TITLE: Fetal growth, high altitude, and evolutionary adaptation: A new perspective

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AUTHORS:
Kathryn Wilsterman
Zachary A. Cheviron

AFFILIATIONS:
Division of Biological Sciences, University of Montana, Missoula, MT 59812

CORRESPONDING AUTHOR:
Kathryn Wilsterman
Division of Biological Sciences
Health Sciences Building, Room 104
University of Montana
Missoula, MT 59812

484-241-0631
kathrynwilsterman@gmail.com

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AUTHORS:
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Zachary A. Cheviron

AFFILIATIONS:
Division of Biological Sciences, University of Montana, Missoula, MT 59812

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Abstract: Residence at high altitude is consistently associated with low birth weight among placental mammals. This reduction in birth weight influences long-term health trajectories for both the offspring and mother. However, the physiological processes that contribute to fetal growth restriction at altitude are still poorly understood, and thus our ability to safely intervene remains limited. One approach to identify the factors that mitigate altitude-dependent fetal growth restriction is to study populations that are protected from fetal growth restriction through evolutionary adaptations (e.g., high altitude-adapted populations). Here, we examine human gestational physiology at high-altitude from a novel evolutionary perspective that focuses on patterns of physiological plasticity, allowing us to identify (1) the contribution of specific physiological systems to fetal growth restriction and (2) mechanisms that confer protection in highland-adapted populations. Using this perspective, our review highlights two general findings: first, that the beneficial value of plasticity in maternal physiology is often dependent on factors more proximate to the fetus; and second, that our ability to understand the contributions of these proximate factors is currently limited by thin data from altitude adapted populations. Expanding the comparative scope of studies on gestational physiology at high altitude and integrating studies of both maternal and fetal physiology are needed to clarify the mechanisms by which physiological responses to altitude contribute to fetal growth outcomes. The relevance of these questions to clinical, agricultural, and basic research combined with the breadth of the unknown highlight gestational physiology at high altitude as an exciting niche for continued work.

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I. Introduction

High altitude environments (defined here as > 2500 m above sea level) have a long history as focal sites for studying fundamentals of physiology. The reduced oxygen availability and relatively low ambient temperatures that characterize these environments present unavoidable, physiological challenges to residents and transients alike. Despite these challenges, animals including humans have repeatedly colonized high altitude environments. In many of these cases, the novel selective pressures associated with the abiotic challenges of high altitude have driven evolutionary changes that improve Darwinian fitness at altitude (i.e., evolutionary adaptations). Fitness in this sense is comprised of two components: survival and reproduction. Of these, traits that influence survival continues to be the primary focus of research aimed at understanding adaptations to high altitude (1–5), in part because altitude so obviously affects performance (and thus survival) through lower oxygen availability. Although high altitude also impacts the other major component of fitness, reproduction, we still understand relatively little about reproductive adaptations.

Gestation at high altitudes is associated with dose-dependent reductions to birth weight in humans (Fig. 1) and other mammals. In domesticated guinea pigs and sheep, gestating at altitude or under simulated hypobaric hypoxia can result in a dramatic 30% decline in birthweight (6–8); similar but more moderate reductions in birthweight occur in mice and humans (9, 10). These reductions in birth weight are associated with long-term risks to newborn survival and health in humans and other animals (11–16). Given the consequences of these adverse outcomes on reproductive success, protection of fetal growth should be an important aspect of evolutionary adaptation to altitude. Indeed, altitude-adapted populations, including indigenous Andean and Tibetan humans, display reduced altitude-dependent fetal growth restriction (Fig. 1).

Understanding the physiological bases of evolutionary adaptations that protect fetal growth in altitude-adapted populations is of interest to both basic and applied research. These adaptations can offer novel insights into potential targets for interventions that would limit altitude-dependent growth restriction in humans and livestock. To draw biomedical insight from evolutionary adaptation to altitude and its effects on fetal growth restriction, we need answers to two broad questions:

(1) Which physiological processes contribute to fetal growth restriction in lowlanders gestating at altitude? and
(2) How have these processes been shaped by evolutionary adaptation to protect fetal growth in highland-adapted populations?

In this review, we provide new insight into these questions by summarizing the current state of the field using a perspective based in evolutionary theory. This perspective can be broadly applied to help identify physiological traits or processes that are likely contributors to fetal growth outcomes at altitude. We then identify key areas where new approaches or questions are needed to advance our understanding of hypoxia-dependent fetal growth restriction from an evolutionary vantage point.

II. Which physiological traits or processes influence fetal growth at altitude?

Hypobaric hypoxia is likely the ultimate cause of fetal growth restriction at altitude. However, oxygen availability can influence fetal growth through both direct and indirect mechanisms. Direct effects of oxygen limitation refer to the inability of the fetus to acquire sufficient oxygen for growth, whereas indirect effects refer to the response of maternal, placental, and fetal physiology to environmental hypoxia, which can then secondarily restrict fetal growth. Indirect effects of hypobaric hypoxia on fetal growth thus include physiological changes in the mother that alter the fetal environment. At altitude, many animals undergo plastic changes to their physiology (i.e., acclimatization) to preserve arterial oxygen content and delivery to tissues. Acclimatization can include remodeling function and structure of cardiovascular, metabolic, and pulmonary systems (for further examples and discussion beyond pregnancy, see (17). Downstream of maternal cardiopulmonary systems, placentation and fetal growth may also respond to oxygen tension directly or to changes in maternal physiology (such as blood viscosity or pressure). With this in mind, a large number of maternal and feto-placental traits may directly or indirectly contribute to fetal growth at altitude, and the degree and nature of physiological plasticity in these traits may also be important. For the purposes of this review, we have grouped traits into four “steps” along the oxygen transport cascade from the environment through maternal circulation and into fetal circulation (Fig. 2): (a) maternal oxygen transport capacity, (b) blood delivery to the fetoplacental unit, (c) organization and function of the placenta, and (d) fetal hematology.

III. Physiological plasticity and adaptation

In the field of placental and fetal hypoxia, any plasticity in maternal, fetal, or placental function or structure is often referred to as an “adaptation” to hypoxia, meant to convey simply that the system is responding to hypoxia; these types of responses can be described more specifically as acclimatization. In contrast, adaptation in the evolutionary sense specifically refers to responses that enhance Darwinian fitness. This specificity is important within the context of hypoxia responses because maladaptive, or counterproductive, acclimatization responses are well-known components of the integrated, physiological responses to altitude in lowlanders (5, 17, 18). The prevalence of maladaptive plasticity is thought to reflect evolutionary adaptation to lowland conditions in an ancestral population. Unfortunately, some of the physiological responses that evolved to cope with acute and/or localized hypoxia in low-elevation conditions produce misdirected, maladaptive responses under the chronic and global hypoxia at high altitude (17). For example, in lowland environments, tissue hypoxia may result from anemia, in which case increasing production of red blood cells (erythropoiesis) can facilitate greater oxygen carrying capacity within the blood and thus alleviate hypoxia. Importantly, in this scenario, erythropoiesis returns hematocrit from pathologically low levels into a healthy range. At high altitudes, tissue-level hypoxia resulting from environmental (rather than physiological) factors stimulates this same response (increased erythropoiesis). However, in this case, hematocrit is already within a healthy range, and the excessive erythropoiesis can increase blood viscosity. At

extreme levels, elevated blood viscosity places excessive strain on the heart (19), and it can hinder cardiac output and oxygen delivery to the systemic circulatory system (e.g., (20).

Understanding and developing treatments for diseases or pathologies at altitude depends on differentiating between the aspects of physiological plasticity that are maladaptive and those that are adaptive. Harmful versus beneficial value can be assessed through correlations between physiological trait values (e.g., maternal hematocrit) and birth outcomes (e.g., birthweight) or by quantifying a hazard ratio, but there are several limitations to these approaches. As aforementioned, many physiological trait values that influence fetal growth are remodeled at altitude as part of maternal acclimatization. Thus, correlations between trait values and birth outcomes can appear because both are independently responding to the same environmental cues, rather than being causally linked. For example, up-regulation of common transcription factors that are sensitive to hypoxia (like hypoxia-inducible factor, HIF) can induce correlated responses across independent systems. In addition, we might expect that there are particular oxygen content or nutrient delivery thresholds relevant for fetal growth below or above which a relationship between the predictor and outcome (here, fetal growth) is no longer apparent because that variable has been effectively saturated.

