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Ventilatory and heart rate responses to hypoxia in pre- and post-menopausal ethnically Tibetan women residing at ∼3800 m in Mustang, Nepal

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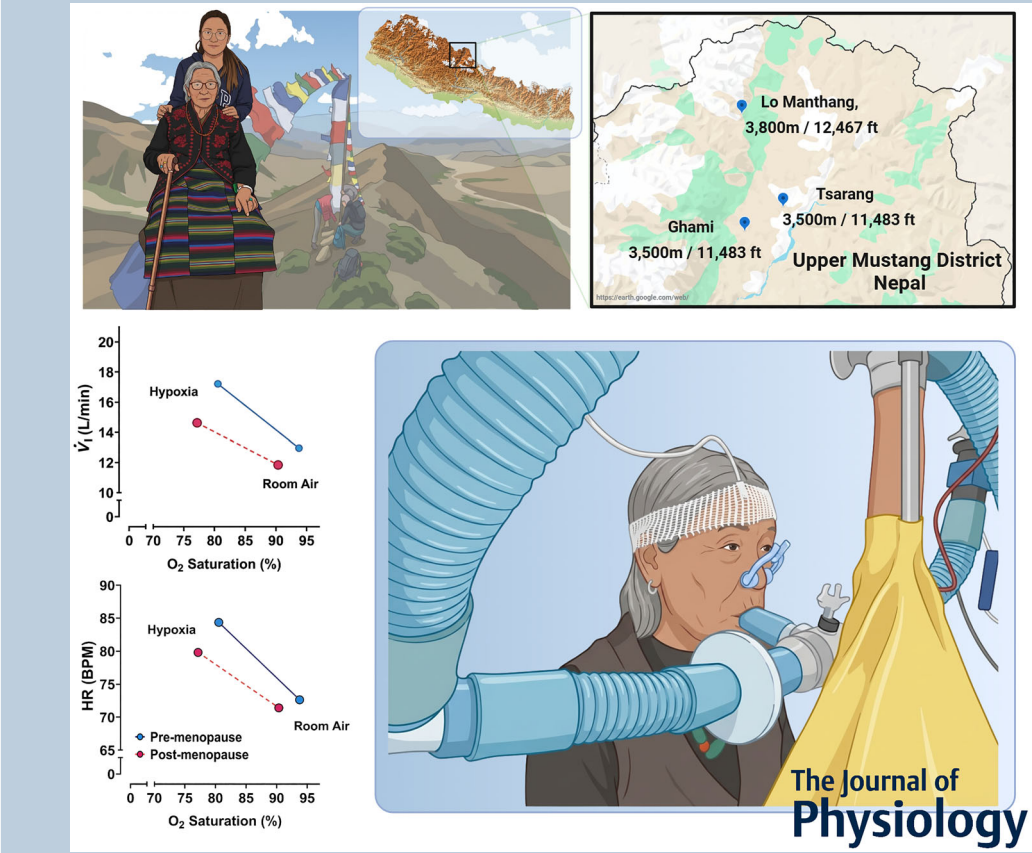

E. A. Moya and J. J. Yu contributed equally to this work.

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Abstract figure legend Tibetan women livingat high altitude exhibit distinct physiological traits that can enhance oxygen transport in chronic hypoxia. Menopausal status influences cardiopulmonary responses to hypoxia in women living at low altitudes. Therefore, we studied the effects of menopause on ventilatory and heart responses to hypoxia in 374 ethnically Tibetan women (46–86 years old) living at high altitude in Mustang, Nepal. Pre-menopausalwomen had significantly higher ventilatory and heart rate responses to hypoxia and higher oxygen saturation. Genetic analyses revealed genotype-phenotype associations with both end-tidal carbon dioxide in room air and ventilation during hypoxia. Hence, potentially advantageous ventilatory and cardiac responses to hypoxia wane after menopause in Tibetan women living at high altitude.

Abstract Humans residing at high altitude exhibit distinct physiological traits, some of which may enhance oxygen transport under conditions of chronic hypoxia. Highlanders exhibit variation in their responses to acute hypoxia, including differences in their hypoxic ventilatory response (HVR) and hypoxic heart rate response (HHRR). Little is known about whether variations in these measurements are influenced by menopausal status. We hypothesized that pre-menopausal women living at high altitude would exhibit greater HVR and HHRR than their post-menopausal counterparts. We measured HVR and HHRR in 374 ethnically Tibetan women (46–86 years of age) living in Mustang, Nepal (>3500 m). Pre-menopausal women had higher oxygen saturation ($P < 0.0001$) and minute ventilation ($P = 0.002$) while breathing room air, as well as higher HVR ($P < 0.0001$) and higher minute ventilation in acute isocapnic hypoxia ($P < 0.0001$). HR did not differ between groups while breathing room air, but HR ($P < 0.0005$) and HHRR ($P < 0.0001$) were higher in pre-menopausal women during isocapnic hypoxia. HVR and HHRR were associated with higher oxygen saturation in both groups ($P < 0.0001$) and negatively associated with age only in the post-menopausal group ($P < 0.0001$). Genetic analyses revealed genotype–phenotype associations with both end-tidal carbon dioxide (P_{ETCO_2}) in room air and ventilation during hypoxia. These data suggest ventilatory and heart rate responses to hypoxia wane in Tibetan women residing at high altitude after menopause, when their contributions to reproductive fitness shift from bearing additional children to supporting the survival and care of existing offspring.

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Key points

- Hypoxic ventilatory (HVR) and heart rate responses (HHRR) vary among high-altitude Tibetans, but the contribution of menopausal status to this variation has been largely unknown.
- In 374 Tibetan women living >3500 m in Nepal, pre-menopausal women had higher oxygen saturation and ventilation at rest and during acute hypoxia than post-menopausal women, while resting heart rate did not differ by menopausal status.
- Pre-menopausal Tibetan women also showed significantly higher minute ventilation and heart rate during isocapnic hypoxia, as well as higher HVR and HHRR.
- HVR and HHRR positively correlated with oxygen saturation at both life stages but declined with age only in post-menopausal women.
- These findings demonstrate that menopause and ageing independently reduce hypoxic cardiorespiratory responses, highlighting life-stage-specific physiological adaptation in high-altitude Tibetan women.

Introduction

Humans who ascend or reside permanently at high altitudes face the unavoidable environmental challenge of decreased availability of oxygen (O_2) in each breath due to hypobaric hypoxia. An increase in ventilation is the first physiological response to reduced O_2, occurring within seconds to minutes of hypoxia exposure, and is referred to as the hypoxic ventilatory response (HVR). This response

is largely mediated by activation of the peripheral chemoreceptors in the carotid body, which sense a decrease in the arterial partial pressure of O_2 (P_{aO_2}) (Iturriaga et al., 2021; Pamenter & Powell, 2016; Powell et al., 1998). A persistent hypoxic stimulus (i.e., from approximately two days up to two months) leads to a secondary increase in ventilation, termed ventilatory acclimatization to hypoxia (VAH), which reflects modifications to the HVR across different time domains of hypoxia exposure (Pamenter & Powell, 2016; Powell et al., 1998).

Ventilatory responses to hypoxia are among the most important physiological responses of lowlanders acutely exposed to high altitude. However, high ventilation is not always observed at altitude. On average, Tibetan and Sherpa individuals born and living at high altitude exhibit high ventilation and HVR similar to that observed in acclimatizing lowlanders, while many Andean-born individuals exhibit a lower ventilation and HVR, similar to lowlanders who reside long term at high altitude (Beall, 2007; Beall et al., 1997; Brutsaert, 2007; Curran et al., 1995; Gilbert-Kawai et al., 2014; Hackett et al., 1980; Moore, 2000; Zhuang et al., 1993). Although genetic factors have been hypothesized to contribute to these differences (Beall et al., 1997; Brutsaert et al., 2005; Goldberg et al., 2017; Julian & Moore, 2019; Oeung et al., 2023; Petousi & Robbins, 2014; Simonson, 2015; Yu et al., 2022), genotype–phenotype associations have not been reported. Both ventilation and HVR show substantial variability, yet the sources of variation within populations remain poorly understood. The variation in ventilation and ventilatory control may influence O_2 saturation and ultimately contribute to evolutionary fitness in high-altitude resident women. This is particularly important among Tibetan women as higher O_2 saturation correlates with greater lifetime reproductive success (Ye et al., 2024).

