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Sleep-disordered breathing in pregnancy: a developmental origin of offspring obesity?

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Review

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Abbreviations:
AHI, apnea hypopnea index; BMI, body mass index; BW, birth weight; DoHaD, Developmental Origins of Health and Disease; FA, fatty acids; IH, intermittent hypoxia; IR, insulin resistance; LGA, large for gestational age; OSA:, obstructive sleep apnea; SDB, sleep-disordered breathing; SGA, small for gestational age; SF, sleep fragmentation; SNS, sympathetic nervous system

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Abstract

Sleep-disordered breathing (SDB) worsens over pregnancy, and obstructive sleep apnea is associated with serious maternal complications. Intrauterine exposures that provoke insulin resistance (IR), inflammation, or oxidative stress may have long-term offspring health consequences. In obesity, worsening maternal SDB appears to be an exposure that increases the risk for both small- or large-for-gestational-age (SGA, LGA, respectively), suggesting distinct outcomes linked to a common maternal phenotype. The aim of this paper is to systematically review and link data from both mechanistic rodent models and descriptive human studies to characterize the impact of maternal SDB on fetal development. A systematic review of the literature was conducted using PubMed, Embase, and CINAHL (01/2000–09/2019). Data from rodent (9 studies) and human models (48 studies, 5 meta-analyses) were included and reviewed using PRISMA guidelines. Evidence from rodent models suggests that intermittent maternal hypoxia results in mixed changes in birth weight (BW) followed by accelerated postnatal growth, while maternal sleep fragmentation results in normal BW followed by later metabolic derangement. Human studies support that maternal SDB is associated with both SGA and LGA, both of which may predispose offspring to later obesity. Evidence also suggests a link between SDB, inflammation, and oxidative stress that may impact maternal metabolism and/or placental function. SDB is common in pregnancy and affects fetal growth and development. Given that SDB has significant potential to adversely influence the intrauterine metabolic environment, larger, prospective studies in humans are urgently needed to fully elucidate the effects of this exposure on offspring metabolic risk.

Introduction

Disturbed sleep is a known risk factor for metabolic dysregulation but in pregnancy, it remains under-recognized and poorly understood. Altered sleep patterns due to normal physiologic changes in pregnancy are common, but can be debilitating. They may pose significant risk to both the mother and developing fetus, particularly in obese women with commonly co-occurring risk factors. Disturbed sleep is implicated in a multitude of serious maternal/fetal complications that are exacerbated in obesity. These include gestational hypertension and preeclampsia,[1–9] gestational diabetes mellitus,[10,11] preterm birth, and unplanned cesarean delivery.[12,13] Sleep-disordered breathing (SDB) is one of the most common sleep disorders and impacts up to 32% of pregnancies.[14]

By definition, SDB is a continuum that ranges from mild inspiratory flow limitation to obstructive sleep apnea (OSA) (see Dempsey *et al.* [2010]).[15] Mild SDB is characterized by snoring from inspiratory flow limitation.[16] OSA is the most severe form of SDB in which partial or complete collapse of the upper airway results in decreased airflow (hypopnea) or cessation of breathing (apnea) and frequent arousals.[17] Loud snoring and somnolence (excessive daytime sleepiness) are common features of OSA. Apneas and hypopneas result in sleep fragmentation (SF) to restore airway patency. While the development of SDB is likely multifactorial, one of its strongest predictors is obesity[18]; increasing fat in airway muscles and neck fat pads[19] make collapse of the upper airway more likely. Investigators have consistently reported that frequency of self-reported snoring increases through pregnancy.[3,20] This is likely due to the anatomical and physiological changes associated with pregnancy, such as increased blood volume, gestational weight gain, and increasing abdominal pressure due to the enlarged uterus.[21]

Obesity is a state of insulin resistance (IR) in most individuals.[22,23] Pregnancy itself produces an IR state as a normal adaptation to ensure an adequate supply of maternal fuels to the meet the metabolic demands of the placenta and growing fetus. IR in pregnancy is largely a result of placental hormones such as human placental growth hormone, human placental lactogen,

increased levels of Tumor Necrosis Factor-alpha, and decrease in adiponectin.[24,25] With increasing fetal growth, IR is maximal in the late 2nd and 3rd trimesters when there is an approximate 50% decrease in insulin-mediated glucose disposal and a 200%–300% increase in insulin secretion in response to glucose.[26,27] It has been demonstrated that women with obesity enter pregnancy with heightened IR, upon which the effects of pregnancy are additive.[26–29]

Pregnancy IR may be exacerbated by worsening SDB. Although the association between IR and SDB is likely bidirectional,[30] there is evidence suggesting that sleep disruption similar to that experienced in severe SDB precedes altered insulin sensitivity and glucose metabolism, suggesting causality.[31–34] The exact mechanisms underlying this relationship are not understood, but several hypotheses have been proposed. SF and intermittent hypoxia (IH) may increase IR through over-activation the sympathetic nervous system (SNS),[35–37] activation of the hypothalamic-pituitary-adrenal axis with increased cortisol release,[38] or increased inflammation and reactive oxidative stress.[39,40] Interestingly, IH, increased inflammation, and increased oxidative stress, particularly early in pregnancy, can also impair placental function and blood flow.[41] Thus, it is possible that the duration and severity of SDB results in opposite growth outcomes to the fetus. Mild SDB that worsens over pregnancy may exacerbate pregnancy IR, resulting in nutrient over-exposure and offspring large-for-gestational age (LGA). In contrast, preexisting chronic OSA may increase risk of endothelial dysfunction and hypertensive disorders in pregnancy, result in abnormal placentation with reduced blood flow, and lead to earlier delivery and offspring small-for-gestational age (SGA). Both LGA and SGA are risk factors for childhood metabolic disease. Fig. 1 highlights the potential mechanisms by which SDB may exacerbate both IR and changes at the placenta.

Both animal and human models support that in utero development is a time of tremendous plasticity during which the fetus is exquisitely sensitive to exposures within the intrauterine environment. In accordance with the Developmental Origins of Health and Disease (DOHaD) framework, in utero plasticity allows for the creation of environmentally matched phenotypes that are best suited to promote survival under altered conditions, such as under- or overnutrition, or IH.[42] These phenotypes, however, are vulnerable to dysregulation with reversal of those conditions postnatally (i.e., an environmental mismatch). After birth, a background of preset functional capacity and gradual loss of plasticity, in combination with an obesity-promoting postnatal environment, is thought to set the stage for offspring obesity and chronic disease risk.[42,43] During pregnancy, maternal factors such as nutrient intake, metabolic disturbances, and hypoxia shape fetal environmental conditions; even normal variation in these exposures is now appreciated to have long-term offspring consequences. Sleep may influence these maternal factors, affecting fetal development and growth. Birth weight (BW) and body composition, specifically increased fat mass at birth, are strong predictors of future metabolic disease.[44] Emerging data continue to demonstrate that low and high BWs predict higher odds for overweight/obesity in school-aged children (OR 1.91–2.34),[45] and fat mass at birth is a stronger predictor of childhood obesity risk than BW.[44]

Childhood obesity in the United States affects nearly one in five preschool children, suggesting a role for early environmental factors.[46] Because the risk for childhood obesity appears to be propagated by a number of in utero environmental conditions, and SDB is common, a better understanding of its potential impact on fetal outcomes might inform interventions that optimize the intrauterine environment, mitigating chronic disease risk beginning during fetal development. Accordingly, the aim of this paper is to systematically review and link data from both mechanistic rodent models and descriptive human studies to characterize the impact of maternal SDB on fetal development. While the data suggest that SDB in pregnancy may be an exposure to the developing fetus, we emphasize that controlled, appropriately designed, and prospective data are required to provide stronger support for this relationship. Significant confounders in human investigations, potential reasons for discrepant findings, and suggested areas for future research are also discussed.