An inferential framework that is rooted in evolutionary theory can help circumvent some of these challenges and provide new insight. Natural selection acts on plastic traits differently depending on whether the induced response is beneficial (adaptive) or harmful (maladaptive). When plasticity is adaptive, natural selection acts to preserve or even enhance the magnitude of the plastic response (21). In contrast, if plasticity is maladaptive, selection should favor a blunted response that prevents the expression of the maladaptive trait value in the novel environment (22, 23). Empirical data support these theoretical predictions (see refs. (21–23) for further explanation and examples).

In practice, these evolutionary expectations allow for the inference of the adaptive value of plastic responses at altitude (21). Put simply, a lowlander response to altitude can be inferred to be adaptive if it moves the trait value closer to that expressed by the locally adapted highland population (Fig. 3A). Conversely, maladaptive plastic responses either move the trait value further from the locally adapted phenotype (Fig. 3B) or overshoot it (Fig. 3C). Despite the potential biomedical insight this evolutionary framework could provide, these inferential arguments have not yet been used to interpret the large body of data addressing how altitude shapes physiology and thus affects fetal growth.

IV. Using an evolutionary framework to assess evidence for adaptive and maladaptive plasticity in gestational physiology.

In utilizing this framework to assess the adaptive value of plasticity in a specific gestational trait, there are several important factors that should be considered. First, because the framework requires an understanding of the ancestral and derived phenotypic states, the colonization history must be known. In the case of high altitude adaptation in humans, the well-studied highland populations are definitively derived from lowland ancestors (e.g., (24–27). Our understanding of ancestral gestational plasticity in lowland humans comes primarily from studies of descendants of European

immigrants living at high elevation in the Andes and Rocky Mountains and of Han Chinese living at high elevation on the Tibetan Plateau. These data can be contrasted with similar data from well-studied indigenous populations in the Andes (principally Quechua and Aymara) and Tibet (Tibetans, including Sherpa). Ideally, contrasts should be drawn between highlanders and their closest lowland relatives; however, this can be difficult when the genealogical histories of focal populations are not fully understood. The history of genetic admixture between focal highland and lowland populations is a related issue. Modern-day movement of humans across the globe has resulted in widespread admixture among historically separated populations. As a result, formal analysis of genetic ancestry is often necessary for correct population assignment. Here, we primarily restricted our review to only those studies that assessed the genetic ancestry of sampled individuals to avoid errors in inference based on incorrect population assignment. In a few cases, however, we did include studies that only used surname analyses for population assignment (28–31); these include foundational studies of placenta histology that were published prior to wide availability or use of genetic approaches.

Second, physiological traits rarely function or evolve in isolation. Many of the physiological systems that support gestation are highly interconnected and interdependent, and this interdependence may place constraints on the evolutionary trajectories of individual traits. As a result, the adaptive value of any particular evolutionary change may be context dependent, and subject to evolutionary and functional constraints imposed by interacting systems. Relatedly, not all phenotypic differences affect fitness. Population differences in a phenotype may reflect neutral population genetic processes, and as a result, simply documenting a phenotypic difference between highlanders and lowlanders may not be sufficient to infer adaptation without additional information (32). A more powerful approach is to look for shared features across multiple, independent instances of adaptation (e.g., plasticity that is modified similarly in both Tibetans and Andeans). Such convergent changes provide particularly strong evidence for adaptive evolution and demonstrate that evolution of these solutions is not precluded by or dependent on other functional or evolutionary constraints specific to one group. As a result, these convergent solutions may be particularly promising targets for intervention. Differences in plasticity remodeling among adapted populations can suggest multiple solutions for the same biological problem, but their effectiveness may depend on unique interactions between gestational and maternal physiology as well as genetic background. Although understanding these contingencies could prove insightful for personalized medicine, population-specific solutions will be more difficult to understand because of the complex interconnectedness of relevant traits. With this in mind, using evolutionary frameworks to assign adaptive or maladaptive value to traits relevant to fetal growth should be based on at least two independently-derived highland populations (e.g., Andean and Tibetan; Ethiopian highlanders may be able to serve as a third group for confirmation in the future, however gestational adaptations have not been characterized in this population to-date and thus they are not included in this review).

Here, we first review what is known about altitude acclimatization during gestation in lowland populations to establish general patterns of plasticity in lowlanders. We then contrast these patterns with data from highland populations to infer the adaptive value

of lowlander responses. We also include other types of information on adaptive value when available, such as hazards ratios and associations between trait values and outcomes like birth weight. Finally, we identify key areas for future work that will broaden and strengthen the utility of evolutionary frameworks for understanding fetal growth restriction at altitude. Throughout, we discuss only those traits for which there is consistent or sufficient evidence to characterize plasticity in lowlanders. For traits where the published evidence is scant or equivocal, summaries and relevant citations can be found in Table 1.

i. Maternal oxygen and nutrient transport capacity

A major challenge to physiology at high altitudes is simply preserving oxygen delivery to tissues. This challenge can be at least partially offset by changes in cardio-pulmonary function and the oxygen carrying capacity of the blood.

Ventilation and heart rate: Acclimatization to high altitude increases ventilation (L/min) and heart rates in lowlanders compared to sea-level values (33–36). While increasing heart rate can improve delivery of oxygen, increasing ventilation rate contributes to pulmonary oxygen uptake as well as respiratory alkalosis, which can affect the off-loading of oxygen at target tissues by altering blood chemistry (see section below). These acclimatization responses persist during pregnancy: women of lowland ancestry that are gestating at altitude display greater ventilation (L/min) and their heart rates tend to be elevated relative to women of similar genetic backgrounds gestating at sea-level (35, 37, 38).

Indigenous Andeans and Tibetans differ in their ventilatory adaptations to altitude (39), and these differences are also maintained during pregnancy. Specifically, pregnant Andean women at altitude maintain lower ventilation at term relative to Europeans (40), whereas Tibetans maintain greater ventilation (41). Interestingly, elevated ventilation rates appear to have a positive impact on birth weight for both Tibetans and Andeans, but there does not appear to be a similar benefit of elevated ventilation to birthweights in lowland groups (40, 41). These patterns suggest that increasing ventilation at altitude is adaptive, but the benefit to fetal growth may be dependent on interactions with downstream physiological traits that augment oxygen delivery and/or acid-base balance in the blood through other mechanisms.

In contrast, both Tibetans and Andeans display lower heart rates throughout pregnancy at altitude compared to women with lowland ancestry (37, 40–42). In addition, lower pulse rates in Tibetans have been linked to improved pregnancy outcomes (including total pregnancies and survival of the child up to one year; see ref. (43). These patterns suggest that the acclimatization-dependent increase in heart rate of lowland women at altitude is likely maladaptive. Increasing heart rate may have detrimental effects on blood pressure or stress on the heart, but evidence is limited (see section on blood pressure below). Alternatively, the maladaptive pattern in heart rate may reflect underlying maladaptive patterns of catecholamine synthesis (e.g., (44, 45), which can drive sustained peripheral vasoconstriction at altitude.

Hematocrit and hemoglobin: Oxygen-carrying capacity in the blood is determined by a combination of the concentration and functional properties of hemoglobin, as well as the blood biochemistry. Exposure to high altitude is generally associated with an increase in hematocrit and hemoglobin concentrations during pregnancy in women with lowland ancestry (35, 38, 42, 46–52). Elevated hematocrit in pregnant women at altitude may be due to insufficient blood volume expansion during pregnancy (52): the absolute concentrations of both hematocrit and hemoglobin decline with pregnancy at any altitude (52, 53) as plasma volume increases, but pregnancy-associated increases in plasma volume (and by association, blood volume) are apparently blunted by residence at high altitude in women with lowland ancestry (52).