Historically, most studies of ventilatory control have focused on men traveling to high altitudes (Forster et al., 1971; Hupperets et al., 2004; Sato et al., 1992; Weil et al., 1970, 1971; Zhuang et al., 1993). Relatively few studies have addressed the physiological effects of high altitude on women (Beall et al., 1997, 2010; León-Velarde et al., 2001; Raberin et al., 2023; Regensteiner et al., 1989; Richalet et al., 2020; Tatsumi et al., 1997; Ye et al., 2024; Yu et al., 2022), highlighting the need for further investigation (Horakova et al., 2023). Hormones at different phases of the menstrual cycle and throughout life stages may impact the control of breathing (Behan & Wenninger, 2008; Gargaglioni et al., 2019; Macnutt et al., 2012; Raberin et al., 2023; Regensteiner et al., 1989; White et al., 1983), which may contribute to inconsistencies observed in HVR studies involving women (Aitken et al., 1986; Macnutt et al., 2012; White et al., 1983). For example, at low altitude, Pokorski & Marczak (2003) found no significant differences in the HVR between women of 71.0 ± 1.3 and 24.2 ± 0.4 years of age, while Lhuissier et al. (2012) reported a significant effect of menopause on HVR, showing lower HVR during resting conditions. Additional studies need to account for age and life cycle stage.

Other hypoxia-induced changes may contribute to increased O_2 saturation and, indirectly, enhance evolutionary fitness. Although less studied, acute hypoxia exposure causes an increase in heart rate (Ainslie & Poulin, 2004; Simon et al., 1995; Steinback & Poulin, 2008), known as the hypoxic heart rate response (HHRR), which is generated by mechanisms including activation of the adrenergic system (Richalet et al., 2023). The effects of menstrual cycle and menopause on HHRR have been studied in individuals exposed to hypoxia (Lhuissier et al., 2012; Richalet et al., 2020), showing lower heart rate responses to hypoxia in post-menopausal women, an effect attributed to age. However, the HHRR has not been extensively measured in populations with permanent high-altitude residence.

The study of HVR and HHRR is important for understanding potential adaptations in high-altitude populations, as these responses are crucial for the delivery and transport of O_2 to vital organs (Luks & Hackett, 2022; Richalet et al., 2023; Teppema & Dahan, 2010). We hypothesized that pre-menopausal Tibetan women residing at high altitude exhibit higher ventilatory and heart rate responses to acute hypoxia than post-menopausal women, and that the higher responses correlate with higher O_2 saturation. To test this hypothesis, we measured ventilation and heart rate in response to acute hypoxia in 374 ethnically Tibetan women residing in the high-altitude region of

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Mustang, Nepal, and evaluated the relationships between menopausal status and HVR and HHRR. Given the hereditary component of the HVR (Beall et al., 1997; Brutsaert et al., 2005; Golder et al., 2005; Han & Strohl, 2000), the potential genetic contribution to physiological responses to hypoxia (Lancaster et al., 2020; Moya et al., 2024; Petousi et al., 2014; Song et al., 2020; Yu et al., 2022), and the genetic elements of O_2 homeostasis (Semenza, 2012), we also conducted a genome-wide association study (GWAS) and further tested for associations with selection-nominated candidate genes.

Methods

Ethical approval

This study conformed to the standards set by the latest revision of the Declaration of Helsinki except for registration in a database. The study procedures were approved by properly constituted ethics committees: the institutional review boards of Case Western Reserve University (IRB 2017–2082), Dartmouth College (STUDY00023374) and the Nepal Health Research Council (Reg. No. 256/2018). The research team included US-based researchers, ethnic Tibetan female nurses and research assistants. The nurses and trained research assistants used the local dialect of the Tibetan language to review and discuss the consent form with potential participants and answer questions. The participants provided written informed consent to participate in the study.

Participants

As previously reported, the cohort examined in this study included a total of 417 individuals who self-identified as ethnically Tibetan women between 46 and 86 years of age (Ye et al., 2024). All participants were native residents of Upper Mustang District, Nepal, in villages ranging between 3500 and 4100 m (11,550–13,530 feet) above sea level. We measured the HVR and HHRR in 376 of those participants. Two of these participants did not provide menopausal status or did not fulfill physiological measurement requirements; therefore, 374 women were included in the analysis. Additionally, we excluded one participant's HR data due to technical difficulties with that measurement. Data collection was performed in temporary laboratories installed in three of the main area villages: Lo Manthang (3800 m; 29°10′N, 83°57′E, Tsarang (3500 m; 29°5′N, 83°56′E) and Ghami (3500 m; 29°3′N, 89°53'E) reporting barometric pressures between 481 and 497 mmHg during t months of measurements in these locations.

Anthropometric measurements

We measured height and weight and calculated body mass index (BMI) in all participants (Table 1). Research assistants asked participants if they were still menstruating (i.e., 'yes', 'no' or 'irregularly'). The six women who answered 'irregularly' were combined into a single group with those who responded 'yes'. None of the women reported the use of hormone replacement therapy.

Physiological measurements

For physiological measurements of HVR and HHRR, participants sat in a chair, breathing through a mouthpiece (Hans Rudolph, Shawnee, KS, USA) with a nose clip (Fig. 1*A*). The mouthpiece was connected to a one-way, rebreathing circuit with a breathing valve (2700 Series, Large, Hans Rudolph) to produce a decrease in the fraction of inspired oxygen (F_{IO_2}) when the rebreathing circuit was closed to room air. The protocol consisted of one to three bouts of acute hypoxia during which tidal volume (V_T) and respiratory frequency (f_R) were measured using a Fleisch pneumotachograph (model CD15, Validyne, Northridge, CA, USA), heart rate (HR) and oxygen saturation (S_{pO_2}) were measured with a pulse oximeter using a surface probe placed on the forehead (Nellcor model N395, Medtronic, Minneapolis, MN, USA), and end-tidal CO_2 (P_{ETCO_2}) and O_2 (P_{ETO_2}) were measured with a gas analyser (Model 17620 and Model 17515A for P_{ETCO_2} and P_{ETO_2} respectively, VacuMed, Ventura, CA, USA) (Fig. 1*B*). All analog signals were processed through a PowerLab 8/30 (ADInstruments, Colorado Springs, CO, USA) and sent digitally to a laptop computer (HP Probook, HP Inc., Palo Alto, CA, USA). Participants were given a minimum of 5 minutes of rest between hypoxic events, and testing resumed once they reported being ready, and the average was calculated across women who completed one ($n = 32$), two ($n = 86$) or three ($n = 258$) bouts of acute hypoxia.

The protocol began with baseline measurements breathing room air for 2–3 minutes with the three-way valve in the rebreathing circuit open to room air. This was followed by a hypoxic stimulus (3–5 minutes) induced by connecting the rebreathing circuit to a weather balloon. Once S_{pO_2} decreased 10%, an air pump added room air into the circuit and the hypoxia was maintained in isocapnic conditions by forcing air through a CO_2 scrubber positioned in parallel to the rebreathing circuit with a regulating fan. Data collected during the acute hypoxia stimulus were discarded if P_{ETCO_2} changed by more than 2 mmHg or S_{pO_2} decreased less than 10% from baseline values. The partial pressures of inspired O_2 and expired CO_2 were calculated using daily measurement of barometric pressure. Inspired gas volumes were corrected

Table 1. Population characteristics (mean ± SD) of Tibetan women in Mustang, Nepal

Parameter	Total	Menstrual status		*t* test *P*
	(*n*)	Pre-menopause (*n*)	Post-menopause (*n*)	
Age (years)	59 ± 9.1 (374)	49.3 ± 3.4 (67)	61.3 ± 8.5 (307)	****
Height (m)	1.50 ± 0.09 (374)	1.52 ± 0.05 (67)	1.49 ± 0.10 (307)	*
Weight (kg)	48.0 ± 8.3 (374)	50.7 ± 7.4 (67)	47.4 ± 8.3 (307)	**
BMI (kg/m^2)	21.2 ± 3.0 (374)	21.8 ± 2.8 (67)	21.1 ± 3.1 (307)	n.s.

Student's *t*-test, ***$P < 0.0001$, **$P < 0.01$, *$P < 0.05$ significant pre-menopause *versus* post-menopause.

to reflect body temperature, ambient pressure and gas saturated with water vapour (BTPS) conditions. Prior to each hypoxic exposure, a baseline value was obtained by averaging at least 30 seconds of stable recordings collected while breathing room air. The hypoxic response was calculated by averaging 30 seconds of stable signals from the final minute of hypoxia. Graphical examples of baseline and response values are shown as shaded areas in Fig. 1*B*.

These 30-second averages were used to calculate minute ventilation ($\dot{V}_I$), the HVR (change in ventilation per decrease in S_{pO_2}, $\Delta\dot{V}_I/S_{pO_2}$) and the HHRR (change in heart rate per decrease in S_{pO_2}, $\Delta HR/\Delta S_{pO_2}$). Given hypoxia produced a negative ΔS_{pO_2}, we took the absolute value of $\Delta V\ \dot{V}_I/\Delta S_{pO_2}$ and $HR/\Delta S_{pO_2}$.

