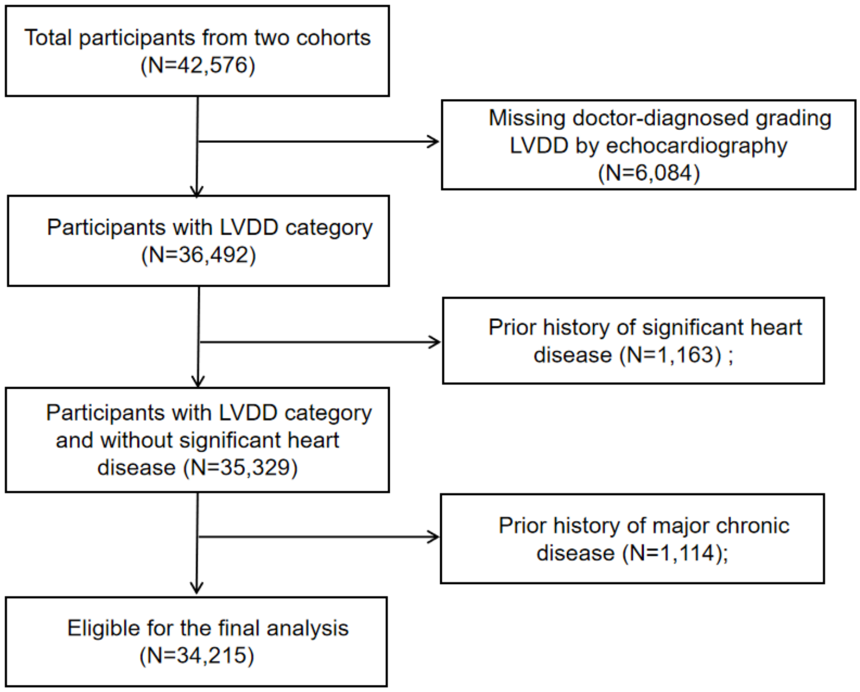

Figure S1. Flow chart of participants included and excluded in the study