AJPM FOCUS
INCLUSIVITY IN PEOPLE, METHODS, AND OUTCOMES
REVIEW ARTICLE

A Scoping Review of the Relationship Between Maternal BMI and Offspring Incidence of Respiratory Infection: Where Do We Go From Here?

Anastasia V. Warmington, RN, MSc,[1] Dawn M.E. Bowdish, PhD,[1,2] Diana Sherifali, RN, PhD, CDE,[3] Deborah M. Sloboda, PhD[4,5,6,7]

Introduction: Pregnancy complications, including high maternal BMI, are associated with altered early development and child health outcomes. A growing body of work links the prenatal environment, specifically maternal BMI, with respiratory infections in offspring. In this rapid review, the authors review the literature supporting the hypothesis that high maternal BMI during pregnancy is associated with childhood respiratory infection incidence.

Methods: The authors employed systematic search criteria in known databases—EMBASE, EMCARE, MEDLINE, CINAHL, and PsychINFO—searching from inception to January 2023. Included were primary research studies that involved (1) human pregnancy, (2) pregravid or gestational overweight or obesity, and (3) childhood respiratory infection with or without hospitalization.

Results: Only 7 population-based cohort studies met the criteria, investigating maternal BMI as an exposure and childhood respiratory infection as an outcome (age 6 months to 18 years). Therefore, the authors conducted a qualitative analysis, and outcomes were reported. The authors found that >85% of the albeit few published studies support the hypothesis that maternal BMI may have independent and profound consequences on respiratory infection risk across childhood.

Discussion: This area of research needs large-scale, well-controlled studies to better understand the relationship between maternal BMI and childhood respiratory infection. Possible resources such as cohort catalogs and combined databases are discussed. These findings add to the growing evidence that early environmental factors influence lifelong respiratory health. By incorporating a life course approach to infectious disease risk, policy makers can put this research to work and target health vulnerabilities before they arise.

INTRODUCTION

Respiratory infections are among the most common causes for pediatric emergency department visits in North America and are responsible for almost 20% of all infectious deaths of children aged <5 years worldwide.[1–4] Children who survive these infections are at risk of serious long-term consequences. Indeed, recurrent respiratory infection in childhood has been identified a predictor of asthma, poor lung function, and chronic obstructive

From the [1]Department of Medicine, McMaster University, Hamilton, Ontario, Canada; [2]Firestone Institute for Respiratory Health, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada; [3]School of Nursing, McMaster University, Hamilton, Ontario, Canada; [4]Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada; [5]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada; [6]Farncombe Family Digestive Health Research Institute, Hamilton, Ontario, Canada; and [7]Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada

Address correspondence to: Deborah M. Sloboda, PhD, Department of Biochemistry and Biomedical Sciences, McMaster University, 1280 Main Street West, Hamilton, ON Canada L8S 4L8. E-mail: sloboda@mcmaster.ca.

2773-0654/$36.00
https://doi.org/10.1016/j.focus.2024.100234

pulmonary disease in adulthood, one of the leading causes of hospitalization and the third most common cause of adult mortality worldwide.[5–10] Globally, particularly in low- and middle-income countries, childhood environment conditions (water, sanitation, hygiene), below optimal nutrition, and low birth weight are clearly linked to respiratory infection.[11–13]

A growing body of evidence points also to the early life environment, where factors arising during critical periods of development influence adaptations in lung and immune function, which could lead some children to be more susceptible to infectious illnesses and their consequences.[14] Thus, investigating early life risk factors in the context of respiratory infection susceptibility in childhood is critically important as a first step in preventing long-term lung damage and the global burden of respiratory disease. The prenatal environment is an undeniable factor influencing lifelong health and disease risk for offspring.[15] In particular, maternal metabolic homeostasis (including BMI and glucose metabolism) has been associated with negative consequences on the developing child. Rising global incidences of high BMI and adiposity make this one of the most common complications during pregnancy.[16] High pre-pregnancy BMI and excessive gestational weight gain are associated with increased risk of many obstetric and neonatal complications, including caesarean delivery, maternal infection, gestational hypertension, diabetes, chorioamnionitis, pre-eclampsia, preterm birth, and macrosomia.[16]