Methods

PubMed, Embase, and CINAHL were searched using terms that included: "sleep disordered breathing" OR "obstructive sleep apnea" OR "snoring" OR "sleep fragmentation" OR "intermittent hypoxia" AND "pregnancy" OR "placenta" OR "fetus" OR "infant" OR "birthweight". Original studies were included if: (1) full text was available; (2) written in English; (3) publication was between 01/2000 and 09/2019; and (4) infant outcomes were reported (e.g. BW, intrauterine growth restriction [IUGR], small or large for gestational age [SGA, LGA, respectively]) in relation to SDB. Animal studies were included if the disruptions common to SDB (SF or IH during the sleep period) were used in pregnant animals and metabolic outcomes of the offspring were assessed. Notably, only studies where IH, not chronic hypoxia, were included because in the human condition, SDB is limited to IH during the sleep period. PRISMA guidelines were followed for the review. Quality of studies was reviewed using the NIH tool for observational studies and NIH tool for case–control studies[47] in humans and the SYRCLE tool[48] for animal studies. For human studies, control for the major confounders of maternal age, gestational age, BMI, gestational hypertension, diabetes, and smoking was assessed in each study.

Results

Fig. 2 shows the flow of study selection. Initially, a total of 1374 abstracts were retrieved from the 3 databases. After careful review, 57 articles (48 in humans and 9 in rodents) in which assessment of maternal SDB during pregnancy with fetal, placental or infant birth-weight outcomes were included. Additionally, five meta analyses met criteria for inclusion and were reviewed. All studies in humans were descriptive or case–control studies. Table 1 provides information on studies reviewed in rodents, and Table 2 provides information on studies reviewed in humans. The quality review of human studies is summarized in Table 3. Supplementary Table S1 provides quality ratings of the animal studies.

Rodent models of gestational SDB show metabolic aberrancies in offspring growth and development

Rodent models (mice and rats) of the effects of gestational SDB allow for mechanistic investigation of the *independent* effects of SF and IH as separate exposures to the developing offspring. In the human SDB condition, it is not possible to isolate the effects of IH vs SF due to co-occurrence and interacting effects. While all of the studies in rodents were randomized control trials, most of the reports lack description of the key bias indicators such as similarity of groups at baseline, sequence generation and random housing (Table S1).

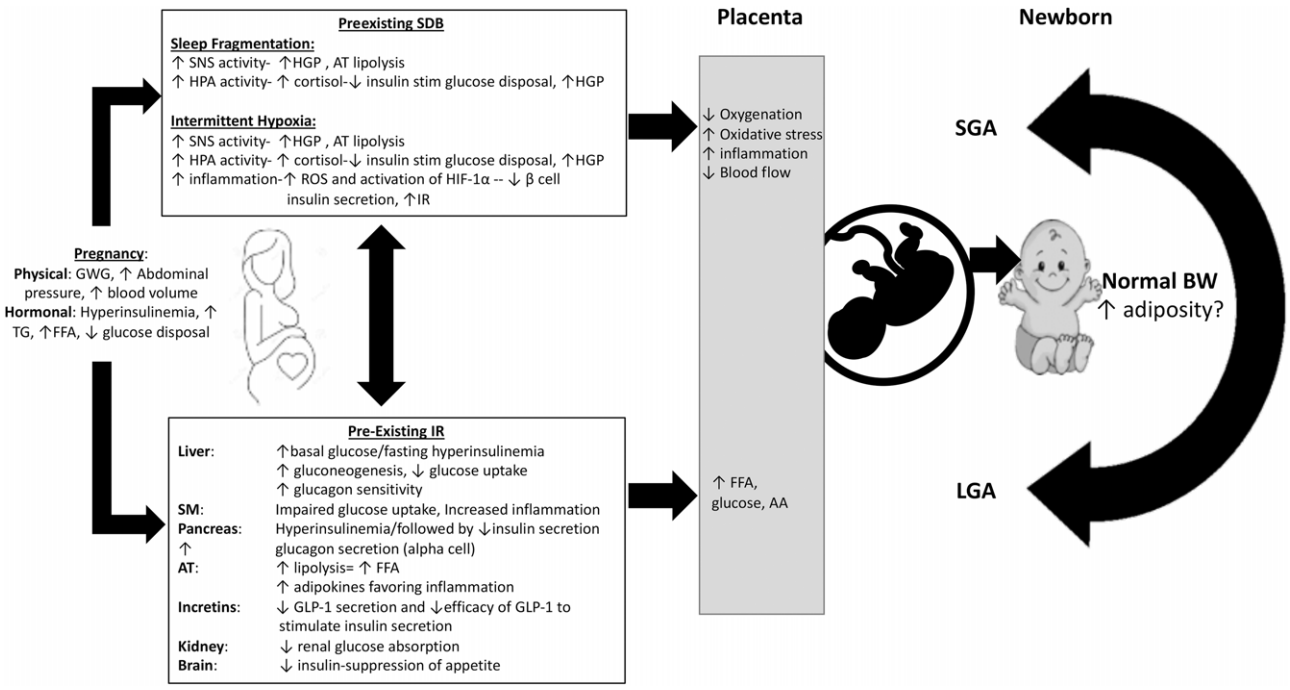

Fig. 1. Sleep-disordered breathing in pregnancies affected by obesity: two offspring phenotypes. Pregnancy is a state of increased insulin resistance (IR) and increasing weight which exacerbates both SDB symptoms and preexisting IR of obesity. Preexisting IR is understood to be multifactorial and known mechanisms are listed. SDB involves intermittent hypoxia, sleep fragmentation, or a combination, which activate pathways that further increase IR. Severe SDB, manifested as OSA, may result in extreme sleep fragmentation and intermittent hypoxia that alters placental development. In extreme cases, altered placental functioning may lead to small-for-gestational age (SGA) infants. However, exacerbation of IR due to worsening SDB also may result in excessive fetal-placental nutrient exposure, leading to large-for-gestational age (LGA) infants. Alternatively, exposure to SDB and increased IR may result in newborns born with normal birthweight but increased adiposity or subclinical alterations in metabolism. Developmental Origins Theory posits that risk of future disease is along a continuum with both extremes (both SGA and LGA) leading to increased risk of future disease. AA, amino acids; BW, birthweight; FFA, free fatty acids; IR, insulin resistance; OSA, obstructive sleep apnea; ROS, reactive oxygen species; SDB, sleep disordered breathing; SNS, sympathetic nervous system; GLP-1, glucagon-like peptide-1; HGP, hepatic glucose production; AT, adipose tissue; SM, skeletal muscles; HPA, hypothalamic pituitary adrenal axis.