To assess the repeatability of the hypoxic test, we measured the HVR in 10 Tibetan women, with repeated measurements separated by at least 7 days. Repeatability

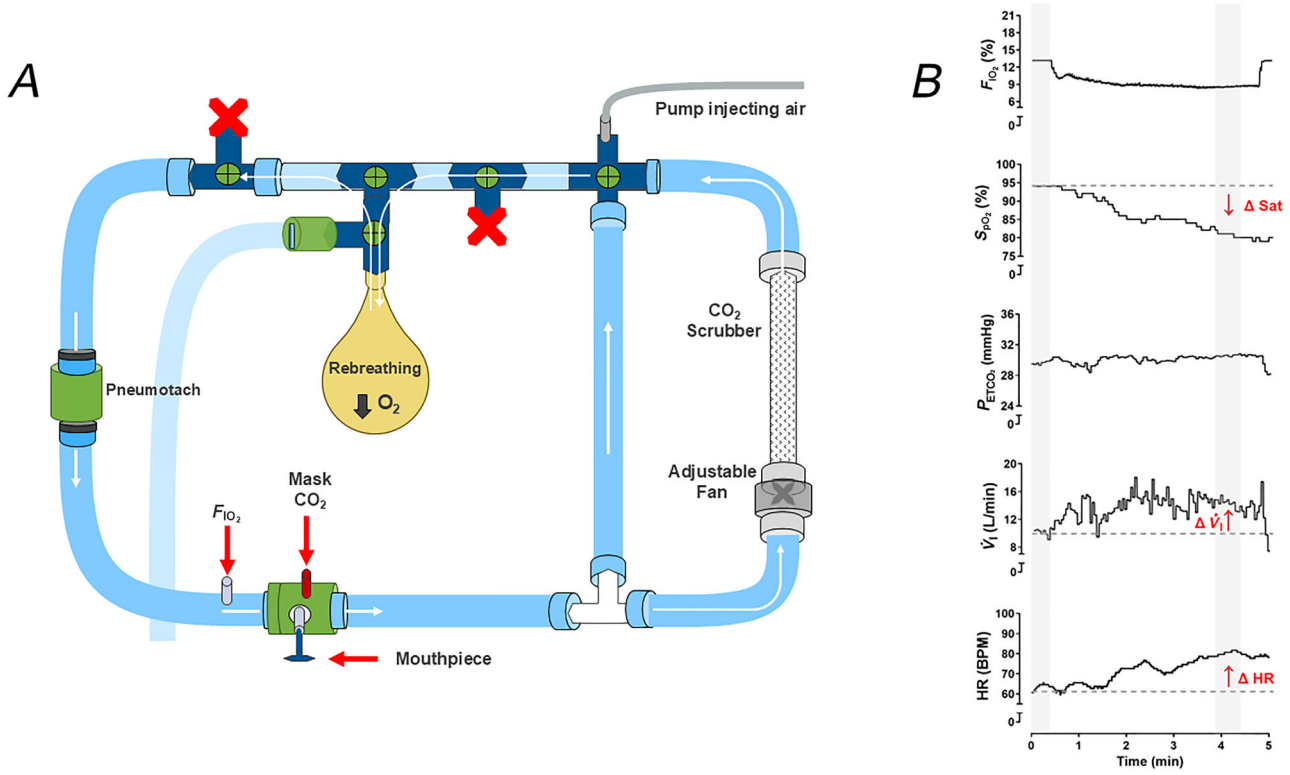

Figure 1. Set-up using a modified rebreathing method to produce isocapnic hypoxia
Each volunteer breathed through a mouthpiece connected to a one-way rebreathing system (with one-way valves) to induce acute hypoxia exposure. Mask CO_2 was measured in front of the participant's mouthpiece, whereas inspired O_2 was measured in the upstream tube. Inspired volume was also measured with a pneumotach upstream of the participant mouthpiece. The rebreathing-induced decrease in O_2 levels was stopped by adding room air to the system by controlling a pump, and constant levels of CO_2 were achieved by controlling an adjustable fan to re-route air through a CO_2 scrubber (*A*). Example of a recording of a 5-minute acute hypoxia event, showing simultaneous fraction of inspired O_2 (F_{IO_2}), O_2 saturation (S_{pO_2}), end-tidal CO_2 (P_{ETCO_2}) minute ventilation ($\dot{V}_I$) and heart rate (HR) (*B*).

was evaluated using Bland–Altman analysis (Bland & Altman, 1986; Giavarina, 2015) and by examining the correlation between the two measurements. Additionally, to assess within-day repeatability in the same individual, we compared HVR responses to a first, second and third hypoxic stimulus performed on the same day. Bland–Altman and correlation analyses were applied to the pairs of first–second, first–third and second–third hypoxic events. Repeatability analysis of HHRR of our dataset was reported by Ye et al. (2024).

Genetic analyses

We conducted a GWAS using previously published genotype data (available at https://datadryad.org/stash/dataset/https://doi.org/10.5061/dryad.bp46m) for approximately 3.5 million single nucleotide polymorphisms (SNPs) for this same cohort of women (Jeong et al., 2018). We tested SNPs for genome-wide significance with physiological variables related to ventilation (HVR, V_T in room air and hypoxia, $\dot{V}_I$ in room air and hypoxia, f_R in room air and hypoxia, S_{pO_2} in room air and hypoxia, and P_{ETCO_2} in room air and hypoxia) using GEMMA v0.94.1 (Zhou & Stephens, 2012) with a similar analysis performed for genome-wide significance (Ye et al., 2024). A univariate linear mixed model (LMM), as implemented in GEMMA (https://github.com/genetics-statistics/GEMMA), controlled for both population structure and genetic relatedness. We included SNPs with a minor allele frequency $\geq$5% and performed a stepwise regression with covariate age, age^2, altitude, relative wealth, menopausal status, F_{IO_2} in room air, fingertip perfusion and temperature, and selected the regression model with the lowest Akaike information criterion (AIC) values.

We further employed the iSAFE (Integrated Selection of Allele Favored by Evolution) algorithm (Akbari et al., 2018) for genomic data from a larger cohort of 417 individuals, which included all 374 individuals with HVR measurements, to identify genomic regions exhibiting significant signals of natural selection. These data were segmented into 5-megabase bins to identify the favoured variant within a large genomic region. Variants with an iSAFE score of $\geq$0.2 were used to define selection candidate genes, which are genes within regions that exhibit a signal of selection. The overlap of these selection candidate genes, including genes within 200 kilobases up- and downstream of the highest iSAFE signal, and a list of genes related to the control of breathing based on existing literature (referred to as *a priori* functional candidate genes) (Supp. Table 1) revealed a set of prioritized genes for testing (see Table 4). These prioritized candidate gene regions did not overlap with any of the significant GWAS findings.

Statistical analysis

Data are expressed as the mean $\pm$ SD. For comparison between two groups, we used unpaired two-tailed Student's *t* test. For statistical analysis considering two categorical variables (menopausal status, acute hypoxia and their interaction), we performed two-way ANOVAs followed by Bonferroni's *post hoc* analysis (Prism 10, version 10.4.0).

To study potential relationships between variables, we used Pearson's correlation coefficients and 95% confidence intervals (95% CI). We also compared simple linear regressions between pre- and post-menopausal women and determined whether there were significant differences of slopes and intercepts using Prism software. $P < 0.05$ was considered statistically significant and reported the effect size (slope). Additionally, we used mixed-effects models to evaluate the relationship of age and menopausal status with HVR and HHRR. These mixed-effects models were completed to predict the effect of menopause on HVR or HHRR utilizing the package lme4 (Bates et al., 2015) (Version 1.1.35.1). Model assumptions were checked with the package DHARMa (Version 0.4.6). The ultimate mixed-effects model predicting HVR or HHRR included age and menopausal status as covariates.

Results

Anthropometric measurements

Anthropometric values for the entire sample of women (total) and separated by menopausal status (pre- and post-menopause) are listed in Table 1. Post-menopausal women were significantly older, shorter and weighed less than pre-menopausal women. However, no significant differences were observed in BMI between the groups.