Although it is important to consider that children born preterm require more respiratory health service usage over time, the same is true for newborns that are large for gestational age—a risk factor in pregnancies complicated by high maternal BMI.[17] High maternal BMI is associated with adverse neonatal respiratory outcomes, including respiratory distress syndrome, chronic lung disease, and requirement for ventilatory support postnatally.[18] Beyond infancy, a high maternal BMI and excess gestational weight gain are consistently associated with childhood asthma,[19,20] bronchodilator use,[21] decreased lung function,[22] and wheezing.[23]

To date, the link between maternal BMI and adiposity and offspring noncommunicable disease risk has investigated changes to lung and immune function independently, but the emerging hypothesis that infectious disease risk may have early origins is gaining evidence. The authors set out to review whether there are sufficient published data on the hypothesis that maternal BMI may have independent and profound consequences on respiratory infection risk across childhood. By understanding the origins of the susceptibility to respiratory infections and applying a life course approach, it may be possible to begin to understand who is at risk and why.

METHODS

The authors conducted a systematic search of published articles between the years 1946 and 2023, which yielded 22,489 titles and abstracts (Appendix Figure 1, available online). Two additional articles were manually searched from relevant reference lists and added to title and abstract screening, with a total of 94 articles being reviewed for full-text screening (Appendix Figure 1, available online). Of the 22,489 titles and abstracts that were found using the selection criteria (Appendix 1, available online, and Appendix Table 1, available online), only 7 population-based cohort studies met the inclusion criteria. Studies that examined the relationship between maternal pregravid or gestational BMI and childhood respiratory infections in offspring aged from 6 months to 18 years were included in the review. According to assessments using the Effective Public Health Practice Project tool,[24] study quality ranged from moderate to strong for all studies (Table 1[25–31]). The studies were from a range of countries, reflecting different healthcare systems, prenatal care protocols, and levels of access to public health care. Study populations were predominantly from higher-income countries: Norway,[25] Taiwan,[26] Australia,[27] the United Kingdom,[28] Sweden,[29] Israel,[30] and the U.S.[31] Table 2[25–31] summarizes the characteristics of the studies. Because the search yielded such a limited number of studies with varying methodologies, a qualitative assessment and narrative summary were then completed.

RESULTS

All included studies recruited pregravid or pregnant participants and collected postnatal data to monitor for incidence of child respiratory and infectious outcomes. Five of the studies collected data from questionnaires, interviews, or surveys[25–27,31]; of the remaining 2, one study combined data from several birth, inpatient, and death registers[29]; the other sourced information from a single tertiary medical centre.[30] Total population sample sizes in the cohorts ranged from 2,778 to 838,756 mother–child pairs[27,29] (Table 2[25–31]).

To calculate maternal BMI, 5 studies collected self-reported height and weight obtained by interviews and questionnaires.[25–27,31] One study used a combination of self-reported height and measured weight to calculate BMI.[29] Two studies calculated BMI using records of measured height and weight.[28,30] Most studies based their categorization of obesity on WHO definitions of underweight (<18.5 kg/m^2), optimal weight (BMI of 18.5–24.9 kg/m^2), overweight (BMI of 25.0–29.9 kg/m^2), and obesity (BMI ≥30 kg/m^2).[25,27–29] In contrast,

Table 1. EPHPP Tool Quality Assessment Summary

Study	Håberg et al.[25]	Chen et al.[26]	Cameron et al.[27]	Rajappan et al.[28]	Videholm et al.[29]	Gutvirtz et al.[30]	Gutierrez et al.[31]
Are the individuals selected to participate in the study likely to be representative of the target population?	Somewhat likely	Somewhat likely	Somewhat likely	Very likely	Very likely	Very likely	Somewhat likely
What percentage of selected individuals agreed to participate?	<60% agreed	80%–100% agreed	80%–100% agreed	80%–100% agreed	Not applicable	Not applicable	Not applicable
Rank this section	Moderate	Strong	Strong	Strong	Strong	Strong	
Study design	Population-based cohort study	Prospective birth cohort study	Prospective birth cohort study	Longitudinal cohort study	Population-based cohort study	Population-based retrospective cohort study	Prospective birth cohort study
Rank this section	Strong	Strong	Strong	Strong	Strong	Moderate	Moderate
Confounders: Were there important differences between groups prior to the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rank this section	Strong	Strong	Strong	Strong	Strong	Strong	Strong
Blinding: Was (were) the outcome assessor (s) aware of the intervention or exposure status of participants?	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain
Were the study participants blinded to their allocation and/or the research question?	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain	Unable to ascertain
Was the data collection tool valid?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