Both insufficient blood volume expansion and elevated hematocrit are independently associated with pregnancy complications (52) (and citations therein) and low birth weight (49, 52–54) but see ref. (42). Elevated hematocrit has also been linked to irregular morphology of the placenta (48). The causal mechanism by which these factors might lead to low birth weight remains unclear. Elevated hematocrit may drive physiological changes that alter placental morphology and/or constrain fetal growth. Alternatively, elevated hematocrit and fetal growth restriction may reflect other upstream physiological constraints.

One of the notable adaptations seen in highland-adapted Tibetans is an attenuation of the acclimatization-related increase in circulating hematocrit and hemoglobin. Recently, regulation of plasma volume has also been recognized as important to adaptive changes in hematocrit concentration in male and non-gestating female Tibetans (55). It is unclear whether these patterns persist during high altitude pregnancies. While some studies show that both pregnant Andeans and Tibetans tend to maintain lower hematocrit and hemoglobin concentrations in the blood relative to pregnant women with lowland ancestry (41, 42, 50), others find no difference (37, 40, 56). Moreover, blood and plasma volume appear generally similar between European and Andean women at altitude (37, 40). Nonetheless, elevated hematocrit is still associated with reduced fetal growth in Tibetans and Andeans, and lower hemoglobin is associated with greater fertility and survival of children through their first year of life in Tibetans (43). These patterns suggest that altitude-dependent increases in hematocrit are universally maladaptive above a certain threshold.

Blood chemistry and oxygen content: In concert with changes to hematocrit and hemoglobin content, shifts in blood biochemistry alter hemoglobin affinity for oxygen. Altering hemoglobin-oxygen affinity affects both blood oxygen saturation at the lungs and the dynamics of oxygen off-loading at tissues. Generally speaking, humans with lowland ancestry experience a rightward shift in hemoglobin's affinity for oxygen ($Hb\text{-}O_2$ affinity) in whole blood at altitude, which is driven by an increase in the erythrocytic concentration of a potent allosteric cofactor, 2,3-biphosphoglycerate (BPG) (57, 58). While these changes can improve oxygen offloading at the tissues, they can also reduce oxygen loading at the lungs, resulting in an overall decrease in oxygen saturation in the circulatory system (17, 59). We have no information on how erythrocytic concentrations of allosteric cofactors are altered by altitude specifically in pregnant women, however, $Hb\text{-}O_2$ dissociation in whole blood (which will reflect interactions of allosteric factors with hemoglobin binding affinities) from pregnant

women with lowland ancestry are left shifted at altitude (35). This leftward shift means that hemoglobin has a greater affinity for oxygen at altitude during pregnancy, which counters the general pattern in humans with lowland ancestry (17, 60, 61). The leftward shift in pregnant women may be attributable to ventilation-dependent respiratory alkalosis (see above), which drives a decrease in P_aCO_2 and an increase in blood pH during gestation in women with lowland ancestry (35, 38, 42, 50, 62). Ultimately, women with lowland ancestry gestating at altitude tend to have a lower oxygen saturation when compared to gestating women of similar genetic backgrounds nearer sea-level (35, 38, 42, 50).

These patterns could suggest that fetal growth restriction is simply the result of decreased oxygen availability in circulation. Surprisingly, even with decreases in oxygen saturation (S_aO_2) in gestating women at altitude (35, 38, 42, 50), several studies show that arterial oxygen content (in mL per unit blood volume) is actually *greater* in women with lowland ancestry at high altitude compared to women with lowland ancestry at sea level (35, 38, 42, 50); this difference may be explained by increased hemoglobin concentrations (see previous section). Like women with lowland ancestry, both Andean and Tibetan women also experience increases in blood oxygen content with altitude such that their blood oxygen content at altitude tends to be similar to or *lower* than that of women with lowland ancestry gestating at altitude (37, 40–42, 50). These changes in oxygen content in highland-adapted populations are also associated with a decrease in P_aCO_2 and increases in blood pH (42, 50). The fact that altitude-dependent shifts in oxygen saturation that occur in lowlanders are exaggerated or maintained in altitude-adapted populations suggests that the increase in oxygen content is more important than saturation and that blood oxygen content in lowlanders at altitude is sufficient to maintain fetal growth. Thus, other interacting physiological processes or determinants of oxygen transport and utilization seem more likely to be directly responsible for limiting fetal growth at altitude (63).

Blood pressure: Many of the changes to cardiovascular function, blood biochemistry, and vasoconstrictive factors (i.e., catecholamines) described above can contribute to elevated blood pressure, and hypertensive complications of pregnancies are more common at altitude (52, 64, 65). However, there is mixed evidence for elevated blood pressure in pregnant women at high altitude. Most studies find that blood pressure does not vary with altitude in pregnant women with lowland ancestry or between those with lowland and highlander ancestry (46, 52, 66–72), but others, including two large longitudinal studies, find that blood pressure is indeed elevated in high altitude pregnancies (41, 42, 49, 65, 73). There are at least three important caveats to those majority of studies finding no effect of altitude on blood pressure. First, most studies specifically exclude women who are hypertensive during pregnancy, even if they have no other complications. Given that women at altitude are more likely to have hypertensive disorders during pregnancy (52, 64, 65), this exclusion criteria results in a bias towards women that are able to remain normotensive at altitude. Second, blood pressure changes across a normal pregnancy, meaning that altitude-dependent increases in blood pressure may only be detectable or relevant during specific periods across gestation; of the studies we reviewed, the majority only report measures taken in the 3rd trimester or near-term. Finally, few studies are longitudinal, which could help

detect relatively small differences in blood pressure that might persist even among women classified as normotensive. In support of the importance of these caveats, the two large cohort, longitudinal studies reporting blood pressure across gestation (65, 73) do detect relatively small increases in blood pressure at altitude compared to low-altitude counterparts specifically during early pregnancy (weeks 15-25). Additional longitudinal blood pressure measures from gestating women of highland ancestry across altitudes are needed.

ii. Blood delivery to the feto-placental site

Maternal vascular remodeling and growth: In a healthy pregnancy, remodeling and growth of the uterine artery and associated vasculature facilitates dramatic increases in blood flow to the feto-placental unit, allowing sufficient delivery of gas and nutrients to the placenta. Blood flows to uterine artery from the common iliac artery via the internal iliac artery (see Fig. 2), however most studies present measures from the common and external iliac arteries. Neither the common nor the external iliac arteries experience substantial pregnancy-dependent remodeling in lowland women at low (68) or high altitudes (37, 38, 42, 68). In contrast, the uterine artery increases 1.5-times in diameter, facilitating an incredible 20-fold increase in flow during pregnancy at low altitude (68). Altitude exposure is consistently associated with reduced uterine artery diameters (indicative of insufficient remodeling) and lower volumetric blood flow (mL/min) during pregnancy in women with lowland ancestry (Han Chinese, presumed-European [in Colorado, USA], eastern European, and Arab genetic backgrounds; (38, 42, 68, 74, 75). One interesting counterpoint to this general pattern are European descendants in South America, who tend to show either an increase or no change in uterine artery diameter while pregnant at high-altitude compared to lowland pregnancies (56, 76, 77). This pattern may be the result of admixture between native Andeans and European-descendants which is common in these populations (see Section V.i).

Between the uterine artery and the placenta lie the myometrial arteries, which are functionally altered by altitude exposure during pregnancy in lowlanders. Women of presumed European-descent residing in the Rocky Mountains exhibit blunted nitric oxide (NO)-dependent vasodilation of myometrial arteries (78). NO is an important contributor to vasodilation of local vasculature during pregnancy (79), suggesting that blunted NO-dependent vasodilation could contribute to fetal growth restriction by limiting blood delivery to the placenta or by locally elevating blood pressure and/or strain on the vasculature. Conversely, AMPK-dependent vasodilation of myometrial arteries is *increased* in women with European ancestry residing at high altitudes (80). How these changes in NO and AMPK vasodilation contribute to fetal growth trajectories at altitude is not well-understood.