Hypoxic ventilatory responses

Table 2 shows that isocapnic hypoxia during the HVR measurements significantly decreased S_{pO_2} ($P < 0.0001$) and significantly increased $\dot{V}_I$, V_T, f_R and HR in the full sample of participants. Pre-menopausal women breathing room air had higher $\dot{V}_I$ (13.0 $\pm$ 2.0 *vs.* 11.9 $\pm$ 1.8 L/min, $P < 0.002$) and S_{pO_2} (93.8 $\pm$ 2.4 *vs.* 90.4 $\pm$ 3.9%, $P < 0.0001$, Fig. 2*A*) than post-menopausal women. As expected, ventilation increased in both groups with acute hypoxia but to a significantly higher value in the pre-menopausal group ($\dot{V}_I$ in pre- *vs.* post-menopausal women: 17.2 $\pm$ 3.5 and 14.6 $\pm$ 2.9 L/min, $P < 0.0001$, respectively, Fig. 2*A*), resulting in a significantly higher S_{pO_2} during hypoxia (80.5 $\pm$ 3.8%) compared to post-menopausal women (77.2 $\pm$ 4.6%, $P < 0.0001$, Fig. 2*A*). Pre-menopausal

Table 2. Physiological parameters (mean ± SD) during room air and acute hypoxia conditions

Parameter	Tibetan women		*t* test *P*
	Room air (*n*)	Acute hypoxia (*n*)	
Inspired O_2 (mmHg)	102.6 ± 1.8 (374)	69.9 ± 4.9 (374)	****
S_{pO_2} (%)	91.0 ± 3.9 (374)	77.8 ± 4.7 (374)	****
$\dot{V}_I$ (L/min)	12.01 ± 1.90 (374)	15.10 ± 3.10 (374)	****
V_T (L)	0.640 ± 0.107 (374)	0.750 ± 0.157 (374)	****
f_R (BrPM)	19.2 ± 3.3 (374)	20.4 ± 3.5 (374)	****
P_{ETCO_2} (mmHg)	31.3 ± 2.6 (374)	31.4 ± 2.6 (374)	n.s.
HR (BPM)	71.6 ± 8.9 (373)	80.6 ± 9.7 (373)	****

Student's *t*-test, ***$P < 0.0001$, significant in acute hypoxia *versus* room air.

Tibetan women also had significantly higher isocapnic HVR values (0.34 ± 0.25 L/min%) compared to post-menopausal women (0.22 ± 0.18 L/min%, $P < 0.0001$, Fig. 2*B*).

We further explored whether these differences were due to changes in V_T or f_R. We found that pre-menopausal Tibetan women had higher V_T while breathing room air (0.70 ± 0.13 L) and during acute hypoxia (0.86 ± 0.18 L) compared with post-menopausal women (0.63 ± 0.10 L, $P = 0.0001$ for room air; and 0.73 ± 0.14 L for hypoxia, $P < 0.0001$, Fig. 2*C*). However, we did not find significant differences in f_R ($P > 0.999$ for both room air and hypoxia, Fig. 2*D*), nor in P_{ETCO_2}, between groups while breathing room air (30.90 ± 2.16 and 31.41 ± 2.65 mmHg for pre- and post-menopausal women, respectively, $P = 0.54$).

Heart rate response to hypoxia

No differences in HR were observed between pre- and post-menopausal women in room air conditions (72.7 ± 8.3 BPM for pre- *vs.* 71.5 ± 9.0 BPM for post-menopausal Tibetan women, $P = 0.650$). However, during exposure to acute, experimental hypoxia at high altitude, pre-menopausal women had significantly higher HR (84.4 ± 8.5 BPM) and HHRR (0.91 ± 0.38 BPM/%) compared to post-menopausal Tibetan women (HR = 80.0 ± 9.7 BPM, $P < 0.0005$, Fig. 3*A* and HHRR = 0.65 ± 0.29, $P < 0.0001$, Fig. 3*B*).

Effects of age and menopause status on hypoxic ventilatory and heart rate responses

Given that other studies have reported changes with age in the HVR and HHRR measured during exercise (Lhuissier et al., 2012; Richalet & Lhuissier, 2015), we analysed our data to determine if an age effect explains differences observed between pre- (49 ± 3.4 years old) and post-menopausal (61 ± 8.5 years old) Tibetan women at rest (Table 1). We compared linear regressions of HVR *versus* age for the two groups of Tibetan women and found that HVR and HHRR correlated negatively with age in post- ($P \leq 0.0001$) but not pre-menopausal women ($P = 0.458$ for HVR and 0.277 for HHRR, Fig. 4*A* and 4*B*).

Linear regression analysis did not show significant differences in slopes between groups for either HVR or HHRR *versus* age ($P = 0.760$ for HVR and 0.819 for HHRR, Fig. 4*A* and *B*). To determine whether the differences in HVR and HHRR are due to age or also involve menopausal status, we performed a mixed-effects model with age and menopausal status as covariates. The mixed-effects model revealed that increased age ($P < 0.0001$) and menopausal status were independently associated with lower HVR ($P = 0.0056$, Fig. 4*A*) and HHRR ($P = 0.0059$, Fig. 4*B*) but did not show an interaction.

Increased HVR and HHRR correlate with higher percentage O_2 saturation of hawereemoglobin while breathing room air

For both menopausal status groups, women with higher HVR had higher S_{pO_2} saturation (pre- and post-menopausal, $P = 0.0003$ and $P < 0.0001$, respectively, Fig. 5*A*). Analysis of linear regressions for HVR *versus* room air S_{pO_2} showed no significant differences in slopes between these groups ($P = 0.199$, Fig. 5*A*, red *vs.* blue lines). Similarly, positive correlations were found between HHRR and S_{pO_2} in room air for Tibetan women in both pre- and post-menopausal ($P \leq 0.0001$, Fig. 5*B*) stages. Linear regression analysis for both groups revealed no significant differences in slopes ($P = 0.15$); however, the intercepts were lower among the post-menopausal women ($P < 0.0001$, Fig. 5*B*, red *vs.* blue lines).

HVR and HHRR are positively correlated in pre- and post-menopausal women

A significant positive correlation was found between HVR and HHRR in both groups ($P < 0.0001$) (Fig. 6). No

significant differences were noted between the slopes for pre- *versus* post-menopause ($P = 0.2532$), although post-menopausal women had lower HHRR at a given HVR (intercepts were significantly different, $P < 0.0001$, blue *vs*. red line, Fig. 6).

HVR repeatability analysis revealed that women with a higher average HVR had the smallest differences between two within-day repeated measures (see Fig. 7*A* and *B*), and we found a significant correlation between these measurements ($P < 0.05$; Pearson $r = 0.5773$, 95% confidence interval, CI = [−0.0823 to 0.8852]) (see Fig. 7*C* and Table 5). These results were confirmed when we performed Bland–Altman analysis for all pairs of hypoxic events (first–second, first–third and second–third, see Fig. 8). We found significant correlations for all pairs of hypoxic stimulus ($P < 0.0001$ for all three pairs; see Fig. 9; correlation *P*, Pearson's *r* and 95% confidence intervals are indicated in Table 5).

Genetic analyses

To assess whether the biological variables related to HVR are associated with genetic variation, we performed a GWAS from data presented in Ye et al. (2024). Of the physiological variables presented above, $\dot{V}_I$ in hypoxia was associated at genome-wide significance ($P < 5 \times 10^{-8}$), showing an effect size of ±1.32 L/min (Table 3) for the minor allele. The single SNP associated with $\dot{V}_I$ in hypoxia (rs34947371 on chromosome 3) is located within an intronic region of *Calsyntenin 2* (*CLSTN2*). P_{ETCO_2} in room air was associated with SNPs spanning approximately 80 kilobases on chromosome 1 at a genome-wide significance ($P = 5 \times 10^{-8}$) and an effect size of ±1.31 mmHg for the minor allele (Table 3). This region does not overlap with any known genes, and the closest potentially functional genetic component encodes the pseudogene *Cyclin Dependent Kinase 4 Pseudogene 1* (*CDK4P1*) (Kent et al., 2002) approximately 23 kilobases