(*continued on next page*)

Table 1. EPHPP Tool Quality Assessment Summary (*continued*)

Study	Håberg et al.[25]	Chen et al.[26]	Cameron et al.[27]	Rajappan et al.[28]	Videholm et al.[29]	Gutvirtz et al.[30]	Gutierrez et al.[31]
Was the data collection tool reliable?	No	No	Yes	Yes	Yes	Yes	Yes
Rank this section	Weak	Weak	Moderate	Moderate	Moderate	Moderate	Moderate
Withdrawals and drop outs: Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?	Not applicable	Yes	Yes	Yes	Not applicable	Not applicable	Not applicable
Indicate the percentage of participants completing the study (if the percentage differs by groups, record the lowest)	Not applicable	80%–100%	80%–100%	80%–100%	Not applicable	Not applicable	Not applicable
Rank this section	Not applicable	Strong	Strong	Strong	Not applicable	Not applicable	Not applicable
Global Ranking: 1 strong=no weak ratings; 2 moderate, all moderate ratings or 1 weak rating; 3 weak, 2 or more weak ratings	Moderate	Moderate	Strong	Strong	Strong	Strong	Strong

EPHPP, Effective Public Health Practice Project.

Table 2. Characteristics of Included Studies

Study	Setting	Study design	Recruitment setting and methods	Cohort size	Length of follow-up	Confounders	Funding sources
Håberg et al.[25]	Norway	Prospective birth cohort	Norwegian Mother and Child Cohort Study: Routine ultrasound appointment at 13−17 weeks gestation; questionnaires at the ages of 6, 12, and 18 months.	33,192	Age of 18 months	From questionnaires: Maternal asthma; educational level; income; age; marital status; parity; and smoking during pregnancy, smoking after birth, breastfeeding, and daycare attendance versus care at home. From birth records: child's sex, caesarean delivery, birthweight, gestational age, diabetes, gestational diabetes, hypertension, and pre-eclampsia.	Norwegian Ministry of Health, Division of Intramural Research, National Institute of Environmental Health Sciences, NIH.
Chen et al.[26]	Taiwan	Prospective birth cohort	Taiwan Birth Cohort Study: Random sampling from national birth registry and interviews; interviews at age of 6 months.	24,400	Age of 6 months	Prenatal conditions: Medication use during pregnancy, pregravid BMI, gestational weight gain, morbidities of gestation, tobacco smoking, betel nut chewing, shift work, and exposure to environmental tobacco smoking. Postnatal conditions: Sex of the baby, gestational age, birth weight, vaccination of *Hemophilus influenzae* type B, parental education level, family income level, number of siblings at home, and congenital cardiopulmonary disease. Environmental conditions: Exposure to cockroaches, water damage, visible mold on walls of home, carpeted flooring, incense burning, and pet ownership	Not available
Cameron et al.[27]	Australia	Prospective birth cohort	Environments for Healthy Living Cohort: Surveys during routine antenatal appointments in third trimester from 3 public maternity hospitals and admitted patient data from Queensland Hospital.	2,778	Age of 5 years	Maternal factors: Education, marital status, age, diabetes (pre-existing or gestational), cigarette smoking, recreational drug use and/or high-level alcohol consumption, number of other children living in the household, partner's employment status, and income quintile. Child and birth factors: Sex, plurality, gestational age, mode of delivery, newborn admission to intensive or special care, and birth weight.	Griffith University
Rajappan et al.[28]	United Kingdom	Prospective birth cohort	Southampton Women's Survey Cohort: Interviews at preconception, 11 and 34 weeks of pregnancy, and 6, 3, and 12 months after birth.	2,799	Age of 12 months	Maternal factors: Age, height, parity, education, late-pregnancy 25-hydroxyvitamin D status, smoking in pregnancy, smoking in child's infancy, and asthma. Paternal factors: Age, height, and asthma. Child and birth factors: Birthweight, gestation, age at last breastfeed, exposure to smokers in the home other than the mother, and adiposity gain between birth and 6 age of months.	Medical Research Council, British Heart Foundation, Food Standards Agency, Dunhill Medical Trust, the European Union's Seventh Framework Program, projects Early Nutrition and Dr Katharine Pike was supported by a grant from the British Lung Foundation.