Data on highland-adapted populations have been limited to artery diameter and flow metrics; no data on vasodilatory function have yet been published. Variation in the diameter and blood flow through the common and external iliac arteries are not consistent between altitude-adapted populations – both are greater in Andeans compared to Europeans at altitude (37, 42), but lower in Tibetans compared to Han Chinese at altitude (41). Diameter and blood flow through common and external iliac arteries are thus unlikely to be a major factor in evolutionary protection of fetal growth

restriction at high altitude. In contrast, uterine artery diameter and/or flow tends to be greater in both pregnant Andeans and Tibetans at altitude compared to lowlanders at altitude (37, 41, 42, 56, 76, 77, 81). The fact that highlanders consistently have larger uterine artery diameters relative to lowlanders suggests that attenuation of uterine artery expansion in lowlanders is likely maladaptive for fetal growth at altitude. However, correlations between fetal growth and uterine artery diameter or blood flow vary among studies. In most cases where multiple populations and/or altitudes are examined, associations between uterine artery metrics and fetal growth occur only within a single population and altitude (37, 38, 41, 56, 68). More importantly, the group in which this association can be detected varies across studies. For example, whereas Julian et al. (68) find that uterine artery flow has a marginal, positive relationship with birthweight in European women at high altitude (but not at low altitude), Zamudio et al. (38) document a significant relationship between uterine artery flow and birthweight in European women at low altitude (but not high altitude). This disagreement among studies could reflect real variability among or within groups, unmeasured explanatory factors, or operator and instrument error. While variability among studies could undermine the general importance of uterine artery diameter or flow as a determinant of fetal growth at altitude, loci that contribute variation in these traits bear genetic signatures of a history of natural selection in some altitude-adapted populations. For example, allelic variation in *PRKAA1*, a gene previously identified to have experienced selection in Andeans (82, 83), has been linked to uterine artery diameter and birth weight in European and Andean women (84); *PRKAA1* encodes AMPK and may regulate eNOS-dependent vasodilation in myometrium (85). These results suggest that traits related to dynamic function of the artery like vasodilation, rather than static measures, may be important for fetal growth. If true, measurements of artery diameter or flow under a single set of conditions may be insufficient to fully characterize adaptive variation in the uterine artery in high-altitude adapted populations. Measuring dynamic changes in artery diameter and flow using accessible model systems may therefore be essential to understanding how uterine artery physiology influences fetal growth outcomes.

iii. Nutrient and gas exchange in the placenta

Nutrient and gas exchange are determined by both the structure and function of the placenta. Placental structure determines the total surface area for transfer as well as the rate at which blood will move along that surface, whereas placental function, which includes gene and protein expression and regulation, influences capacity to move solutes from maternal to fetal circulation and placental metabolism.

Placental structure: Altitude exposure is associated with a reduction in absolute placental size in lowlanders, however the ratio of placental to fetal mass tends to increase at altitude because fetal growth restriction outpaces the reduction in placental mass (28, 42, 48, 50, 70, 74, 86–97). In Andeans, the absolute size of the placenta is not affected by altitude (28, 42, 50), and the ratio of placental to fetal mass is unaltered. Changes in the mass of the placenta alone is therefore not likely to be a critical determinant of fetal growth trajectories of humans at altitude.

The placenta contains distinct functional structures and compartments that could be independently altered in ways that further constrain or support fetal growth without

altering overall placental mass. Many of these are altered by altitude residence in women with lowland ancestry. For example, villi within the placenta (see Fig. 1), sites of nutrient and gas exchange, tend to be shorter and occupy less total placental volume at altitude in women with lowland ancestry (28, 29, 48, 70, 86, 98, 99). Conversely, vasculature in and around villi are more abundant and larger in lowlanders at high-altitude, perhaps to counteract the decrease in villi volume. Similarly, placental arteries originating from the maternal endometrium are more numerous at high altitude in women with lowland ancestry (91), and fetal capillaries within the villi are often more numerous and/or larger in volume (29, 48, 49, 62, 70, 86, 91, 92, 97, 99, 100). Finally, the villous membrane in apposition with fetal cells thins with altitude, which may improve nutrient and gas exchange (30, 31, 100) but see ref. (70). These changes to vascular structure and organization within the placenta may protect total placental diffusion capacity despite a general decrease in size of the villous portion (98, 99) but see (70, 100).

The only data on placenta structure in altitude-adapted populations comes from studies on Andeans. Note that these studies, all published in the 1980s, used surnames to differentiate highland and lowland ancestry rather than genetic markers, and thus are potentially prone to misassignment of ancestry. Nonetheless, the villous portion is decreased in Andean placentas during pregnancies at high-altitude, and the magnitude of decrease is similar to that seen in lowland natives at altitude (28, 98). However, the structure of villi in Andean placentas differs from that of lowlanders at altitude. Andeans maintain longer chorionic villi and, within the villi, fetal capillaries are also longer at high altitude compared to lowlander placentas at altitude (29). Andean placentas also display smaller fetal capillary diameters relative to lowlanders at altitude (29). As with lowlanders, the villous membrane of Andean placentas thins at altitude (30, 31). Together, these structural changes to the villi seen in Andean placentas could underlie an increase in the efficiency of nutrient and gas transfer beyond that seen in lowlanders by both increasing surface area *and* decreasing diffusion distance. The fact that Andeans at altitude protect villi and fetal capillary length but retain thinning of the villous membrane and the relative decrease in villous volume suggests that placental structural remodeling that lowlanders express at altitude reflects a mix of adaptive and maladaptive responses.

Function of the placenta: Changes to various functional aspects of the placenta could augment structural change to preserve or improve nutrient delivery and gas exchange. Alternatively, plasticity in placental function could exacerbate bottlenecks in nutrient and gas exchange. Functional components of the placenta include the activity and abundance of receptors and transporters along the villous membrane, placental metabolic activity, and the production of hormones critical for altering maternal physiology in ways that support fetal growth.

In women with lowland ancestry, the placenta at altitude displays altered regulation of stress-related pathways, including those involved in hypoxia and oxidative damage. The hypoxia-inducible factor (HIF) pathway is generally up-regulated in high altitude placentas from women with lowland ancestry such that HIF subunits and their transcriptional targets are both up-regulated within the placenta (67, 69, 72, 101). At the same time, gene expression of inhibitory enzymes, including Factor inhibiting HIF-1

(FIH-1) and von Hippel-Lindau protein, which tags HIF subunits for degradation, may also be elevated in placentas from women of lowland ancestry gestating at altitude (72, 92). The combined up-regulation of HIF subunits and the factors that tag them for degradation could explain disagreement among studies as to whether HIF and its targets are up-regulated at the protein level (92, 101). Important to note here is that these studies generally focus on term placentas, which include samples from both vaginal and cesarean deliveries. Vaginal birth results in considerable ischemic and oxidative stress to the placenta, meaning that measurements of markers for hypoxia and oxidative stress from these tissues may reflect the effects of birth rather than *in situ* conditions. Although most studies acknowledge and statistically assess differences between placentas from vaginal and cesarean deliveries, power is often low to detect differences within groups due to small sample sizes, and cesarean deliveries are usually predominant specifically at altitude. Further explicit attention to these differences would be useful to resolve the potential influence of mode of birth on placental markers of hypoxia at altitude.

Genes in angiogenic pathways in the placenta are generally upregulated by altitude exposure in women with lowland ancestry. Many HIF-targets are angiogenic (69, 92), and these factors tend to be up-regulated with other angiogenic genes, such as those in the renin-angiotensin system (101). Increased progesterone, a sex steroid with angiogenic function, at altitude may also promote vascularization of the placenta bed. Progesterone concentration in maternal circulation tends to be greater in high altitude pregnancies for women with lowland ancestry (77, 102), and the placenta is the primary source of progesterone during mid to late gestation in humans (103).