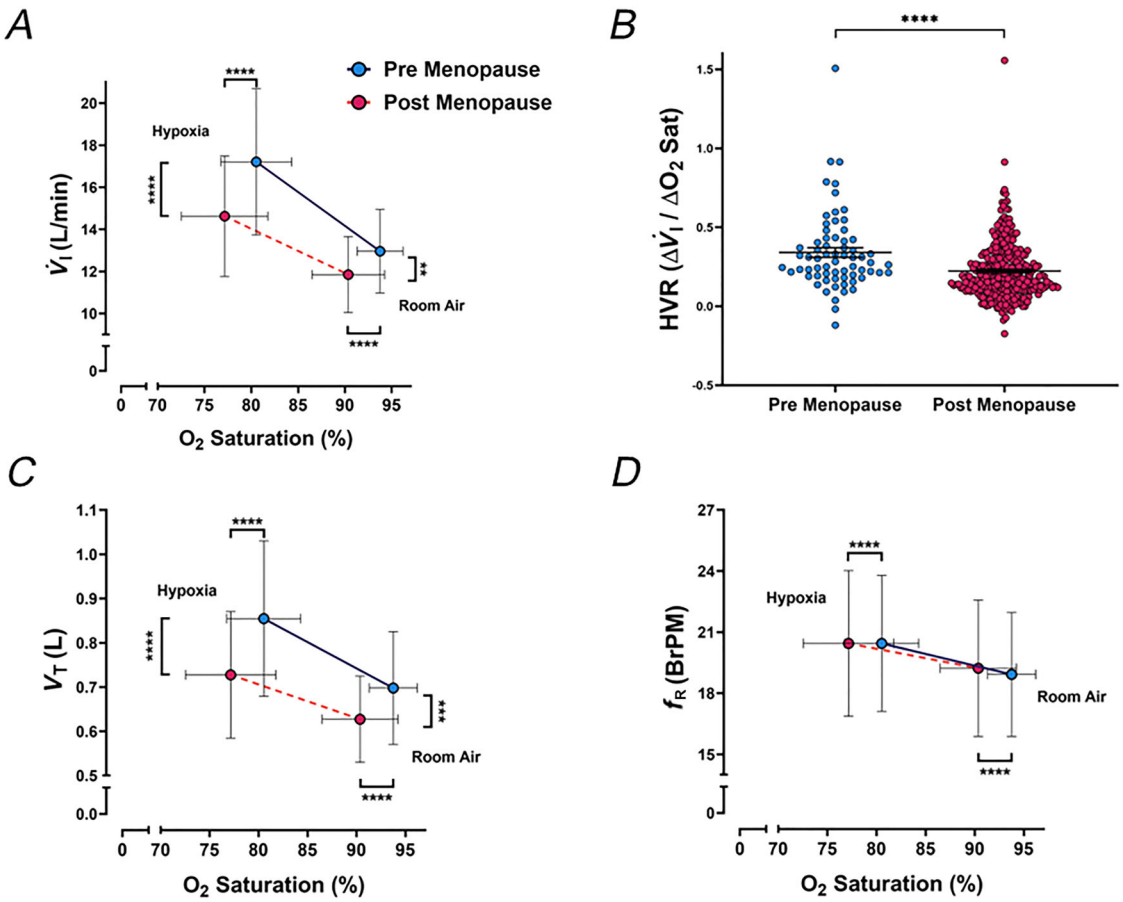

Figure 2. Ventilatory responses to hypoxia in pre- and post-menopausal Tibetan women
Measurement of minute ventilation (*A*, $\dot{V}_I$), hypoxic ventilatory response (*B*, HVR), tidal volume (*C*, V_T) and respiratory frequency (*D*, f_R), as well as their simultaneous measurement of O_2 saturation (for *A*, *C* and *D*) in Tibetan women while breathing room air or during a hypoxic-event stimulus. Bonferroni correction after two-way ANOVA was performed to determine differences between Tibetan women with pre- or post-menopause for *A*, *C* and *D*; or a Student's *t* test for *B*. $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$; $n = 67$ for the pre-menopause group and $n = 307$ for the post-menopause group.

away. The relevance of the effect sizes observed for $\dot{V}_I$ in hypoxia and P_{ETCO_2} in room air can be estimated by comparison with the 50% of their corresponding standard deviations (Table 2), as observed in patients with chronic diseases (Norman et al., 2003).

To assess whether regions of the genome under positive selection are associated with control of breathing, we identified SNPs under positive selection using iSAFE (Akbari et al., 2018), which aims to determine variants favoured by selection within a genomic region without demographic or functional information (Akbari et al., 2018). We examined selection candidate genes within 100 kilobases of these SNPs. In parallel, we compiled a list of genes whose function is related to the control of breathing (functional candidate genes). The genes shared between these two lists (found in Supp. Table 1), considered prioritized candidate genes, include *Endothelial PAS Domain Protein 1* (*EPAS1*), *Peroxisome Proliferator Activated Receptor Gamma* (*PPARG*), *Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 2* (*CHCHD2*) and *Egl-9 Family Hypoxia Inducible Factor 1* (*EGLN1*, Table 4), although none of these were associated with the phenotypes measured.

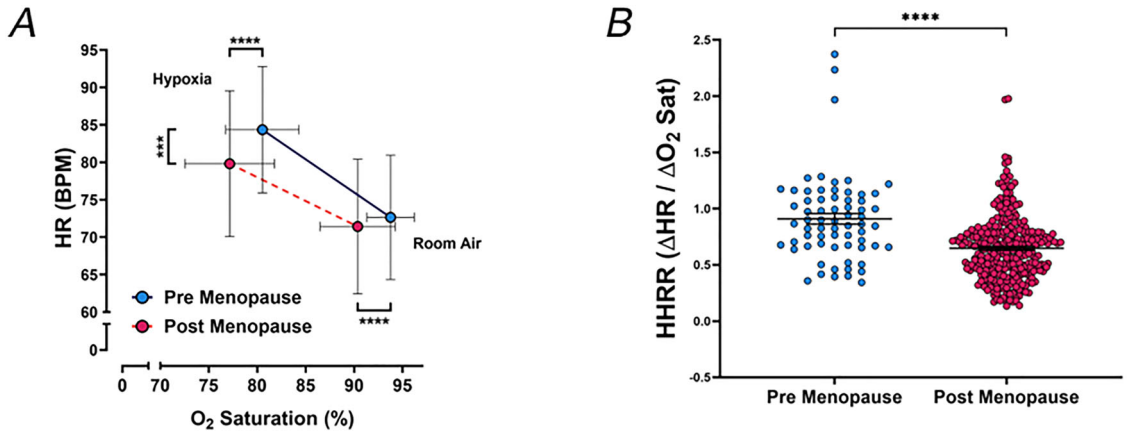

Figure 3. Heart rate responses to hypoxia in pre- and post-menopausal Tibetan women
Measurement of heart rate (*A*, HR) and hypoxic heart rate response (*B*, HHRR), as well as their simultaneous O_2 saturation (for *A*) in Tibetan women while breathing room air or during a hypoxic-event stimulus. Bonferroni correction after two-way ANOVA was performed to determine differences between Tibetan women with pre- or post-menopause for *A*; or a Student's *t* test for *B*. $^*P < 0.05$, $^{****}P < 0.0001$; $n = 67$ for the pre-menopause group and $n = 306$ for the post-menopause group.

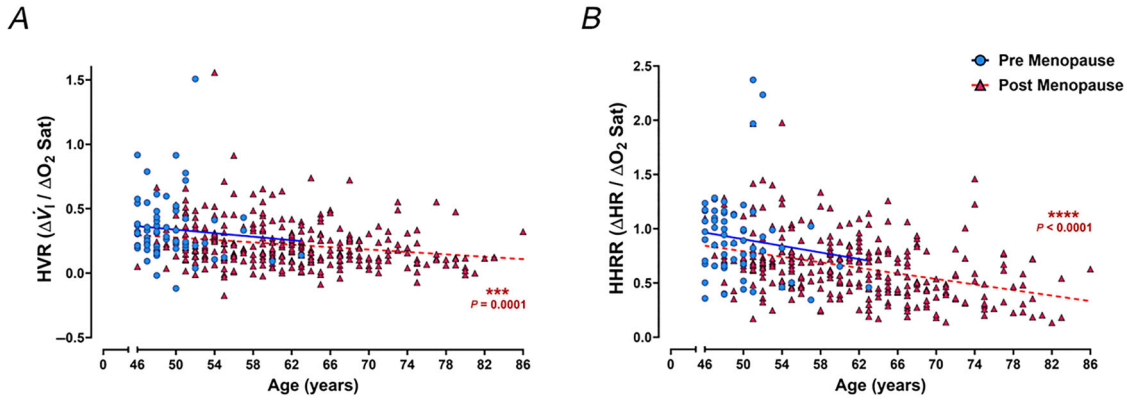

Figure 4. Relationships of hypoxic ventilatory response and hypoxic heart rate response with age in pre- and post-menopausal Tibetan women
Correlation analysis of hypoxic ventilatory response (*A*, HVR) and hypoxic heart rate response (HHRR, *B*) with age was significant only for the group of post-menopausal Tibetan women (red triangles, dashed lines) but not for the pre-menopausal group (blue circles, continuous line). *A*, for HVR pre-menopausal women: $r = -0.09302$, 95% CI = [−0.3277 to 0.1524], slope −0.006686; for HVR post-menopausal women: $r = -0.2176$, 95% CI = [−0.3217 to −0.1083], slope −0.004550. *B*, for HHRR pre-menopausal women: $r = -0.1359$, 95% CI = [−0.3659 to 0.1098], slope −0.01524; for HHRR post-menopausal women: $r = -0.3752$, 95% CI = [−0.4677 to −0.2747], slope −0.01277. $n = 67$ for *A* and *B* in the pre-menopause group and $n = 307$ for *A* and $n = 306$ for *B* in the post-menopause group.