(*continued on next page*)

Table 2. Characteristics of Included Studies (*continued*)

Study	Setting	Study design	Recruitment setting and methods	Cohort size	Length of follow-up	Confounders	Funding sources
Videholm et al.[29]	Sweden	Population-based retrospective cohort	Data from the Swedish Medical Birth Register, the National Inpatient Register, the Cause of Death Register, the Total Population Register, and the Longitudinal integration database for health insurance and labor market studies.	838,756	Age of 5 years	Maternal age, maternal education level, maternal smoking, parity, geographic region, and time trends (year of birth).	This study was supported by a grant from the Oskarsfonden (Box 36, 932 51 Bureå, Sweden).
Gutvirtz et al.[30]	Israel	Population-based retrospective cohort	Singleton deliveries from a single regional tertiary medical center (Soroka University Medical Center).	249,840	Up to first hospitalization for infection morbidity or 18 years of age.	Maternal age, maternal hypertensive disorders of pregnancy (chronic hypertension, gestational or pre-eclampsia with or without severe features, and eclampsia), maternal diabetes mellitus (pregestational and gestational), chorioamnionitis during labor, preterm delivery, birthweight, lack of prenatal care, and mode of delivery	Not available
Gutierrez et al.[31]	U.S.	Prospective birth cohort	Boston Birth Cohort: Predominantly urban, low-income minority cohort recruited at birth in the Boston Medical Centre. Data points sourced from epidemiologic questionnaires, EMR, and clinical measurements at all primary care visits.	2,790	Age of 12 months	Maternal factors: Maternal age at delivery, race/ethnicity, parity, maternal smoking during pregnancy, education level, and cardiometabolic conditions during pregnancy (chronic and gestational diabetes, hypertensive disorders of pregnancy). Child and birth factors: Gestational age at birth, season of birth, delivery type, and breastfeeding (ever breastfed versus never breastfed) during the first year of life.	Johns Hopkins School of Medicine; the Academy of Allergy, Asthma and Immunology Foundation; NIH

EMR, electronic medical record.

Table 3. Summary of Findings From Included Studies

Study	Exposure of interest	BMI category (kg/m^2)				Outcome of interest	Findings
		Underweight	Normal	Overweight	Obese		
Håberg et al.[25]: Maternal obesity in pregnancy and respiratory health in early childhood	Self-reported (height and weight) maternal pregravid BMI	<18.5	18.5–24.9	25.0–29.9	≥30	Maternal report of LRTI, Hospitalization for LRTI	LRTI: aRD=0.6 (p=0.724 [95% CI= −1.0, 2.2]) Hospitalization for LRTI: aRD= −0.5 (p=0.570 [95% CI= −1.5, 0.5])
Chen et al.[26]: Prenatal and postnatal risk factors for infantile pneumonia in a representative birth cohort	Self-reported (height and weight) maternal pregravid BMI	Not applicable	≤24	>24	Not applicable	Maternal/caregiver report of pneumonia up to age 6 months	Pneumonia: AOR=2.09 (p<0.001 [95% CI=1.4, 3.07]) aAR=14.8
Cameron et al.[27]: Maternal pregravid body mass index and child hospital admissions in the first 5 years of life: results from an Australian birth cohort	Self-reported (height and weight) maternal pregravid BMI	<18.5	18.5–24.9	25.0–29.9	≥30	Childhood all-cause (including infectious and respiratory) hospitalization as defined by ICD-10-AM coding up to age 5 years	All-cause hospitalization: aRR=1.48 (p<0.01 [95% CI=1.10, 1.98]) Infectious disease hospitalization: aRR=2.3 Respiratory disease hospitalization: aRR=1.3
Rajappan et al.[28]: Maternal body mass index: relation with infant respiratory symptoms and infections	Measured maternal pregravid BMI and gestational weight gain	<18.5	18.5–24.99	25.0–29.99	≥30	Maternal report of wheeze, cough, and/or respiratory infections at ages of 6 and 12 months	Pregravid obesity + LRTI: aRR=1.23 (p=0.02 [95% CI=1.03, 1.48])
Videholm et al.[29]: Maternal weight and infections in early childhood: a cohort study	Self-reported (height) and measured weight for maternal gestational BMI at 8–12-week gestation	<18.5	18.5–24.9	25.0–29.9	≥30	Childhood infection –related hospitalization as defined by ICD-10 coding up to age 5 years	LRTI: aIRR=1.19 (95 % CI=1.15, 1.24) URTI aIRR=1.19 (95% CI=1.14, 1.24)
Gutvirtz et al.[30]: Maternal Obesity and Offspring Long- Term Infectious Morbidity	Measured maternal gestational BMI at first prenatal visit	Not applicable	Not applicable	Not applicable	≥30	Childhood infection –related hospitalization as defined by ICD-9-CM coding up to age 18 years	Total infectious-related hospitalizations: aHR=1.125 (p=0.017 [95% CI=1.021, 1.238]) Respiratory infection hospitalizations: Higher rate in children born to mothers with obesity than in those born to non-obese mothers (6.3% vs 5.5%, p=0.04).