There are considerably fewer data addressing functional aspects of the placenta in altitude-adapted human populations. Comparable data on oxidative damage, stress pathways, or angiogenic genes in placentas from altitude-adapted populations that could be contrasted with that from women with lowland ancestry is extremely limited (Table 1). However, based on patterns in gene expression, one recent study suggests that placentas from Tibetan women at altitude may experience less stress from the ischemia of labor compared to placentas of women with European ancestry at altitude (104). These results imply some population-specific resilience to hypoxia and oxidative damage within the placenta at altitude. There is also some evidence that Andeans tend to have higher concentrations of estrogens and progesterone in maternal circulation at altitude relative to women with European ancestry at altitude (77), which could suggest that elevated progesterone that occurs in lowlander pregnancies at high altitude is adaptive. It is possible that these angiogenic hormones could support greater vascularization of the implantation site and remodeling of maternal vasculature. Linking differences in circulating sex steroids to variation in vascularization in or around the placental bed could help advance this argument.

iv. Fetal hematology

Blood chemistry and hematocrit in the fetus can also influence capacity to exchange gas and nutrients. There is some evidence to suggest that fetuses with lowland ancestry are capable of extracting and consuming similar amounts of oxygen from maternal blood at high altitude and near sea level (400 m, (50), despite changes in maternal arterial oxygen content and blood flow through local vasculature. However, fetal

hematological measures generally show that the fetus at high altitude still senses relative maternal hypoxia. Fetal erythropoietin, hematocrit, and hemoglobin concentration are all elevated at altitude (50) but see (49). The pH of fetal blood is also elevated (50, 51) and bicarbonate content decreases (50, 51). These hematological changes are consistent with improved fetal O_2 extraction at high-altitude.

We might expect that fetal hematological changes like increased hematocrit also have maladaptive side effects, as they do in adults, in which case we would expect altitude-dependent increases that occur in lowlanders to be blunted or absent in altitude-adapted populations. Surprisingly, Andean fetuses display increases in hematocrit and hemoglobin similar to those seen in fetuses with lowland ancestry (50), whereas Tibetan infants retain lower hematocrit relative to Han Chinese infants (105). Andean fetuses at altitude are also similar to infants with lowlander ancestry in that they display lower umbilical bicarbonate, and they have even more basic blood pH (50). Although there may be changes in regulatory regions upstream of fetal hemoglobins in Andeans and Tibetans (106, 107), there are no known coding changes to these genes in either altitude-adapted population (106–108). Andean fetuses may also extract and consume similar amounts of oxygen per gram of fetal weight when compared with fetuses with lowland ancestry regardless of altitude (50).

In general, fetal responses to hypoxia (including increases to hematocrit and hemoglobin) may be sufficient to overcome any altitude-dependent decreases in oxygen delivery regardless of ancestry (50); additional studies to confirm these patterns are desirable.

v. Summary

Many maternal, placental, and fetal physiological traits are altered by exposure to high altitude in humans with lowland ancestry, but evidence for the contribution of any specific change in these traits to fetal growth outcomes remains limited. The simplest explanation for fetal growth restriction at altitude would be that lower oxygen directly limits growth of the fetus. However, plasticity in the placenta and/or fetal hematology appear sufficient to achieve necessary uptake and consumption of oxygen in lowlanders and highlanders alike. Altitude-dependent fetal growth restriction is therefore likely linked to indirect effects of low oxygen on gestational physiology that constrain fetal growth trajectories. Relevant factors may include vascular stress in and around the placenta and change in nutrient delivery to the fetus, but there are relatively few data quantifying these factors *in situ*, especially during early development.

V. Challenges and Opportunities

Many traits that support nutrient and oxygen transport during gestation are plastic in response to the persistent hypobaric hypoxia of altitude. The same appears to be true for structural components of the placenta. Unfortunately, we are limited in the extent to which we can assess adaptive or maladaptive value of these plastic responses because we lack data on the responses of highland-adapted populations, or the data that do exist are inconclusive. Similarly patterns of plasticity in women with lowland ancestries can be inconsistent across studies. Below we offer suggestions for progress.

i. A call for greater breadth in model systems

The literature on gestational adaptation is dominated by work in humans. Human adaptation to altitude continues to be a major area of basic and applied research, and there is clinical importance to understanding gestational physiology at altitude specifically in humans because human pregnancy has unique attributes, including aspects of placental structure and development, that cannot be studied in any non-primate model system. Still, using humans as a model for understanding the evolution of gestational traits is limited by both practical and ethical concerns. To both meet the need for understanding human gestational physiology and overcome limitations of working in humans, we suggest two complimentary avenues that are likely to be fruitful, particularly if they are pursued in parallel. First is expanding the breadth of human populations we study, and second is the development of animal models that can be studied within a comparative, evolutionary framework.

To-date, the human literature on gestational adaptations to altitude has largely focused on women of presumed European ancestry in the Rocky Mountains in Colorado, USA and women from populations living in and around the Andes (see Table 1). Our ability to assemble a comprehensive picture of human gestational physiology at altitude is limited by constraints unique to each population.

First, studies in the Rockies are limited by the fact that the low altitude comparison group has historically been based in Denver, Colorado, at 1600 m elevation. This moderate altitude corresponds to more than 15% reduction in oxygen availability (19.6 kPa at sea level versus ~16 kPa in Denver), and (perhaps unsurprisingly) birthweight is reduced at this elevation relative to sea level (109, 110). Thus, these studies may be prone to miss relevant changes in physiology or correlations between physiology and birth weight because the difference between populations in Denver and those at higher altitudes is likely to be smaller. Recent efforts to include populations from lower elevations provide useful comparative data, and future efforts in this direction with attention to maintaining comparable genetic ancestry will be useful for expanding our understanding of the physiology shaping fetal growth restriction across altitude gradients.

Populations in the Andes also present challenges to drawing generalizable conclusions about gestational adaptation. Indigenous highland groups in the Andes (namely, Aymara and Quechua) represent a single instance of adaptation to altitude. As discussed in Section IV, in can be difficult to distinguish phenotypic responses that arise from natural selection from those that arise from genetic drift when focusing a single colonization of high altitude (32). Moreover, it can be difficult to account for context-specific adaptive responses that arise from interactions between interrelated systems or other constraints on the adaptive process. For example, Andeans and Tibetans, two independent adaptation events to high altitude environments, differ in how the ventilatory system has adapted to altitude (39, 111, 112). Comparing patterns of plasticity in ventilation between lowlanders and these highland groups independently would lead to different conclusions about the adaptive value of increasing ventilation rates at altitude. When instead viewed together, we can more accurately infer that the adaptive value of ventilation patterns at altitude may depend on the function of

interrelated physiological systems. Studying gestational physiology in Tibetans (including Sherpa) and Ethiopian highland groups (namely, Oromo and Amhara) will be important to confirm the adaptive value of plasticity based on comparisons between Andeans and Europeans alone.

Inferences based on Andean highlanders are also limited by the relatively recent colonization of high altitude by Andeans (112) combined with a history of admixture between highland indigenous groups, Europeans, lowland indigenous groups and west Africans (Yoruba) in and around the Andes (24, 113). Both recent colonization and prevalent admixture can contribute to lower genetic differentiation between highland and lowland populations, which can result in populations displaying similar phenotypes, including plastic responses. Again, adding comparative data from other independent adaptive events, especially those where gene flow has historically been low for longer periods, will be important for confirming adaptive and maladaptive patterns inferred from a single population.

Beyond population-based variation, humans have limited utility as a model for discovery-based research and mechanistic studies because we have limited access to studying dynamic processes across gestation. The majority of studies reviewed here focus primarily on third trimester to late term pregnancies, but many of the processes that organize maternal gestational physiology, vascular remodeling, and placental growth occur at earlier time points (114–116). Early gestation can only be studied *ex vivo* in humans and often relies on limited material. The *in vivo* manipulations and controlled sampling that is needed to study placentation and fetal growth at altitude can only be performed in animal models.