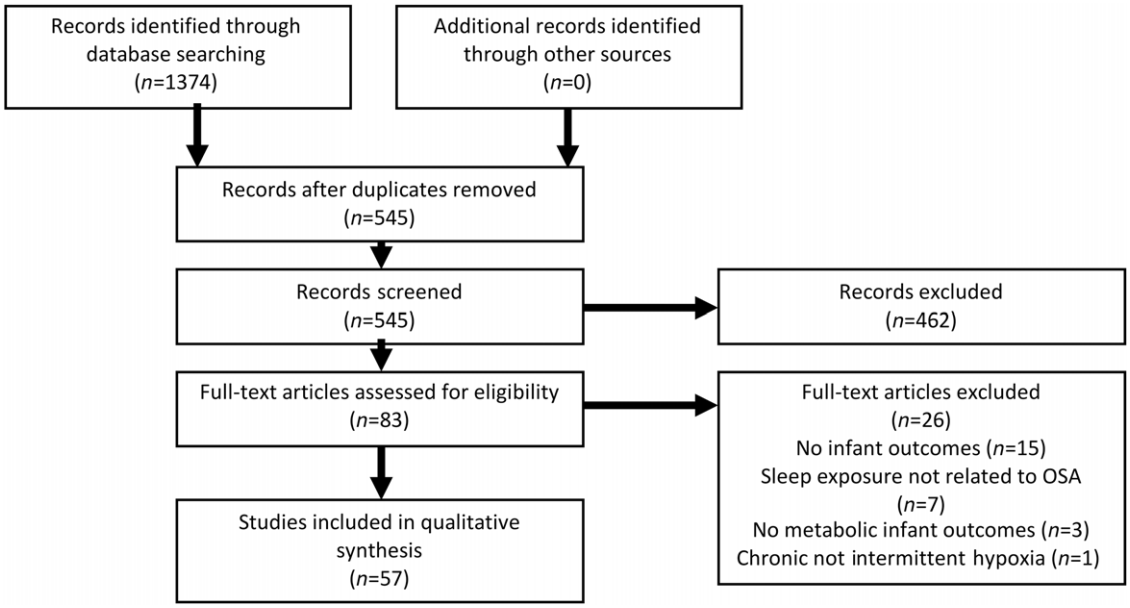

Fig. 2. Prisma flow diagram for selection of articles.

Intermittent hypoxia: Investigators reported either no difference in BW,[49,50] significantly lower BW[51] or growth restriction[52] in offspring exposed to gestational IH during pregnancy compared to control animals. In two studies, IH-exposed offspring had lower BW but rapid catch-up growth,[51,52] which has been shown to be related to increased risk of childhood obesity in humans.[53] At 6–12 weeks of life, male offspring exposed to gestational IH had greater fat mass compared to controls.[52] Khalyfa *et al.* found that male, but not female, offspring exposed late gestational IH (days 13–18 of gestation) had higher body weight and visceral adipose

Table 1. Overview of studies conducted in rodents

Sleep fragmentation (SF)		
Author, year	Outcomes	Findings
Cortese 2015[54]	Body fat, insulin resistance, visceral fat, epigenome of adipose tissue in offspring into adulthood in mice	SF exposed offspring had altered methylation patterns in genes related to obesity/metabolic syndrome (Akt2, Cartpt, Apoe), increased body fat, and insulin resistance which lasted into adulthood
Khalyfa 2014[56]	Body weight, glucose, insulin, fat mass, DNA methylation of Adiponectin gene in mice offspring	Increased body weight, body fat, and adiponectin gene methylation in SF exposed offspring in adulthood
Khalyfa 2015[57]	Glucose, insulin, fat mass, metabolic gene expression, and methylation patterns in mice offspring	Worse metabolic profiles in males exposed to SF, not females
Mutskov 2015[55]	FOXO1 gene regulation, body weight, body fat, glucose, and insulin in mice offspring	Increased histone methylation and acetylation of FOXO1 gene promoter, increased body fat, and glucose/insulin in SF exposed offspring; physical activity early in life reversed changes
Trzepizur 2017[59]	Body weight, glucose, insulin, fat mass, DNA methylation of adiponectin gene of mice offspring in adulthood; effect of SF on double mutant CHOP and GADD4 in mice offspring	Body weight, adipose tissue, glucose, and insulin higher in SF exposed offspring. No effect of SF on double mutant mice
Intermittent hypoxia (IH)		
Author, year	Outcomes	Findings
Gozal 2003[51]	Metabolic rate, body weight of offspring in rats	IH exposed offspring had significantly lower birthweight but rapid catchup growth, no changes in metabolic rate
Iqbal 2013[52]	Growth restriction, body fat, glucose, insulin of offspring in rats	IH exposed offspring were growth restricted at birth, had increased insulin, glucose and body fat into adulthood
McDonald 2016[50]	Body weight of offspring in rats	No difference between IH and no IH exposure
Khalyfa 2017[49]	Lipid profiles, insulin resistance, adipose tissue methylation in mice offspring	Higher body weight in adulthood, insulin resistance and lipid profiles, and altered adipose tissue gene methylation in SF-exposed males but not females

tissue at 24 weeks compared to controls.[49] HOMA-IR and plasma leptin were higher, and plasma adiponectin was lower in these male offspring exposed to maternal IH compared to controls at 24 weeks,[49] suggesting that there may be sex differences in exposure outcomes. The investigators further reported upregulation of gene methylation pathways associated with energy production in adipose tissue of IH-exposed offspring, suggesting a potential mechanism by which IH-exposure may result in increased risk of obesity.[49]

Sleep fragmentation. Exposure to SF in utero may have deleterious effects on offspring metabolism which do not manifest until later in life. In mouse offspring exposed to gestational SF, BW was not different than controls.[54–56] However, as the mice entered adulthood (16–18 weeks of life), offspring of SF-exposed mothers had significantly higher mean body weight, fat mass, blood glucose, and higher fasting total triglyceride and cholesterol concentrations than controls.[55,56] The negative metabolic effects of gestational SF on offspring were more pronounced in males, once again, supporting sex differences.[57] Similar to IH, changes in gene methylation patterns for PPARα activation (critical for fatty acid oxidation, ketogenesis,[58] and hepatic gluconeogenesis) were seen in male offspring exposed to SF compared to controls.[57] In a separate study, offspring exposed to gestational SF had epigenetic changes resulting in overexpression of the FoxO1 gene, a transcription factor that plays an important role in gluconeogenesis and glycogenolysis.[55] Taken together, these findings suggest that SF exposure, especially in males, changes the offspring's ability to regulate glucose and lipid metabolism, increasing risk of future metabolic disease. Alterations in offspring metabolism may, in part, be due to an integrated stress response involving cortisol and sympathetic activation.[59] Offspring of double mutant mice of integrated stress response genes CHP and GADD34 (unable to mount a stress response) exposed to SF did not have metabolic perturbations as seen in normal mice offspring exposed to SF.[59] Importantly, postnatal physical activity implemented early in SF-exposed offspring reduced FoxO1 acetylation and methylation to levels similar to controls.[55]

The evidence from rodent models is compelling; however, it must be underscored that unlike humans, mice and rodents are born with very little fat and size at birth is in part due to the size of the litter and driven more by lean body mass. In summary, evidence from these rodent models suggests distinct mechanisms whereby maternal IH results in normal or low BW and subsequent accelerated postnatal growth, and maternal SF results in normal BW followed by later metabolic derangement.