(*continued on next page*)

Table 3. Summary of Findings From Included Studies (*continued*)

Study	Exposure of interest	BMI category (kg/m^2)				Outcome of interest	Findings
		Underweight	Normal	Overweight	Obese		
Gutierrez et al.[31]: Maternal pre-pregnancy weight and early life lower respiratory tract infections in a low-income urban minority birth cohort	Self-reported (height and weight) maternal pregravid BMI	Not applicable	18.5–24.9	25.0–29.9	≥30	Infant LRTI as defined by presence of bronchiolitis, bronchitis, or pneumonia identified by ICD-9 and ICD-10 coding up to age 12 months	LRTI: AOR=1.43 (p=0.012 [95% CI=1.08, 1.88])

aAR, adjusted attributable ratio; aHR, adjusted hazard ratio; aIRR, adjusted incidence risk ratio; aRD, adjusted risk; aRR, adjusted risk ratio; ICD-10-AM, ICD-10, Australian Modification; ICD-9, International Classification of Diseases, Ninth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

Chen et al.[26] (2012) outlined BMI >24 kg/m^2 as overweight according to criteria for Asian populations[26,32] and also reported nonoverweight participants as having pregravid BMI ≤24 kg/m^2. Gutvirtz et al.[30] (2019) categorized BMI as obese (≥30 kg/m^2) and nonobese (<30 kg/m^2).[30] Neither of these 2 studies reported an underweight BMI category. Cohorts differed in the proportion obese to total participants; in the smallest cohort, the obese BMI category made up 499 of 2,778 total participants.[27] In contrast, the largest cohort was made up of 245,058 participants with obesity of 838,756 total participants.[29] Across cohorts, the proportion of participants in the obese BMI category of the total cohort ranged from 1.3% to 29%.

Five of the 7 studies assessed pregravid BMI.[25–28,31] The remaining 2 studies collected gestational BMI at the time of first prenatal visit and ultrasound assessment visit.[29,30] Chen et al.[26] and Rajappan et al.[28] also measured gestational weight gain. Chen et al.[26] (2012) quantified gestational weight gain as either <16 kg or ≥16 kg; Rajappan et al.[28] (2017) categorized gestational weight gain as inadequate, adequate, and excessive according to Institute of Medicine guidelines, which accounts for pregravid BMI.[28,33,34]

All studies identified potential confounding variables that were controlled for in their analyses (Table 2[25–31]). Most studies included factors such as maternal smoking, parity, and age as confounders. The majority of the studies controlled for gestational diabetes as a maternal confounding variable.[25,27,30,31] Child and birth factors were also considered, including caesarean delivery, prematurity, birthweight, and infant sex (Table 2[25–31]). Rajappan et al.[28] (2017) also collected data on paternal age, height, and history of asthma. Most of the studies also noted sociodemographic factors, including maternal income, education level, marital status, and race (Table 2[25–31]).[25,27–29,31] Of note, Gutierrez et al.[31] sourced maternal–child data from the Boston Birth Cohort, a primarily low-income, urban, minority cohort.

Child follow-up ranged from age 6 months to 18 years. Gutvirtz et al.[30] (2019) had the longest follow-up time of 18 years and terminated follow-up upon first report of the outcome of interest. Defined outcomes ranged from incidence of prolonged cough to upper respiratory tract infection (URTI) or lower respiratory tract infection (LRTI). Cameron et al.[27] (2014) defined outcomes as childhood all-cause hospitalization and reported separate findings on infectious and respiratory disease hospitalizations. Videholm et al.[29] (2019) defined the outcome of interest as childhood infection–related hospitalizations but reported specific statistics on LRTI and URTI. Similarly, Gutvirtz et al.[30] (2019) defined the outcome of interest as childhood infection–related

hospitalizations while also specifying risks of hospitalization for respiratory infection.