Table 3. Genotype-phenotype association signals for responses to hypoxia. pLRT is the *P* value of the likelihood ratio test implemented in GEMMA. Beta is derived from the per-allele effect size of the top SNP

Trait	CHR	Number of SNPs	Rs ID of top SNP	Minor allele frequency	β	SE of β	pLRT
P_{ETCO_2} in room air	1	42	rs55865785	0.32	1.31 mmHg	0.270	$<5 \times 10^{-8}$
$\dot{V}_I$ in hypoxia	3	1	rs34947371	0.31	1.32 L/min	0.316	4×10^{-8}

Discussion

This is the first study to examine the effects of age and menopause on the ventilatory and heart rate responses to hypoxia in Tibetan women residing at high altitude. Our results show that minute ventilation and tidal volume during both room air breathing and acute hypoxia, as well as heart rate and arterial O_2 saturation during acute hypoxia, are significantly lower in Tibetan women after menopause. Notably, we found a negative correlation between age and both HVR and HHRR in the post-menopausal Tibetan women but not in pre-menopausal women. Both HVR and HHRR positively correlated with S_{pO_2}, independent of menopausal status, and HVR is positively correlated with HHRR in both groups. We further identified a genomic region associated with P_{ETCO_2} breathing room air and a single SNP associated with $\dot{V}_I$ in acute hypoxia at genome-wide significance. We also identified signals of selection that overlap with candidate genes for the control of breathing, though none of these genes associated with the physiological variables examined in this cohort.

Ventilatory and cardiac responses to hypoxia

Some of the menopause-related differences we observed may reflect the influence of hormone levels (Behan & Kinkead, 2011; LoMauro & Aliverti, 2021). Progesterone (Okita et al., 1987; Zwillich et al., 1978) and oestrogen (Richalet et al., 2020; Takano, 1984; White et al., 1983) contribute to changes in resting ventilation and HVR. Animal studies have demonstrated that progesterone and/or oestrogen enhance ventilatory response through central mechanisms (Barok et al., 2021; Bayliss et al., 1987; Behan & Wenninger, 2008; Behan et al., 2003; Tatsumi et al., 1997). Thus, it is plausible that the higher values of ventilatory parameters in pre- *versus* post-menopausal women in this study (Fig. 2) may be due to low levels of progesterone and oestrogen in women after menopause. We did not control for the stage of menstrual cycle in the pre-menopausal participants in this study and do not have hormonal data for this sample. Future studies need to determine hormone-driven effects and their contribution to differences in hypoxic responses in different phases of the menstrual cycle and with menopause in Tibetans.

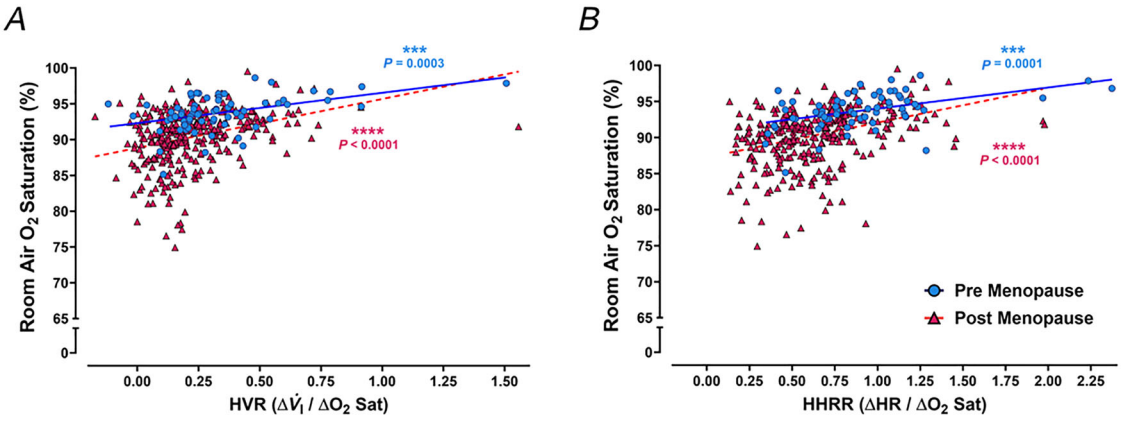

Figure 5. Relationships of hypoxic ventilatory response and hypoxic heart rate response with O_2 saturation while breathing room air
The correlation analysis revealed that hypoxic ventilatory response (*A*, HVR) and hypoxic heart rate response (HHRR, *B*) in Tibetan women are related to O_2 saturation recorded while breathing room air independent of the menopausal status. *A*, for HVR pre-menopausal women: r = 0.4327, 95% CI = [0.2149 to 0.6096], slope 4.349; for HVR post-menopausal women: r = 0.3223, 95% CI = [0.2182 to 0.4191], slope 7.020. *B*, for HHRR pre-menopausal women: r = 0.4572, 95% CI = [0.2437 to 0.6284], slope 2.936; for HHRR post-menopausal women: r = 0.3598, 95% CI = [0.2581 to 0.4536], slope 4.815. n = 67 for *A* and *B* in the pre-menopause group and n = 307 for *A* and n = 306 for *B* in the post-menopause group.

Table 4. Positive selection test within genes of interest for responses to hypoxia. Positive selection scan (iSAFE) showing putatively adaptive genetic candidate genes in Tibetan women

Gene	iSAFE score	Physiological outcome of interest for high altitude	Independent, supporting references
EPAS1	0.617	**HIF-2α** Haemoglobin concentration in Tibetans. Involved in hypoxic ventilatory response in deer mice and carotid body morphology.	Beall et al. 2010; Yi et al. 2010; Ivy et al. 2022; Moreno-Domínguez et al. 2020
PPARG	0.534	**PPARγ** Candidate genes in high-altitude populations.	Simonson et al. 2010; Xing et al. 2013
CHCHD2	0.419	**Eukaryotic CX(9)C protein** Upstream regulator of COX4I2, mitochondrial cytochrome subunit crucial for hypoxic ventilatory response.	Aras et al. 2013; Moreno-Domínguez et al. 2020
EGLN1	0.308	**PHD2** Regulation of HIF activity at high altitude.	Simonson et al. 2010; Bigham et al. 2010; A. W. Bigham & Lee, 2014; Jeong et al. 2018; Petousi et al. 2014

Table 5. Bland–Altman analysis and correlation significance in repeated measurements of HVR performed in Tibetan women in Mustang, Nepal, on days of difference or on the same day for first–second, first–third or second–third hypoxic events (Hypoxia 1–2, 1–3, and 2–3 respectively)

Comparison	*n*	Bias diff. *vs.* avg. [95% limits of agreement]	Bias %diff. *vs.* avg. [95% limits of agreement]	Pearson *r* [95% CI]	Correlation *P*
HVR performed with at least 7 days of difference	10	−0.0414 [−0.2604 to 0.1775]	−29.9 [−156.1 to 96.3]	0.5773 [−0.0822 to 0.8852]	0.0403
HVR performed on the same day					
Hypoxia 1–2	305	0.0213 [−0.2791 to 0.3217]	18.0 [−1026.0 to 106.0]	0.7244 [0.6630 to 0.7737]	<0.0001
Hypoxia 1–3	263	0.02167 [−0.3049 to 0.3483]	−4.9 [−304.5 to 294.7]	0.6100 [0.5280 to 0.6807]	<0.0001
Hypoxia 2–3	289	−0.0045 [−0.2711 to 0.2621]	62.4 [−4694.0 to 4819.0]	0.7053 [0.6422 to 0.7590]	<0.0001

In addition, although we observed higher ventilation and tidal volume in pre- compared to post-menopausal Tibetan women while breathing room air, we did not find significant differences in P_{ETCO_2} between the two groups. Lower alveolar ventilation would predict higher P_{ETCO_2} among the post-menopausal women. However, the elevated P_{ETCO_2} may have been compensated for by lower dead space ventilation or a reduced metabolic rate associated with menopause (Hurtado et al., 2024). Preston et al. (2009) reported no changes in metabolic rate attributable to menopausal status. Therefore, additional studies are needed to determine whether the maintenance of P_{ETCO_2} levels is a specific feature of Tibetan women after menopause.

In our study, Tibetan women at high altitude exhibited higher $\dot{V}_I$ and S_{pO_2} than sea-level residents after 3 weeks of acclimatization at 4300 m as reported by Muza et al. (2001). Leon-Velarde et al. (2001) studied pre- and post-menopausal Andean women residing at Cerro de Pasco, Peru (4300 m), for more than 10 years and found higher S_{pO_2} saturation and lower P_{ETCO_2} in pre-*versus* post-menopausal groups, which was attributed to progesterone. However, S_{pO_2} saturation was lower than expected for the 500 m higher altitude and P_{ETCO_2} was higher than those observed in this Tibetan cohort (Fig. 2 and P_{ETCO_2} mentioned in the Results), consistent with other findings comparing the two populations (Beall et al., 1997).