Human studies: strong link between SDB and birthweight outcomes

Over 30 published reports described a strong association between maternal SDB and birth outcomes in humans, supporting that mechanisms and outcomes in rodent models may have translational relevance. In accordance with the DOHaD model, infants born with IUGR/SGA or LGA are both at risk for future metabolic diseases such as obesity and T2D.[60] Notably, while the purpose and study population were clearly defined in most reports, most lacked power for infant outcomes, made a single assessment of SDB during pregnancy (instead of multiple measures over gestation),

Table 2. Overview of studies conducted in humans in which the association between SDB and infant growth outcomes was examined

Study author and year	Sample size	Outcome(s)	Type of assessment for SDB	Study design	Timing of assessment SDB	Findings
Ayrum, 2011[1]	400	Birth weight	Self-report snoring	Cross-sectional	Labor	–
Bassan, 2016[90]	44	Birth weight; neurological exam	Questionnaire and WatchPAT	Prospective	2nd trimester	–
Bin, 2016[93]	636,227	LGA, SGA	ICD9 code	Retrospective	Previous year	+LGA, −SGA
Bourjeily, 2010[4]	1000	LBW, SGA	Self-report snoring	Cross-sectional	Labor	–
Chen, 2012[9]	4746	LBW, SGA	ICD9 code	Retrospective	Previous year	+
Facco, 2014[69]	188 (1st trimester) 128 (3rd trimester)	SGA, LGA	WatchPAT	Prospective	1st and 3rd trimesters	–
Farabi, 2019[95]	18	%body fat	WatchPAT	Prospective	3rd trimester	±
Franklin, 2000[7]	502	SGA	Questionnaire	Retrospective, cross-sectional	Labor	+
Fung, 2013[31]	371 Questionnaire 41 PSG	SGA/fall in growth percentile >33%	Questionnaire and PSG	Prospective	3rd trimester	+
Ge, 2016[80]	3079	SGA, LGA, LBW	Questionnaire	Prospective	1st and 3rd trimesters	+LGA, +Macrosomia, −SGA
Guilleminault, 2000[91]	267	BW	Questionnaire	Prospective	1st trimester	–
Howe, 2015[94]	633	SGA, LGA	Questionnaire	Prospective	3rd trimester	+ LGA
Higgins, 2011[88]	4074	Birthweight	Questionnaire	Prospective	Labor	+ Birth weight
Kneitel, 2018[67]		SGA/fall in growth percentile >33%	PSG	Retrospective	All gestations	+
Ko, 2013[70]	276	SGA	Questionnaire	Prospective	3rd trimester	–
Leung, 2005[92]	247	BW	Questionnaire	Prospective	1, 2, 3rd trimesters	–
Louis, 2010[12]	57	Birth weight, SGA	PSG	Prospective	All trimesters	+ Birth weight; −SGA
Louis, 2012[87]	175	Birth weight	PSG	Prospective	All trimesters	–
Louis, 2014[66]	55,781,965	poor fetal growth	ICD9 code	Retrospective	Not defined	–
Micheli, 2011[64]	1091	LBW, SGA	Questionnaire	Prospective	3rd trimester	+LBW, −SGA
Miyagawa, 2011[68]	179	SGA	Oxygen saturation	Prospective	3rd trimester	1/22 infants born SGA in OSA group (4.5%); 4/157 in no OSA group (1.5%)
O'Brien, 2013[13]	1689	SGA,LGA	Questionnaire	Prospective	3rd trimester	+
Okun, 2018[81]	439	SGA, LGA	Questionnaire	Prospective	3rd trimester	+LGA (comorbid insomnia and snoring); −SGA
Olivarez, 2011[71]	220	SGA	Questionnaire	Prospective	1st trimester	–
Owusu, 2013[84]	232	LBW	Questionnaire	Cross-sectional	Labor	–
Pamidi, 2016[65]	230	SGA	PSG	Prospective	3rd trimester	+
Perez-Chada, 2007[72]	447	SGA	Questionnaire	Cross-sectional	Labor	–
Pien, 2014[85]	105	LBW	PSG	Prospective	1st and 3rd trimesters	–
Ravishankar, 2015[73]	148	Birth weight, IUGR, placental hypoxia	ICD9 codes for OSA, questionnaires snorers and controls	Retrospective case-control	Delivery for snorers and controls/OSA was previous year	+ Birth weight, + IUGR,
Sahin, 2008[74]	316	Birth weight	PSG	Prospective	3rd trimester	+
Sarberg, 2014[75]	500	SGA	Questionnaire	Prospective	1st and 3rd trimesters	–
Sharma, 2016[86]	209	LBW	Questionnaire	Prospective	1, 2, 3rd trimesters	–

(*Continued*)

Table 2. (*Continued*)

Study author and year	Sample size	Outcome(s)	Type of assessment for SDB	Study design	Timing of assessment SDB	Findings
Spence, 2017[76]	305,001	Poor fetal growth	ICD9 Code	Retrospective Cohort	previous year	–
Tauman, 2012[77]	246	LBW, SGA	Questionnaire	Cross-sectional	Labor	–
Telerent, 2018[79]	155	LGA, SGA	WatchPAT	Prospective	3rd trimester	+ LGA, −SGA
Ugur, 2012[89]	465	Birthweight	Questionnaire	Prospective	3rd trimester/ Labor	±(p = 0.055)
Yin, 2008[78]	178	IUGR	Oxygen saturation	Prospective	3rd trimester	–
Mechanistic studies						
Bourjeily, 2015[102]	190	Fetal markers of well-being	ICD9 code	Case–control	previous year	Estriol lower in OSA; AFP not different after BMI adjusted
Bourjeily, 2015[102]	190	Placental markers of angiogenesis and well-being	ICD9 code	Case-control	Previous year	PAPP-A lower in OSA
Khan, 2017[99]	64	Oxidative and carbonyl stress	ICD9 codes for OSA, questionnaire for controls	Case–control	Previous year	Lower stress markers in OSA
Kidron, 2019[105]	53	Placental length, weight, thickness. Gene expression of VEGF, VEGF receptor, leptin, and PIGF	WatchPAT	Prospective	3rd Trimester	Higher placental weight of women with OSA ($n = 10$) after BMI controlled for. Leptin gene expression higher in placenta of OSA
Koken, 2007[97]	83	Oxidative and carbonyl stress	Questionnaire	Prospective, case-control	2nd or 3rd trimester	GSH lower and MDA higher in snorers
Olivarez, 2010[96]	100	Fetal heart rate	PSG	Prospective	3rd trimester	No correlation between fetal heart rate and OSA symptoms
Salameh, 2018[104]	313	Markers of fetal and placental Wellbeing	Questionnaire	Cross-sectional	Labor	No difference in markers of fetal well being between snorers and non snorers
Salihu, 2015[106]	67	Telomere length	Questionnaire	Cross-sectional	Labor	Shorter telomeres in OSA
Tauman, 2011[98]	122	Fetal erythropoiesis	Questionnaire	Cross-sectional	Labor	+ Erythropoiesis, IL-6, and EPO with OSA
Tauman, 2015[108]	62 (2 days) 52 (1 year)	Infant neurodevelopment	Questionnaire and WatchPAT	Prospective	2nd trimester	−Birth weight, −Neurodevelopmental changes