Three of the studies relied on maternal self-reports, which enabled the authors to report on incidences of respiratory outcomes that did not necessitate hospitalization.[25,26,28] Håberg et al.[25] (2009) collected reports of separate incidences of LRTI, with and without hospitalization. LRTI were identified as maternal reports of respiratory syncytial virus, bronchiolitis, bronchitis, and pneumonia.[25] Chen et al.[26] (2012) collected data on incidences of child pneumonia, identified through maternal reports of a pneumonia diagnosis by a physician and hospital admission as a result of the diagnosis. Rajappan et al.[28] (2017) relied on maternal reports of wheeze, prolonged cough, and/or LRTIs (defined as croup, croupy cough, a doctor-diagnosed chest infection, bronchitis, bronchiolitis, or pneumonia).

The other 4 studies[27,29–31] used International Classification of Disease (ICD) coding—a classification list used to categorize patient information (hospital records, medical charts, visit summaries, and bills)—to define outcomes.[35] There are iterations of ICD across healthcare systems, which varied across the reviewed studies: Gutvirtz et al.[30] (2019) used ICD-9-CM codes,[30] whereas Videholm et al.[29] (2019) used ICD-10 codes, and Cameron et al.[27] (2014) used the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification. Gutierrez et al.[31] (2021) defined LRTIs using ICD-9 and ICD-10 coding but did not specify ICD modifications. Cameron et al.[27] (2014) set the outcome as childhood all-cause (including infectious and respiratory) hospitalization. The other 3 studies defined the desired outcome as a childhood infection−related hospitalization with subcategorizations of respiratory infections[30] or LRTIs and URTIs.[29]

All studies reported adjusted analyses for predetermined covariates. Nearly all (6 of the 7) studies reported significant associations between maternal BMI and offspring respiratory outcomes. Four studies found an association between pregravid overweight or obese BMI and offspring respiratory outcomes and infections.[26–28,31] Chen et al.[26] (2012) reported an increased risk of pregravid overweight (BMI >24 kg/m^2) to be associated with an increased risk of infantile pneumonia up to the age of 6 months (AOR=2.09, $p<0.001$; adjusted attributable risk=14.8, $p<0.001$).

Cameron et al.[27] (2014) examined the associations between pregravid obesity (BMI >30 kg/m^2) and the total number of hospitalizations in person years (PYs) and found that children born to participants with obesity had an increased adjusted rate ratio of all-cause hospitalizations in the first 5 years of life (95% CI=1.10, 1.98).[27] These children suffered 2.3 times the rate of admissions for infectious diseases (19.6 vs 8.6 admissions per 1,000 PYs) as children born to participants in the optimal BMI category (18.5−24.9 kg/m^2) (Table 3[25–31]). Children born to participants who had obese pregravid BMI also had the greatest absolute burden of respiratory hospitalizations, 1.3 times the rate of children born to those with BMI at 18−24.9 kg/m^2 (40.7 vs 31.0 admissions per 1,000 PYs) (Table 3).[25–31] Consistent with these data, Rajappan et al.[28] (2017) found a significant association between high pregravid BMI (≥30 kg/m^2) and LRTI (adjusted rate ratio=1.23, p=0.02 [95% CI=1.03, 1.48]) in United Kingdom children up to age 12 months. Gutierrez et al.[31] (2021) reported a significant association between obese pregravid BMI (≥30 kg/m^2) and infant LRTI (AOR=1.43; 95% CI=1.08, 1.88; p=0.012), an association that persisted after adjusting for ethnicity (Table 3).[25–31] Håberg et al.[25] (2009) identified a modest increase of LRTI with pregravid BMI ≥30 kg/m^2 in crude analyses, which was no longer evident after adjustment for confounding variables. Similarly, hospitalizations for LRTIs were not associated with high pregnancy BMI in this cohort (Table 3).[25–31]