The values of resting ventilation and HVR that we observed are lower than those reported before for Tibetan women ranging from 20 to 94 years old (38 years old on average) by Beall et al. (1997). Different measurements protocols (Oeung et al., 2023; Pfoh et al., 2016), as well as the large number of older women in the present sample, may explain the lower values observed in this study (Fig. 2). It is plausible that hypoxic ventilatory

decline (HVD) may be accentuated in this population; to our knowledge, HVD has not been measured in human participants at high altitude. HVD has been observed between 8 and 14 minutes, and 2 and 23 minutes of isocapnic hypoxia in humans (Bascom et al., 1990; Garcia et al., 2001). However, it is difficult to measure it any earlier in hypoxia given experimental limitations in controlling arterial stimuli.

Ye et al. (2024) found that respiratory traits did not increase Darwinian fitness (i.e., number of livebirths in Tibetan women); however, higher O_2 saturation was associated with more livebirths and higher offspring survival in a sample of Tibetan women including those in the present study (Beall et al., 2004; Ye et al., 2024). Our finding of a positive correlation between HVR, HHRR and O_2 saturation in Tibetan women (Fig. 5*A*) suggests that ventilation and heart rate may be among the many factors contributing to higher O_2 saturation and fitness in Tibetan women, potentially playing a role during pregnancy. Moore et al. (2001) reported that heavier birth weights were associated with higher resting minute ventilation and increased uterine artery blood flow among Tibetan mothers residing at high altitude during the 36th week of pregnancy.

Regarding measurements of HR at high altitude, our results did not show significant differences between pre- and post-menopausal Tibetan women while breathing room air. Our recorded values are comparable to those observed for Tibetan and Andean women breathing room air at 4000 m (Beall et al., 1997) and to Andean women, who did not show significant differences in pulse rate due to menopausal status while breathing room air at high altitude (León-Velarde et al., 2001). Richalet et al. (2020) found that HHRR during exercise was decreased in post-menopausal women. The authors attributed this effect to age differences more than menopausal status because the observed differences in HR were not modified with hormonal treatment. Although the protocols used were different, these results agree with our finding of elevated HR during hypoxia and HHRR values for pre- compared to the post-menopausal Tibetan group (Fig. 3).

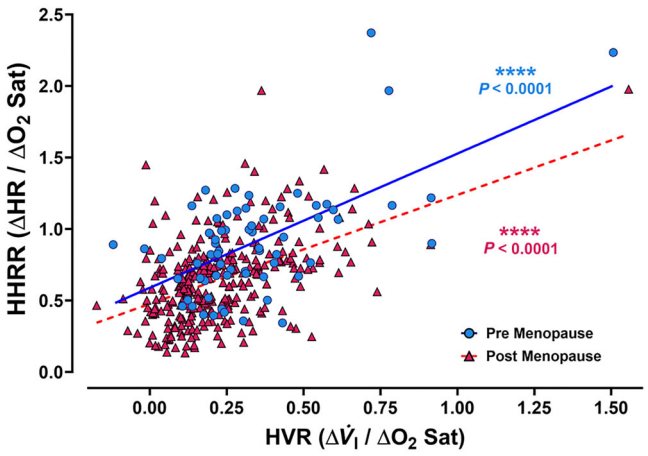

Figure 6. Relationship between hypoxic ventilatory response (HVR) and hypoxic heart rate response (HHRR) in pre- and post-menopausal Tibetan women
Values of HVR and HHRR show a positive correlation in both pre- and post-menopausal Tibetan women. For pre-menopausal women: r = 0.6145, 95% CI = [0.4391 to 0.7447], slope 0.9614; for post-menopausal women: r = 0.4792, 95% CI = [0.3879 to 0.5612], slope 0.7804. n = 67 in the pre-menopause group and n = 306 in the post-menopause group.

Relationship of HVR, HHRR, age and baseline O_2 saturation

We found a significant negative correlation of HVR and HHRR with age in the post- but not pre-menopausal group of Tibetan women. The effects of age on ventilatory and cardiovascular responses to high-altitude hypoxia have been studied in women before (Beall et al., 1997; Lhuissier et al., 2012; Richalet & Lhuissier, 2015; Richalet et al., 2020, 2023). Lhuissier et al. (2012) did not find effects of age on HVR during resting conditions in 30–60-year-old European women exposed to hypoxia, and Beall et al. (1997) did not find significant correlations between HVR and age in a group of Tibetan women 20–82 years of age at 4000 m. These results agree with our finding of no correlation between HVR and age in pre-menopausal Tibetan women (Fig. 4*A*). Lhuissier et al. (2012) found a progressive decrease of resting HHRR after 40 years in untrained European women, similar to data observed in men, but not in trained women. Interestingly, HVR and HHRR during exercise was significantly affected by menopausal status but the administration of hormone therapy did not produce significant differences, highlighting the possibility of different menopause-driven consequences affecting HVR and HHRR at rest *versus* during exercise (Richalet & Lhuissier, 2015; Richalet et al., 2020).

Given HVR and HHRR correlated with age only in post-menopausal Tibetan women studied here, it is possible that pre-menopausal women may experience a protective effect to facilitate oxygen availability during fertile life stages (Fig. 5). Beall et al. (1997) did not find significant correlations between HVR and O_2 saturation, although the authors reported a correlation between resting ventilation and O_2 saturation. Heinrich et al. (2020) found a positive correlation between room air O_2 saturation and HHRR in Andean women and men, demonstrating that an increase HHRR is associated with higher O_2 saturation in other high-altitude populations.

To better understand a coordinated hypoxic response, we tested for correlations between the HVR and HHRR. This showed a positive correlation between HVR and

HHRR in both pre- and post-menopausal women (Fig. 6). This is similar to a previous study conducted at 1300 m that tested poikilocapnic hypoxia in a sample of Tibetan males and females, but this correlation was not observed in Han Chinese individuals (Moya et al., 2024). Brisk ventilatory and cardiac responses to hypoxia may be part of the Tibetan adaptation to hypoxia (Beall & Strohl, 2021; Petousi & Robbins, 2014), and may be a consequence of genetic adaptations (Yu et al., 2022). A reported example of genetic adaptation to hypoxia is observed in deer mice with a high-altitude genetic background, where variants of *Epas1* are associated with elevated alveolar ventilation and enhanced respiratory O_2 uptake (C. M. Ivy & Scott, 2017; Catherine M. Ivy et al., 2022). Zhou et al. (2008) completed sea-level studies in Tibetans born and raised at high altitude (3700 m) who migrated to sea level for four years and compared them with a lowland Han Chinese group. The authors exposed both groups to acute hypoxia in a hypobaric chamber (2 hours, simulating 3700 m) and found that acute hypoxia induced a significant increase in heart rate in the Han Chinese but not in the Tibetan group. Although their study was performed only in male adolescents, it suggests a permanent effect of ancestry and/or developmental exposure on physiological responses to hypoxia. Thus, more studies are necessary to determine how effective

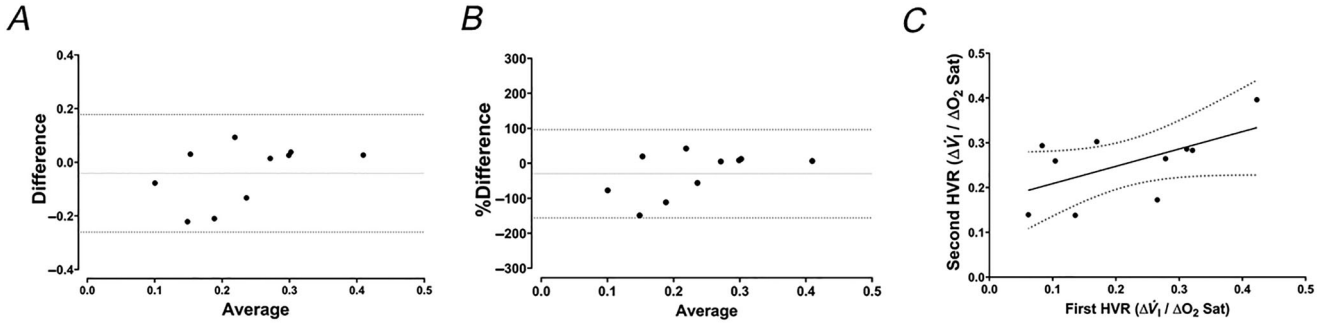

Figure 7. Bland–Altman and correlation analysis and repeatability with days of separation
Ten randomly selected Tibetan women who had a first HVR measurement to perform a second HVR measurement at least 7 days after the first one. Bland–Altman analysis showing the average of the two measurements *versus* the difference (*A*) or *versus* the percentage difference (*B*). The two measurements (*C*) show a significant correlation ($P < 0.05$). Analysis of repeatability of HHRR was reported in this dataset by Ye et al. (2024).