Negative finding (–); Positive finding (+); Trend (±); IUGR, intrauterine growth restriction; LBW, low birth weight; LGA, large for gestational age; SGA, small for gestational age.

did not measure severity of SDB, and body composition at birth was rarely measured (Table 3). In 32 of the 48 studies, investigators attempted to at least partially control for important confounding variables: maternal age, gestational age, BMI, smoking, and preexisting hypertension, which could highly influence growth outcomes (Table 3). It is also notable that all humans studies are descriptive in nature, so cause and effect cannot be determined. Further, even after attempting to control for known confounders, there may still be unmeasureable or unknown variables which can influence study outcomes.

IUGR/SGA. 27 studies were reviewed in which SGA or IUGR were reported as outcomes, three of which were meta-analyses. Ding *et al.* reported a significant association between SDB and IUGR across 8923 women in 11 studies (OR = 1.44 [95% CI: 1.22–1.71]).[61] Similarly, Warland *et al.* reported by meta-analysis that SGA was significantly associated with SDB across 9478 women (13 studies) in which SDB was measured subjectively (adjusted OR = 1.6 [1.1–2.2]) and across 56,423,715 women (7 studies) which included objective measures (adjusted OR = 1.4 [1.1–1.9]).[62] In contrast, Brown *et al.* found no significant association between SDB and SGA by meta-analysis of 21 studies (adjusted OR 1.19, [0.94–1.51]).[63] Findings were mixed across the 24 original (non-meta-analysis) studies reviewed for this manuscript. While investigators reported an association between SDB and growth restriction in nine studies,[7,9,13,31,64–68] no significant association was detected across 15 studies.[4,12,69–81] Mixed findings may be due to lack of consistent assessment of SDB, the severity of the SDB and provocation of IH, and a lack of adequate power

Table 3. Quality review of human studies included in systematic review

Observational studies														
Study author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Ayrum 2011[1]	Y	Y	NR	Y	N	N	N	N	N	N	Y	NR	NA	N
Bassan, 2016[90]	Y	Y	NR	Y	N	Y	Y	N	Y	N	Y	Y	NR	N
Bin, 2016[93]	Y	Y	NA	Y	N	Y	CD	N	Y	N	Y	NR	NA	Y
Bourjeily, 2010[4]	Y	Y	Y	Y	N	N	N	Y	Y	N	Y	NR	Y	Y
Chen, 2012[9]	Y	Y	NA	Y	N	Y	CD	N	Y	N	Y	NR	NA	Y
Facco, 2014[69]	Y	Y	Y	Y	N*	Y	Y	Y	Y	Y	Y	NR	Y	N
Farabi 2019[95]	Y	Y	NR	Y	N*	Y	Y	Y	Y	N	Y	NR	N	Y*
Franklin, 2000[7]	Y	Y	NA	Y	N	N	CD	N	N	N	Y	NR	NA	Y*
Fung, 2013[31]	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	NR	Y	Y
Ge, 2016[80]	Y	Y	Y	Y	N*	Y	CD	Y	N	Y	Y	NR	Y	Y
Guilleminault, 2000[91]	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	NR	NR	N
Higgins, 2011[88]	Y	Y	NR	Y	N*	Y	CD	N	Y	N	Y	NR	NA	N
Howe, 2015[94]	Y	Y	Y	Y	N	Y	N	N	Y	N	Y	NR	NR	Y*
Kneitel, 2018[67]	Y	Y	NR	Y	Y	Y	CD	N	Y	N	Y	NR	NA	Y
Ko, 2013[70]	Y	Y	Y	Y	N	Y	CD	N	Y	N	Y	NR	Y	Y*
Leung, 2005[92]	Y	Y	NR	Y	N*	Y	Y	Y	Y	Y	Y	NR	Y	N
Louis, 2010[12]	Y	Y	NR	Y	N	Y	CD	N	Y	N	Y	NR	NR	Y
Louis, 2012[87]	Y	Y	N	Y	N*	Y	CD	N	Y	N	Y	NR	Y	Y
Louis, 2014[66]	Y	Y	NA	Y	N	N	CD	N	Y	N	Y	NR	NA	Y
Micheli, 2011[64]	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	NR	NA	Y*
Miyagawa, 2011[68]	Y	N	NR	Y	N	Y	Y	N	Y	N	Y	NR	NR	Y*
O'Brien, 2013[13]	Y	Y	Y	Y	Y	Y	CD	Y	Y	N	Y	NR	NA	Y
Okun, 2018[81]	Y	N	NR	Y	N	Y	CD	N	Y	N	N	NR	NA	Y
Olivarez, 2011[71]	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	NR	N/A	Y*
Owusu, 2013[84]	Y	Y	Y	Y	N	N	N	N	Y	N	N	NR	Y	N
Pamidi, 2016[65]	Y	Y	N	Y	Y	Y	CD	Y	Y	N	Y	NR	Y	Y*
Perez-Chada, 2007[72]	Y	N	NR	Y	N	N	CD	N	Y	N	Y	NR	NA	Y
Pien, 2014[85]	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y
Sahin, 2008[74]	Y	Y	NR	Y	N	Y	CD	N	Y	N	Y	NR	NR	N
Sarberg, 2014[75]	Y	Y	NR	Y	N	Y	Y	Y	N	Y	N	NR	N	N
Sharma, 2016[86]	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	NR	Y	N
Spence, 2017[76]	Y	Y	NA	Y	N	N	Y	N	Y	N	Y	NR	NA	Y
Tauman, 2012[77]	Y	Y	NR	Y	N	N	N	Y	N	N	Y	NR	NA	Y*
Telerent, 2018[79]	Y	Y	NR	Y	N	Y	CD	N	Y	N	Y	NR	Y	Y
Ugur, 2012[89]	Y	Y	NR	Y	N	Y	CD	N	Y	N	Y	NR	NR	N
Yin, 2008[78]	Y	Y	NR	Y	Y	N	CD	Y	Y	N	Y	NR	NA	N
Case-Control Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12		
Ravishankar, 2015[73]	Y	Y	N	Y	Y	Y	NR	N	N	Y	Y	N		
Mechanistic studies														
Observational Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Kidron, 2019[105]	Y	Y	NR	Y	N	Y	Y	N	Y	N	Y	NR	NR	Y
Salameh, 2018[104]	Y	Y	N	Y	N	N	CD	N	Y	N	Y	NR	NA	N

(*Continued*)

Table 3. (*Continued*)