To date, domestic sheep are the only animal model that has been used to study in evolutionary adaptations in gestational physiology using a comparative approach. Criollo sheep were introduced to Peru by Spanish colonizers as early as the beginning of 16th century and may have been moved to the highlands of the Andes for farming soon thereafter (117). Many of the physiological responses to altitude that are thought to be adaptive in altitude-adapted humans also occur in highland populations of these sheep. For example, both lowland adult and fetal sheep display increased hematocrit and/or hemoglobin concentration at altitude, but adapted adults maintain lower hematocrit at altitude (6, 118). Data on fetal hematocrit or hemoglobin are not available for the altitude-adapted population. Altitude-adapted sheep also seem to maintain elevated concentrations of angiogenic sex steroids during pregnancy relative to lowlanders (119). Finally, the area of the placenta across which nutrient exchange occurs is increased in altitude-adapted sheep (6, 120), and their placenta contains a greater concentration the vasodilator eNOS (118). Sheep are already a well-studied model for hypoxic and metabolic stress during gestation in lowland environments (121), which makes this a promising system for better understanding constraints of both placental and maternal physiology at altitude that contribute to fetal growth restriction.

There are two important limitations to using this system as a model for evolutionary insight. First, whole-animal physiological adaptations to altitude have not been described – we do not know the extent to which core physiological systems (e.g., pulmonary or cardiovascular) have been adaptively modified outside the context of gestation. Given the interdependency of maternal and feto-placental traits, this characterization is important. Comprehensive efforts to characterize the physiological

basis of adaptation to altitude in these sheep through the integration of functional genomics and physiology would be useful for further developing the utility of this model. Second, the utility of these sheep as a model for evolutionary adaptation to high-altitude is also limited by the fact that these sheep are domesticated and have been since well before they were brought to the Andes. The capacity of any population to adapt to a novel environment is a function of the initial genetic variation available for selection to act upon and the efficacy of selection on fitness-related traits. Domestication events are typically associated with genetic bottlenecks which reduce genetic variation and the efficiency of selection relative to genetic drift (122). Furthermore, artificial selection for specific traits (e.g., body size, time to maturity) may constrain other evolutionary responses to natural selection (122). For these reasons, models for gestational adaptation to altitude that are not subjected to potential confounding effects of domestication would still be desirable.

Identifying useful systems for development as animal models is an important next step towards making experimental progress on this topic. Rodent systems are appealing for many of the same reasons sheep are – there is a large body of research already established for gestational physiology of rodents under acute hypoxia that would facilitate crosstalk between altitude-specific fetal growth restriction research and the broader field of gestational physiology and health. In particular, deer mice (*Peromyscus maniculatus*), which are now well-established as a comparative model for altitude adaptation (18, 123, 124), are a promising system because they offer experimental tractability, genomic resources, and multiple populations that are adapted to both highland and lowland conditions (125). Other wild rodent species, such as *Phyllotis* leaf-eared mice in the Andes, may have similar potential (126, 127).

ii. **Integrating gestational physiology**

The genetic basis for gestational adaptions Andeans and Tibetans is thought to be highly polygenic (42, 43, 56, 128), and thus the mechanisms protecting fetal growth in these populations may involve physiological traits at or across multiple levels between mother and fetus (Fig. 2). Across all the studies we reviewed, most were focused on maternal traits or structural constraints related to the placenta and uterine artery, and they focused on near-term timepoints. Other traits that are likely relevant, especially endocrine and metabolic function of the maternal and placental compartments, have received less attention and/or display equivocal patterns across the small number of published studies (see Table 1). Expanding the set of focal traits, integrating across physiological systems and levels of biological organization, and focusing on developmental trajectories are all necessary to fully understand the major factors that influence birth outcomes at high altitude.

As an example, there is evidence that maternal immune function may be important, but it has received very little attention. Local regulation of the maternal immune system is critical during early placentation (44, 81, 129–131), and inflammatory signals are more abundant at high altitude in the maternal circulation and placentas of lowlanders (44, 46, 67, 72) but see (81), suggestive of immune dysregulation. Given its dual role in erythropoiesis and immune cell production, the spleen (which grows ~50% in size during pregnancy; refs. (132, 133) seems to be a promising target of integrative studies

but has received surprisingly little attention within the context of high-altitude pregnancies. Uterine natural killer cells, which play an important role in establishing the placental bed are also a promising source of new insight for understanding origins of fetal growth restriction at altitude (129, 134, 135).

An integrated view of the materno-feto-placental unit would also be useful for clarifying the ultimate versus proximate factors responsible for fetal growth outcomes. We need a better developmental understanding of how altitude-dependent fetal growth restriction arises. Longitudinal studies, when feasible, would be particularly useful for determining how early events may predict fetal outcomes. Connecting individual traits though physiological networks will also help advance our understanding of the processes that operate at the whole organism-level and translates environmental hypoxia into fetal growth restriction. Computational and experimental approaches for network physiology (e.g., (136–138) may help identify the importance or stability of trait dependencies underlying fetal growth restriction and/or adaptive mechanisms that protect fetal growth at altitude.

Understanding physiological integration among traits and dynamic development across pregnancy in the context of altitude-dependent fetal growth restriction is also likely to advance several adjacent areas of active research. Complex interactions between placental development and physiology and maternal physiology are hallmarks of many gestational complications, including intra-uterine growth restriction, pre-eclampsia, and gestational diabetes. Moreover, the risk for many of these complications are increased in pregnancies at high altitude. Understanding how maternal, placental, and fetal physiologies interact and evolve in the context of high altitude is therefore likely to also shed light on mechanisms relevant to these diseases at lower altitudes. For example, although the ultimate cause of fetal growth restriction at altitude is unique to the environment (persistent hypobaric hypoxia), placental gene expression at term is similar to that seen in placentas from pre-eclamptic pregnancies, where hypoxia may be maternal or placental (69). Thus, even when the etiologies differ, there is good reason to think that what we learn from high altitude adaptation could improve treatments for other gestational complications.

VI. Perspectives and Significance

The relative contribution of individual gestational traits to the broader phenomenon of fetal growth restriction at altitude remains poorly understood, and the evolutionary adaptations that contribute to protecting fetal growth in adapted populations are similarly unclear. We have highlighted many outstanding questions about gestational adaptations and this distinction between plastic responses that are ultimately versus proximately adaptive. Understanding these mechanisms will add valuable new information for both basic science and clinical intervention research aimed at improving human and animal health outcomes across a range of gestational complications that involve hypoxia.