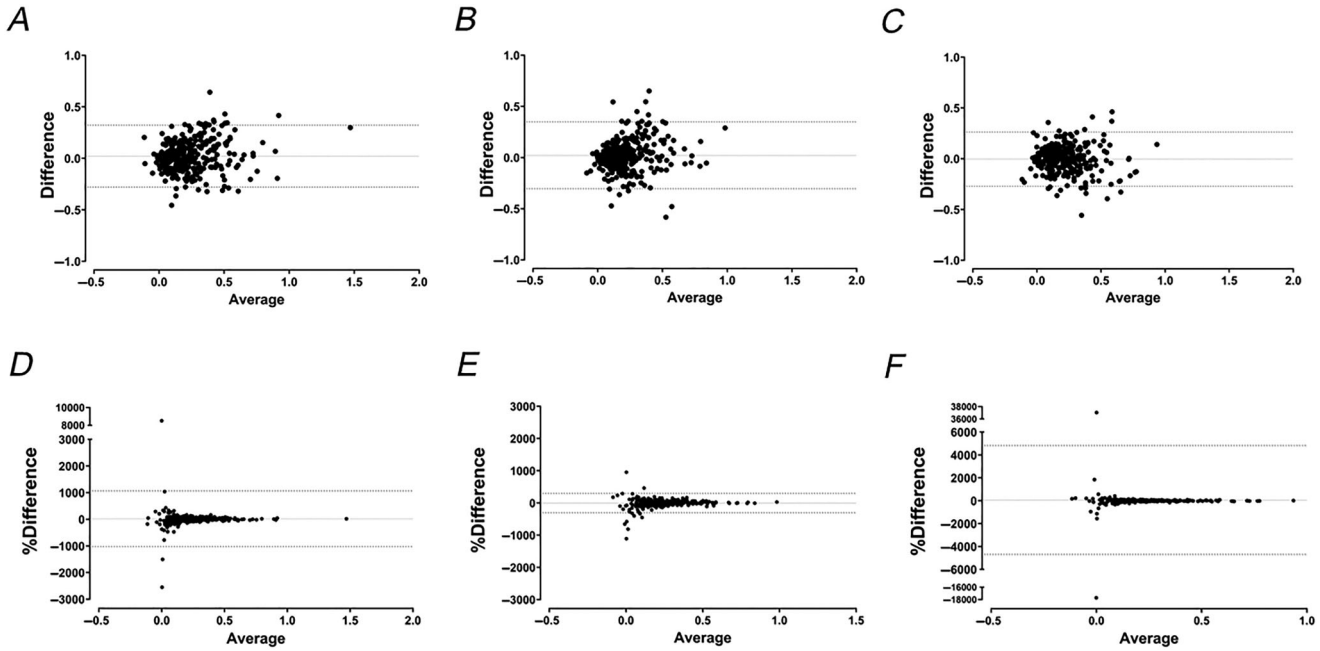

Figure 8. Bland–Altman analysis and repeatability of HVR performed on the same day
Bland–Altman analysis in all participants who had more than one HVR measurement. Average of two paired measurements *versus* the difference (*A*, *B*, *C*) or *versus* the percentage difference (*D*, *E*, *F*) for the pairs of hypoxic events 1–2 (*A*, *D*), 1–3 (*B*, *E*) and 2–3 (*C*, *F*) are shown.

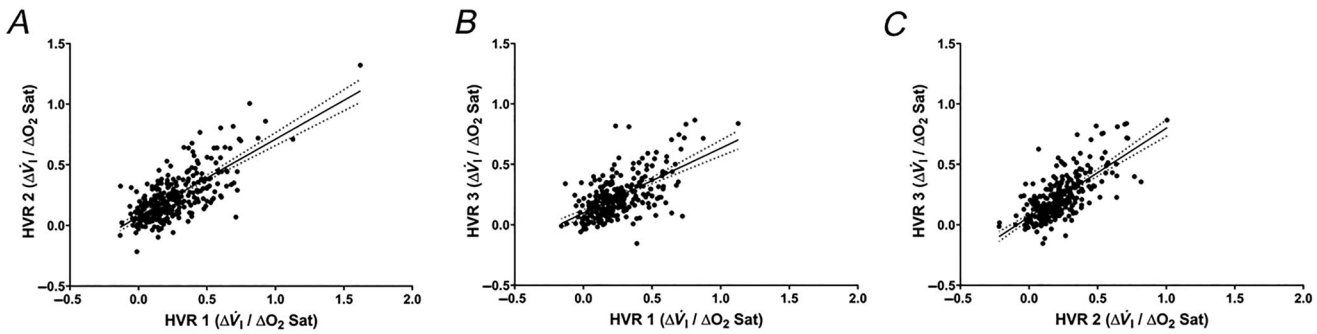

Figure 9. Correlation analysis and repeatability of HVR performed on the same day
Analyses of HVR measurements for hypoxic events in the same person and on the same day and the associations between hypoxic events 1–2 (*A*), 1–3 (*B*) and 2–3 (*C*) exhibit significant correlations for all the pairs of hypoxic events ($P < 0.0001$).

HVR and HHRR are in terms of improving O_2 content and delivery in these populations in both men and women.

Genetic analyses

We identified SNPs associated with P_{ETCO_2} in room air and an SNP associated with $\dot{V}_I$ in hypoxia (β between 1.22 and 1.31 mmHg, and $\beta = 1.32$ L/min, respectively) at the genome-wide significance level (Table 3). To the best of our knowledge, this is the first GWAS conducted in a high-altitude population specifically seeking genetic associations with ventilatory measurements. Although emerging evidence highlights that women's health at high altitude is influenced by the genetic architecture underlying chemosensitivity and cardiopulmonary regulation (Gu et al., 2025), genetic investigations into the control of breathing in high-altitude human populations remain scarce, due largely to the logistical difficulties of acquiring sufficiently large and precise ventilatory control datasets in field conditions. In this same group of Tibetan women examined, low HHRR and a high S_{pO_2} exhibited near genome-wide significant associations, and these traits were also associated with more livebirths, highlighting the importance of these physiological responses on evolutionary fitness (Ye et al., 2024).

We found that SNPs associated with P_{ETCO_2} in room air were closest to the pseudogene *CDK4P1*. Though pseudogenes have historically been thought of as 'junk DNA', studies have shown that pseudogenes may have functional effects on their coding genes (Pink et al., 2011). In this case, *CDK4P1* is a pseudogene for Cyclin Dependent Kinase 4 (*CDK4*), a key player in cell cycle control and tumorigenesis (Baker & Reddy, 2012). To our knowledge, there are no other studies linking this gene to cardiopulmonary control or hypoxic responses. The single SNP associated with $\dot{V}_I$ in hypoxia (rs34947371) is located within an intronic region of *CLSTN2*, which contributes to neuronal development and synaptic organization (Lipina et al., 2016) and is connected to a module of genes that are differentially regulated throughout development in highland deer mice (Schweizer et al., 2023).

Conclusion

The study of high-altitude ethnically Tibetan women shows that age and life-cycle stage contribute to variation in the ventilatory and heart rate responses to additional, acute, experimental hypoxia. Older age and post-menopausal status were independently associated with lower HVR and HHRR, yet higher values of HVR and HHRR correlated with oxygen saturation at both stages of the life cycle. Ventilatory control has been hypothesized as one of the main features of adaptation observed in high-altitude populations; however, this is the first study exploring the contribution of pre- and post-menopausal status on the ventilatory and heart rate responses to acute hypoxia in Tibetan women living at high altitude. Pre-menopausal Tibetan women have higher ventilatory and heart rate responses to acute hypoxia, resulting in higher levels of O_2 saturation. These results underscore the significance of understanding physiological adaptations during different life stages.

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Additional information

Data availability statement

All data supporting the results are provided in the Figures when $n \leq 30$; for datasets where $n > 30$, the data are available as supporting information published with the paper. Relevant datasets are cited in the References.

Competing interests

The authors declare that they have no competing interests.

Author contributions

E.A.M., J.J.Y., S.R.C., A.D., D.W., W.G., B.B., K.P.S., F.L.P., T.S.S. and C.M.B. contributed to the conception and design of this work as well as the acquisition, analysis or interpretation of the data. E.A.M and J.J.Y. wrote the first draft of the manuscript. E.A.M., J.J.Y., S.R.C., A.D., D.W., W.G., B.B., K.P.S., F.L.P., T.S.S. and C.M.B. edited and revised the manuscript. All authors approved the final version submitted for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Keywords

adaptation, aging, high altitude, hypoxia, hypoxic heart rate response, hypoxic ventilatory response, menopause, Tibetan women

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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