Observational studies														
Study author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Salihu, 2015[106]	Y	Y	NR	Y	N	N	CD	N	Y	N	Y	Y	NA	N
Tauman, 2011[98]	Y	Y	NR	Y	N	N	CD	Y	Y	N	Y	NR	NA	Y
Tauman, 2015[108]	Y	Y	NR	Y	N	Y	CD	N	Y	N	N	NR	NA	Y*
Olivarez, 2010[96]	Y	Y	NR	Y	Y	N	CD	N	Y	N	Y	NR	NA	Y*
Case-Control Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12		
Bourjeily, 2015[102]	Y	Y	N	N	Y	Y	NR	N	N	Y	NR	Y*		
Bourjeily, 2015[101]	Y	Y	N	N	Y	Y	NR	N	N	Y	NR	Y*		
Khan, 2017[99]	Y	Y	N	Y	Y	Y	NR	N	N	N	NR	Y		
Koken, 2007[97]	Y	Y	N	Y	Y	Y	NR	N	Y	Y	NR	N		

Y = Yes; N = No; NR = Not Reported; NA = Not Applicable; N*=power analysis reported but not for outcome of interested; Y*=partial control of confounders (maternal age, gestational age, BMI, hypertension, diabetes, or smoking)

Descriptive Studies:	Q1. Research question or objective in this paper clearly stated?; Q2. Study population clearly specified and defined?; Q3. Participation rate of eligible persons at least 50%; Q4. All subjects selected or recruited from similar populations? Inclusion/exclusion criteria prespecified and uniformly applied?; Q5. Sample size justification or power estimate?; Q6. Were the exposure(s) measured prior to the outcome(s)?; Q7. Timeframe sufficient so one could reasonably expect to see an association between exposure and outcome?; Q8. Exposures that vary in amount or level, did study examine different levels of exposure as related to outcome?; Q9. Exposures clearly defined, valid, reliable, and implemented consistently?; Q10. Exposure assessed more than once?; Q11. Outcome measures clearly defined, reliable, and implemented consistently?; Q12. Outcome assessors blinded to exposure?; Q13. Was loss to follow-up after baseline 20% or less?; Q14. Were potential confounding variables (maternal age, gestational age, BMI, hypertension, diabetes, or smoking) measured and adjusted for?
Case-Control Studies	Q1. Research question or objective in this paper clearly stated and appropriate?; Q2. Study population clearly specified and defined?; Q3. Include a sample size justification?; Q4. Controls selected or recruited from same/similar population that gave rise to cases?; Q5. Definitions, inclusion/exclusion criteria valid, reliable, and consistently implemented?; Q6. Cases clearly defined and differentiated from controls?; Q7. If less than 100% of cases and controls selected, were those chosen selected at random?; Q8. Use of concurrent controls?; Q9. Able to confirm exposure/risk occurred prior to development of condition or event defined as case?; Q10. Measures of exposure/risk clearly defined, valid, reliable, and consistently implemented?; Q11. Assessors of exposure/risk blinded to status of participants?; Q12. Key potential confounding variables (maternal age, gestational age, BMI, hypertension, diabetes, or smoking) measured and adjusted for?

Studies were reviewed using the NIH tools for observational or case–control studies.

(Table 3). Timing of maternal SDB assessment varied widely across studies with the majority of subjective SDB assessment done at time of delivery. Type of SDB assessment was also highly varied; the majority of studies included self-reported symptoms of snoring, which does not reflect severity of SDB. Of the 19 studies, only five[13,31,65,71,78] were powered to detect an association between SDB and SGA as the primary outcome; a positive association was reported in three of the studies and no association was reported in two (Table 2). In the majority of the studies ($n = 20$), investigators controlled (at least in part) for important maternal variables (BMI, hypertension, diabetes, smoking) that could influence infant growth outcomes (Table 3). Studies in which severity of OSA is measured objectively throughout gestation (pre-pregnancy through 3rd trimester) in relation to SGA are lacking. In summary, the results from descriptive studies in humans are mixed in support of an association between SDB and SGA which may be due to a lack of consistency of measurement of SDB, a lack of power or other confounding variables that were not measured.

BW: Results from three meta-analyses supported a relationship between SDB and low BW with similar ORs (OR = 1.75 [95% CI: 1.33–2.32],[61] 1.67 [1.0–2.78],[63] 1.39 [1.14–1.65][82]), while Li *et al.* concluded that there was no association between SDB and BW in a meta-analysis across 8749 women (15 studies).[83] OSA diagnosis (documented by ICD-9) was associated with an increased risk of low BW (<2500 g; OR = 1.76 [1.28–2.40], $n = 4746$).[9] Further, self-reported frequent snoring in the 3rd trimester was associated with low BW (RR = 2.6 [1.2–5.4]); however, after adjustment for pre-maturity, snoring was no longer associated with low BW.[64] SDB was not associated with increased risk of low BW in three smaller studies,[84–86] none of which were powered for BW as the outcome. Louis *et al.* reported that compared to women with obesity alone, women with OSA had infants with significantly lower BW (3288 ± 590 vs. 3013 ± 968 g).[12] Diagnosis of OSA was made either before or during pregnancy and continuous positive airway pressure use/adherence was not reported, important because treatment of OSA could have affected BW in the OSA group. In three studies where BW was compared between women with OSA and those without, one group of investigators reported higher BW in women with OSA[71] and two reported no significant difference.[74,87] Higgins *et al.* reported significantly higher BW in infants of women with a positive Berlin Score (high risk of OSA),[88] but Ugur *et al.* reported slightly lower BW in infants of women with a positive Berlin score.[89] Discrepant findings may be due to multiple factors. There was inconsistent timing of SDB measurement throughout the studies from pre-pregnancy to delivery, severity was not consistently assessed, and the degree of IH was usually unreported. BW was used differently across studies; five of the studies used low BW (<2500 g) as a categorical variable[9,64,84–86] (requiring a larger sample to detect an association), while the other 10 studies used BW as a continuous variable.[1,71,74,77,87,90–92] Further, none of the studies were powered on

the BW outcome and body composition was not assessed. Importantly, low BW is different from IUGR as it is not corrected for gestational age (i.e., a preterm infant is expected to have a lower BW but may or may not have growth restriction). In seven of the studies found, investigators made an effort to at least partially adjust for confounding factors, while in nine of the studies, there was no control for confounding factors (Table 3). In summary, overall results from studies support an association between SDB and low BW, but, in over half of the studies, potential confounding variables were not controlled thus limiting the strength of evidence to support this association.