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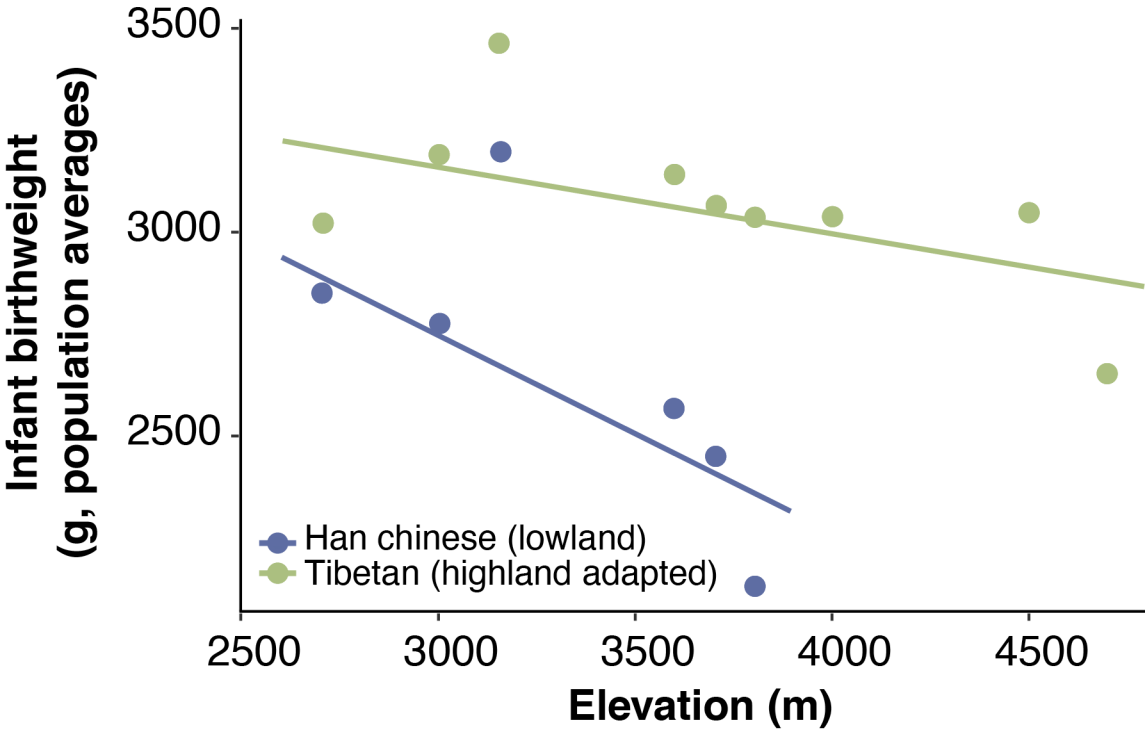
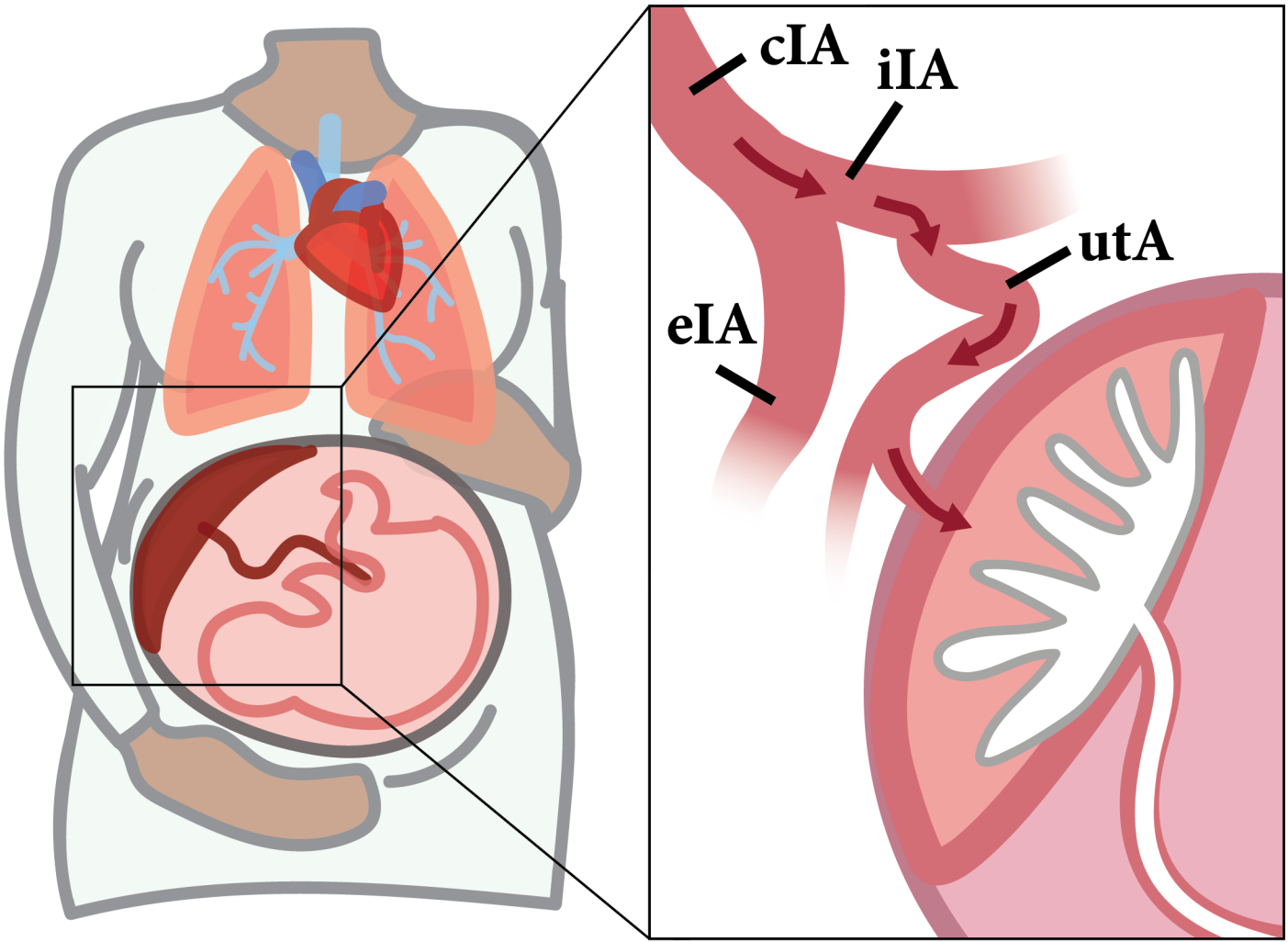
Figure 1 **Human birthweight in lowland populations (data from Han Chinese populations shown here in blue) decreases with increasing altitude.** Highland adapted populations (data from Tibetan populations shown here in green) display reduced or absent altitude-dependent declines in birthweight. Each point represents a population average at a given elevation. Linear regressions between altitude and birthweight are shown for each population (solid lines). Figure reproduced from (143).

Figure 2 **Maternal and fetal systems shaping gas and nutrient exchange.** (a) Gas exchange (including oxygen uptake) and nutrient circulation is determined by maternal pulmonary and cardiovascular function. Maternal blood chemistry can also alter oxygen uptake and delivery. (b) Blood delivery to the fetoplacental unit comes through the common (cIA), which bifurcates to form the external and internal iliac arteries (eIA and iIA, respectively). The iIA leads to the uterine artery (utA), which delivers blood to the placenta. (c) Within the placenta, maternal blood fills the intervillous space (light pink), bathing the villous membrane (grey outline) to facilitate gas and nutrient exchange with the fetal blood supply, which is contained within the villi (white). (d) Fetal blood returns to the fetus via the umbilical cord.

Figure 3 **Patterns of trait values in ancestral (e.g., lowlander) and adapted (e.g., highland) populations in different environments can be used to infer whether plasticity in a given trait is adaptive or maladaptive**. Organisms can often reversibly adjust their physiology, behavior, or morphology in response to novel environmental conditions, however this plasticity can be either beneficial (adaptive) or harmful (maladaptive), depending on the context. Ancestral (lowlander) plasticity is represented in this figure as the arrow between two blue boxplots (A-C), which indicate a hypothetical distribution of ancestral trait values in two different environments, sea level (0 meters above sea level [asl]) or at high altitude (3600 m asl). When plasticity in lowlanders is adaptive (beneficial) at high altitude, altitude-adapted should display similar or even more extreme values for that trait (A). For example, blood pH displays this pattern across altitudes and populations (Table 1). Alternatively, if ancestral plasticity induced in lowlanders at high-altitude is maladaptive, altitude-adapted populations should maintain trait values at altitude similar to those found in the lowland population when near sea level (B). Uterine artery diameter [UA diam.] displays altitude-dependent plasticity that may be consistent with this pattern (Table 1). Finally, maladaptive plasticity can also appear as plasticity in lowlanders that overshoots local optima seen in highlanders (C). Hematocrit shows this pattern in both gestating and non-reproductive women (Table 1).