LGA: One meta-analysis supported an association between SDB and LGA across 678,310 women (7 studies) (OR = 1.6 [95% CI: 1.3–1.9]),[62] while the additional four meta-analyses did not include LGA as an outcome. In eight studies, investigators reported an association between SDB and LGA.[13,69,79–81,93,94] Seven groups found a significant association between SDB symptoms and LGA (BW > 90th percentile) and one group reported a significant association between SDB and macrosomia (defined as BW > 97th percentile). Maternal diagnosis of OSA in the year before or during pregnancy (across 636,227 women) was significantly associated with increased risk of LGA in a large, retrospective cohort (adjusted OR = 1.27 [1.04–1.55], $p < 0.05$), after adjustment for obesity.[93] Similarly, women who self-reported apnea had increased frequency of LGA compared to women who denied apnea (22.4% vs. 12.8%, $p = 0.049$).[13] Maternal report of pregnancy-onset breathing pauses during sleep was associated with LGA (OR = 3.5 [95% CI: 1.3–9.6], $p = 0.01$).[94] OSA+ women (identified via ICD-9 codes) had higher rates of macrosomia (BW > 97th percentile), but this group had a significantly higher rate of maternal diabetes and higher body mass index (BMI) which could also explain the macrosomia rate.[73] Telerent *et al.* reported that the occurrence of LGA was significantly more frequent in infants born to mothers who had mild sleep apnea compared to those who did not.[79] The investigators studied women in their 3rd trimester and excluded women with more severe sleep apnea (apnea hypopnea index [AHI] > 15), which might be expected to result in placental insufficiency and attenuated growth.[79] Facco and colleagues, on the other hand, did not find an association between OSA (diagnosed using in-home objective measurement) and LGA (19.4% LGA in no SDB group vs. 12.5% in Moderate/Severe SDB group).[69] The lack of significant finding for this study may be due to the fact that it was designed to look at maternal and not fetal outcomes and a higher cutoff for definition of LGA (>95th percentile). Across studies, there are limited data on the classes of obesity, and no measures of newborn body composition. We recently completed a study in which we examined the relationship between severity of maternal OSA and infant % body fat in maternal obesity (BMI 30–40). There was no correlation between severity of OSA (by AHI) and infant % body fat ($r = 0.34$, $p > 0.05$)[95]; however, overnight minimum oxygen saturation was correlated with infant % body fat, suggesting that increasing severity of maternal OSA (with greater reduction oxygen saturation) was related to higher newborn fat ($r = -0.63$, $p = 0.02$).[95] Importantly, none of the studies were powered on LGA, the assessment of SDB symptoms were variable and often did not include the degree of hypoxia, and the timing of assessment across studies was inconsistent. However, in seven of the eight studies, investigators attempted to control for confounding factors (Table 3). The available evidence supports an association between more severe maternal SDB and fetal overgrowth even after controlling for maternal BMI (in most studies).

Clinical studies investigating potential mechanisms

Some investigators studied the relationship between SDB in pregnancy and biomarkers that may indicate potential mechanisms for the link between SDB in pregnancy and fetal outcomes.

SDB and fetal stress. Maternal apneas were accompanied by fetal heart rate decelerations in three of four women with OSA,[74] suggesting increased fetal stress with maternal apnea. In contrast, Olivarez and colleagues found no association between degree of oxygen saturation and fetal heart rate in 20 women with OSA (severity of OSA not reported).[96]

SDB, inflammation and oxidative stress. Koken and colleagues[97] reported that markers of oxidative stress (maldondialdehyde [MDA], Myeloperoxidase [MPO]) were higher and an anti-oxidant marker (Glutathione peroxidase [GSH-Px]) was lower in plasma of women who reported snoring compared to non-snorers. Of note, women who snored were older with higher BMI, which may confound the relationships reported, and the gestational week of blood collection was not controlled. In another study, women who reported snoring during pregnancy ($n = 48$) had higher levels of the inflammatory cytokine IL-6 in cord blood compared to women who denied snoring ($n = 75$).[98] Erythropoietin and nucleated (immature) red blood cell counts were higher in the cord blood of women who reported snoring,[98] supporting that exposure to SDB in utero may result in hypoxic changes in the fetus. In contrast, Khan and colleagues reported in a retrospective study that women with diagnosed OSA (vs. self-reported non-snorers) had *lower* oxidative and carbonyl stress markers (Advanced glycation end products [AGE] and advanced oxidation protein products [AOPP]), but *higher* anti-oxidative stress markers (total antioxidant capacity [TAC]).[99] Taken together, these findings support that SDB, and especially OSA, may increase fetal exposure to oxidative stress, inflammation, and hypoxia-induced compensatory enhanced erythropoiesis, however further study is warranted as the findings are inconsistent. This is interesting as inflammation and oxidative stress may exacerbate IR.[100,101]

SDB and placental changes. Placental expression of carbonic anhydrase IX (CAIX), a marker of hypoxia, was higher in women who snored or with OSA compared to non-snoring women ($n = 47$).[73] Fetal normoblastemia (immature red blood cells), a sign of exposure to hypoxia, was significantly higher in placentas of women who snored/had OSA. However, women who snored and women with OSA had significantly higher BMI and higher rates of chronic hypertension and diabetes (vs. non-snorers), which likely contributed to differences in biomarkers (preeclampsia rates were similar between groups).[73] Women with OSA had lower levels of placenta-associated plasma protein-A (PAPP-A)[102] and lower estriol levels[103] compared to women without OSA, suggesting poorer placental and fetal well-being, which could affect growth. Salameh *et al.*, however, showed no differences in markers of fetal well being (PAPP-A, AFP, uE3, hCG, inhibin-A) between snorers and non-snorers.[104] Women with mild OSA (mean AHI 7.8 ± 2.7), objectively measured in the 3rd trimester, had significantly higher placental weight and higher placental leptin mRNA expression compared to women without OSA, even after controlling for maternal BMI.[105] Placental weight was positively correlated with infant adiposity (measured by skinfolds).[105] This was a small study and a power analysis was not reported; however, the findings support that mild OSA may result in placental changes that contribute to increased infant adiposity. The effect of OSA on maternal IR was not explored in any of these studies as a possible mechanism for the increased in adiposity.

SDB and chronic disease risk. Salihu and colleagues reported that women at high risk of OSA (measured by Berlin Questionnaire) had neonates with shorter telomeres than women at low risk of OSA ($n = 64$ women).[106] Telomere length is indicative of chromosomal aging and has been proposed as a mechanism contributing to chronic disease development,[107] suggesting that exposure to OSA could have long-term implications in accordance with DoHad theory.[42]

Long-term implications of SDB exposure in humans. In a single longitudinal study, BW between infants born to mothers with SDB were similar to controls.[108] However, despite similar neurological development, at 1 year, mothers with SDB vs. control were more likely to report infant snoring (41.7% vs. 7.5%, $p = 0.004$).[108] Human studies in which body composition of the infant, and longer term metabolic phenotyping of offspring into childhood and young adulthood are needed to elucidate if SDB exposure that increases risk for future offspring metabolic disease as studies in rodents suggest.

Discussion

SDB is a common problem that worsens throughout pregnancy. Outside of pregnancy, SDB is often associated with obesity, a metabolic syndrome characterized by IR, glucose, and triglyceride elevations that are expected to enhance fetal growth. However, obese women are also at risk of endothelial dysfunction, hypertensive disorders, placental insufficiency and the development of preeclampsia, which could attenuate fetal growth independent of the effect of SDB. Although mechanistic studies using rodent models of SF and IH during pregnancy suggest that these exposures negatively impact long-term offspring metabolic outcomes, investigations in humans have been discrepant, focused mainly on BW, and lacked a focus linking underlying mechanisms to long-term outcomes of gestational SDB exposure. Further, all studies in humans were descriptive. While most investigators made an effort to control for known confounding factors ($n = 32$; Table 3), there is significant possibility that unmeasured and unknown variables could influence the study outcomes. Despite these limitations, the overall evidence suggests a link between SDB, characterized by IH, SF or both, and offspring SGA and LGA, both of which are related to increased future obesity and metabolic disease risk.