Infant birthweight
(g, population averages)
3500
3000
2500
Han chinese (lowland)
Tibetan (highland adapted)
2500
3000
3500
4000
4500
Elevation (m)


cIA
iIA
utA
eIA

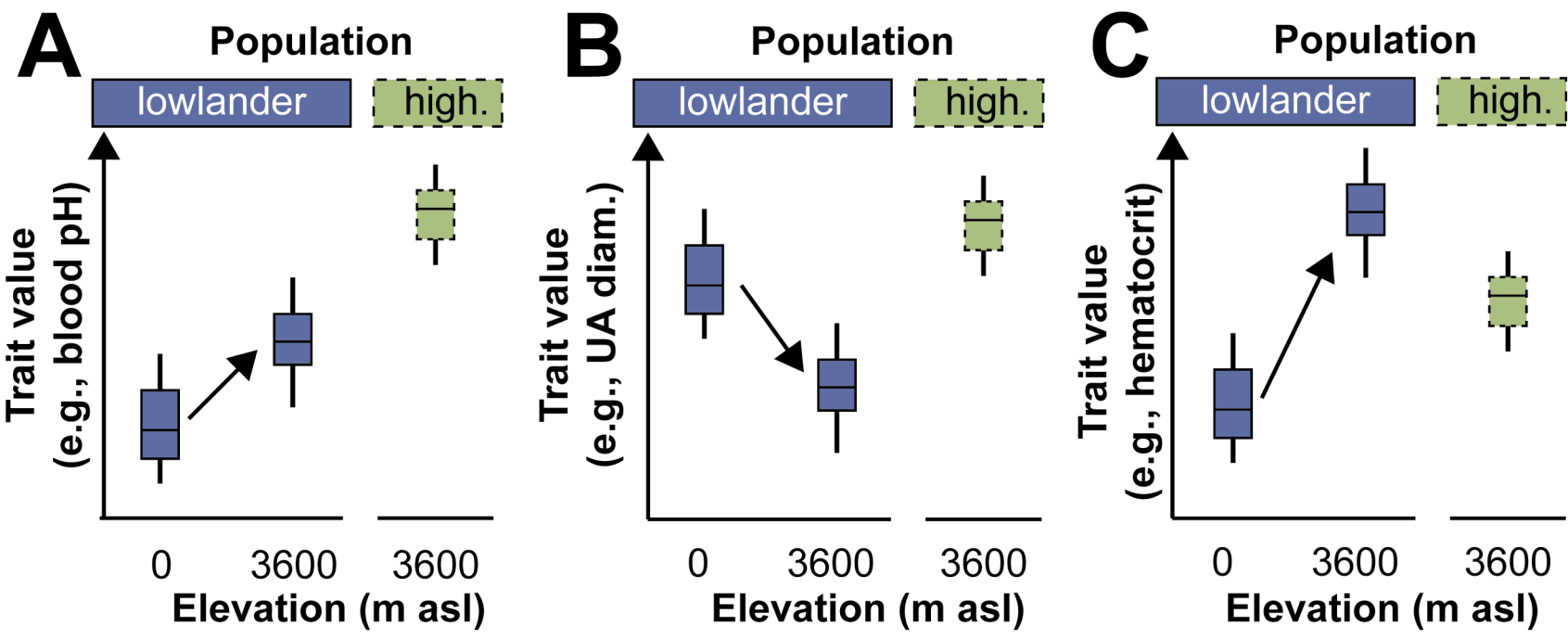

A
Population
lowlander
high.
Trait value
(e.g., blood pH)
0
3600
3600
Elevation (m asl)
B
Population
lowlander
high.
Trait value
(e.g., UA diam.)
0
3600
3600
Elevation (m asl)
C
Population
lowlander
high.
Trait value
(e.g., hematocrit)
0
3600
3600
Elevation (m asl)

Table 1 Comprehensive summary of studies addressed in this review that quantify gestational traits thought to be involved in fetal growth restriction in the context of high altitude. Populations for which data have been published for each trait are indicated in each column as ★. We summarize the direction of plasticity in trait value for women with lowland ancestry, using ↑/↓/= to indicate increase/decrease/no change in women gestating at altitude relative to those lowland environments. **?** indicates uncertainty due to disagreement among studies or limited empirical data. Similar notation is used to summarize plasticity in women with highland ancestry along with ND (no data). We summarize evidence for the adaptive value of lowlander plasticity using A (adaptive), M (maladaptive), N/A (no plasticity in lowlanders), or UNK (insufficient or absent data in either population for assessment).

		LOW ALTITUDE						HIGH ALTITUDE									
Trait		European (Rocky Mountains)	European (Peru and Bolivia)	Han Chinese	Other populations (Saudi Arabia, Kyrgyzstan, Turkey, Pakistan)	Andean (Quechua, Aymara)	Tibetan	European (Rocky Mountains)	European (Peru and Bolivia)	Han Chinese	Other populations (Saudi Arabia, Kyrgyzstan, Turkey, Pakistan)	Andean (Quechua, Aymara)	Tibetan	Direction of plasticity in ancestral (lowland) populations	Direction of plasticity in derived (highland) populations	Within the evolution of plasticity framework, is lowland plasticity more likely adaptive or maladaptive?	Relevant Citations
Maternal physiology	Ventilation (L/min)	★						★	★	★		★	★	↑	↑/↓	A?	(35, 40, 41)
	Heart rate	★	★			★		★	★	★		★	★	↑	=	M	(37, 38, 40–42, 139)
	Hct & Hb	★	★		★	★		★	★	★	★	★	★	↑	=?	M	(35, 37, 38, 40–43, 46–52, 56)
	Blood & plasma volume	★						★	★			★		↓	ND	M?	(37, 40, 52)
	Blood pressure	★	★		★	★		★	★	★	★	★	★	↑/=	=?	M?	(41, 42, 46, 49, 52, 65–73)
	Blood pH	★	★			★		★	★			★		↑	↑	A	(35, 42, 50)
	Arterial O2 content	★	★			★		★	★	★		★	★	↑	↑?	A?	(35, 37, 38, 40–42, 50, 56, 62)
Placental blood delivery	Iliac arteries diameter and/or flow	★	★			★		★	★			★	★	=	↑/=?	N/A	(37, 38, 41, 42, 68)
	Uterine artery diameter and/or flow	★	★	★		★		★	★	★		★	★	↓?	↓/=?	M?	(37, 38, 41, 42, 56, 68, 74–77, 81)
	Vasodilatory responses	★						★						↓	ND	UNK	(78, 80)

	Vasodilators in maternal circulation	★			★			★			★			↑/=	ND	UNK	(46, 66, 68)
Nutrient and O2 exchange capacity	Uteroplacental artery number	★						★						↑	ND	UNK	(91)
	Placenta size	★	★		★	★		★	★		★	★		↓/=	=	M?	(28, 42, 48, 50, 70, 74, 86–97)
	Villi volume (absolute and/or percent of placenta)	★	★		★	★		★	★		★	★		↓	↓	M?	(28, 29, 70, 86, 98, 99)
	Villous membrane thickness	★	★		★	★		★	★		★	★		↓	↓	A?	(30, 31, 70, 100)
	Fetal capillary number and/or volume	★	★		★	★		★	★		★	★		↑?	↑/↓?	UNK	(29, 48, 49, 62, 70, 86, 91, 92, 97, 99, 100)
	Expression of HIF, HIF-targets, and inhibitors (vHL & FIH)	★						★						↑?	ND	UNK	(67, 69, 72, 92, 101)(69, 72)
	Glucose content/transporter expression	★						★						↓	ND	UNK	(71, 93, 95)
	Oxidative stress & damage	★	★			★		★	★			★	★	↑/↓?	ND	UNK	(94–96, 104, 140)
	Mitochondrial abundance or function	★						★									(141)
	Progesterone	★	★			★		★	★			★		↑	↑	A?	(77, 102)
	Estrogens	★	★			★		★	★			★		↑/↓?	↑	UNK	(77, 102)
Fetal hematology	Umbilical vein diameter and/or flow		★		★	★			★		★	★		↓	↓	M	(50, 142)
	Umbilical artery diameter and/or flow	★	★		★	★		★	★		★	★		↓/=?	↓/=?	M?	(37, 50, 68, 74, 142)
	Hct & Hb		★		★	★			★		★	★		↑	↑	A?	(49, 50, 105)
	Blood pH	★	★			★		★	★			★		↑	↑	A?	(50, 51)
	O_2 extraction		★			★			★			★		=?	=?	N/A	(50)

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