Rodent models suggested that pathophysiological changes accompanying SDB during pregnancy may have lasting effects on metabolic regulation in offspring, and BW in offspring may not demonstrate the true deleterious effects of exposure to gestational SDB. Indeed, mice born to mothers exposed to SF had similar BW to control mice; however, as the mice reached adulthood, the exposed mice had significantly more metabolic abnormalities.[54–56,59] Further, animal models suggested that SDB exposure may have a sex-dependent effect.[49,55,59] This supports previous findings that males may be more vulnerable to short-term changes or exposures in the womb, while females may not manifest differences until later, especially in the context of postnatal longer term exposures.[109] There are many limitations to rodent models. Rodent gestation demonstrates marked differences in placental development which result in no spontaneous preeclampsia. The further birth of multiple pups with minimal fat mass at birth, and the strong influence of postnatal development(including fat accretion) make translation to human pregnancies difficult. Importantly, rodents do not spontaneously develop SDB. Instead, investigators mimicked a condition that would not normally exert influence on rodent physiology. Thus, growth and body composition in rodents at birth will not closely reflect what could be expected in humans. Despite these limitations, rodent models support that exposure to gestational SDB may have negative long-term outcomes for the metabolic health of the offspring.

Studies in humans suggested a link between maternal SDB and both SGA and LGA, but a number of considerations impact interpretation of the data. A salient problem across human studies was inconsistency in reporting of infant outcomes. Measurement of SDB also varied widely. While some studies used objective measurement of SDB (such as laboratory or in home polysomnography),[65,69,74,79,85,87] others used a single question about presence of snoring.[1,4,7,72,77,84] Importantly, the majority of studies were not powered to detect a relationship between SDB and infant outcomes. Only five were powered on an infant outcome,[13,31,65,71,78] and none on infant body composition. Investigators found an association in three of the studies and no association in two (Table 2). Thus, many studies may not have detected an association due to inadequate power. Timing of SDB assessment varied widely across studies in humans. Symptoms of SDB (i.e. snoring) were assessed at delivery in many studies, while others assessed SDB earlier in pregnancy. Severity of SDB was not typically reported. It is speculated that women who enter pregnancy with chronic OSA have higher risk for altered placental function that would result in compromised nutrient supply and placental perfusion as well as fetal under-development and growth restriction. Alternatively, we hypothesize that mild SDB without significant hypoxemia and a deleterious effect on placental development may exacerbate pregnancy IR, promoting nutrient excess and fetal overgrowth (Fig. 1). It is possible, and highly likely, that mild SDB either develops or worsens over pregnancy in those affected by obesity, but in many, never becomes severe enough to compromise placental development and perfusion. Thus, while mild IH and SF are speculated to increase oxidative stress and inflammation to some degree, the placenta may still develop normally. If maternal IH and/or SF worsen IR, excess fetal nutrient exposure may result in LGA. Alternatively, with more severe IH, placental insufficiency may attenuate fetal overgrowth in spite of an effect on worsening maternal IR and nutrient excess in late gestation. Assessment of SDB symptoms (i.e. presence/absence of snoring) only at the end of pregnancy provides incomplete information about the timing and severity of an exposure that evolved over gestation. It is also possible that SDB serves as a marker for other underlying conditions, such as obesity, gestational hypertension, IR, inflammation, or elevated glucose levels, which mediate many of the alterations in birth outcomes. Future, more highly controlled, studies in which SDB is objectively categorized into mild/moderate or severe OSA, its occurrence measured in in the 1st, 2nd, and 3rd trimesters, and its associated complications including IR, inflammation, hypoxia, oxidative stress, altered glucose and lipid metabolism, elevated blood pressure, and endothelial dysfunction are better quantified will help to delineate if there truly are opposing effects of the SDB spectrum on infant outcomes, allowing for better understanding of SDB as an exposure.

Based on rodent models, it is also possible that BW may be normal in infants exposed to SDB in utero, but body composition (percentage of body fat) may differ.[110] Higher neonatal adiposity is associated with increased risk for childhood obesity. Results from our lab indicate a potential relationship between severity of maternal OSA and infant adiposity. In a recent study, we found that infant % body fat, measured at 2 weeks postpartum, was significantly correlated with overnight oxygen desaturation in a group of women with obesity who had previously undiagnosed mild

OSA, possibly mediated by higher 24-h glycemic patterns as measured by continuous glucose monitoring.[95] We also found a positive correlation between OSA severity and fasting free fatty acids as well as hepatic IR,[95] suggesting potential mechanisms by which SDB exacerbates IR in the mother and contributes to excessive infant adiposity. Future studies should include measurement of infant body composition as infant adiposity to provide a stronger indicator of future disease risk rather than BW alone.[44]

Mechanistic studies in humans looking at the effects of SDB during pregnancy showed evidence of hypoxia at the level of the placenta, increased inflammation and oxidative stress, and suggested increased risk of disease development in the offspring (telomere length). However, these studies are limited by very small sample sizes, lack of objective measurement of SDB, and were not carefully controlled. Controlled studies in which participants are carefully enrolled based on like phenotypes are needed to elucidate mechanisms behind the relationship between SDB, inflammation and IR, such as the role of HIF1-α, a transcription factor induced by hypoxia, linked to both inflammation and IR. In Fig. 1, we highlight other potential mechanisms by which SDB could exacerbate IR including at the level of smooth muscle, adipose tissue, or the liver, as well as effects on hormones, such as GLP-1 and cortisol, and sympathetic stimulation.

In summary, prevailing evidence across human and rodent models implicates in utero exposure to SDB as a developmental origin of future metabolic health. Since OSA is tightly linked to obesity, prenatal screening of obese pregnant women for risk of SDB may help to identify women who have undiagnosed OSA for treatment prior to pregnancy. Prenatal counseling that directly promotes weight loss prior to pregnancy may help to further prevent worsening SDB with pregnancy. Treatment of SDB may be important to eliminate the exposure of hypoxia and alleviate exacerbation of the IR of pregnancy resulting in altered glucose and lipid metabolism and inflammation. While there remain no large prospective studies in humans investigating the impact of SDB treatment on offspring outcomes, the evidence suggests that treatment targeting factors such as IH and SF may reduce future offspring disease risk. Prospective human trials over the course of pregnancy designed to discern the mechanistic pathways by which SDB influences placental development, fetal growth, and future risk of offspring metabolic disease are of paramount importance to inform timing and type of interventional therapy. With the ever-rising prevalence of obesity both in pregnancy and in childhood, understanding if SDB during pregnancy, still largely unrecognized in clinical practice, has important long-term implications for offspring is vital as it may be one modifiable contributor of significant morbidity from metabolic disorders in adulthood.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174420000355

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