When evaluating maternal pregravid BMI and associations with outcomes, it is important to recognize that a significant proportion of people enter pregnancy in 1 BMI category but gain gestational weight beyond the recommended amount.[36] Of the 2 studies that measured gestational weight gain, neither Chen et al.[26] (2012) nor Rajappan et al.[28] (2017) found significant associations between gestational weight gain and respiratory outcomes of interest. Videholm et al.[29] (2019) examined the relationship between first trimester BMI and incidence rates of child hospitalization for infectious disease up to age 5 years in PYs. They found that children of participants who were obese in their first trimester (BMI >30 kg/m^2) were 18% more likely to be admitted to hospital for infectious disease (adjusted incidence rate ratios [aIRRs]=1.18 [95% CI=1.16, 1.21]) and more specifically were at a 19% increased risk of LRTI (aIRR=1.19 [95% CI=1.15, 1.24]) and URTI (aIRR=1.19 [95% CI=1.14, 1.24]).[29] These data suggest that not only is maternal BMI an important factor to consider, but weight gain within different trimesters may have more or less impact on development and therefore neonatal and child health.

Consistent with these data, Gutvirtz et al.[30] (2017) examined the relationship between first trimester BMI and infection-related hospitalizations in children up to age 18 years. This study grouped all non-obese categories together to form a comparator group (BMI <30 kg/m^2) and identified a significant and independent association between maternal obesity and long-term risk for

infectious-related hospitalization in offspring (adjusted hazard ratio=1.125, p=0.017 [95% CI=1.021, 1.238]),[30] where children of participants with high early pregnancy BMI (BMI <30 kg/m^2) had a significantly increased risk of respiratory infections compared with children of healthy weight participants (6.3% vs 5.5%, p=0.04).[30]

DISCUSSION

The authors systematically reviewed the literature to answer the question of whether sufficient human data exist to suggest that maternal BMI and/or gestational weight gain influences neonatal and childhood respiratory infection risk. They found that relatively few primary studies have been published investigating the relationship between maternal BMI and adiposity before and during pregnancy and offspring respiratory infection. Despite this limitation, of the 7 studies that met the criteria for review, 6 studies reported that a high prepregnancy/early pregnancy BMI (BMI >30 kg/m^2) was associated with a greater risk of child respiratory infections across different developmental stages. Specific covariates (e.g., maternal age, race, smoking, income) differed across studies; however, adjustment for these covariates had a negligible impact on the primary finding that a high maternal BMI increased the risk of respiratory infections in offspring.

In terms of the impact of maternal BMI, the early life environment has a significant role to play in establishing health and disease risk and forms the foundation of the Developmental Origins of Health and Disease paradigm.[15,37] One of the many factors thought to drive changes in offspring phenotype is early life exposure to inflammatory environments. Indeed, the proinflammatory milieu observed in cases of high pregravid/gravid BMI (BMI >30 kg/m^2) has been suggested to alter offspring immune and respiratory development.[38] In some studies, a high BMI before and during pregnancy leads to an increase in immunomodulatory cytokine production, systemic inflammation,[39] and macrophage accumulation in the placenta.[40,41] Circulating monocytes of babies born to mothers who are overweight or obese exhibit decreased inflammatory cytokine production in response to infectious stimuli, suggesting that these prenatal inflammatory exposures might result in fetal adaptations to immune development and blunted responses to later pathogenic insults.[42–44]

Prospective studies found that high BMI during pregnancy was associated with decreased lung function in children up to age 5 years.[22] Animal models of obesity during pregnancy have observed increased immune cell infiltration and subsequent collagen deposition in lung tissues of offspring born to mothers with obesity.[45] Others have observed decreased lung compliance[46] and increased proinflammatory cytokine expression in lung tissues of offspring born to dams fed an obesogenic diet.[47] Furthermore, these offspring were more susceptible to severe disease after respiratory syncytial virus infection,[47] suggesting that obesity in pregnancy is a primary catalyst in these respiratory and immunologic consequences and subsequent infection susceptibility. Some data suggest that a proinflammatory in utero environment may influence fetal immune development and priming; studies using umbilical cord immune cell profiling as a marker have noted associations between maternal BMI and cord blood immune cell frequencies[42,48,49] and function.[50]

Limitations

The authors set out to systematically examine the literature and determine whether human data support the hypothesis that high maternal BMI was associated with offspring respiratory infection throughout childhood. However, of the 20,143 searched articles, only 7 effectively tested this hypothesis, highlighting a significant gap in the literature. Exposure–outcome relationships are more complex in the human context, and as a result, the primary limitation of these studies related to the heterogeneity in the methodology, data collection, and characterization of the exposure and controls.

In terms of categorization of BMI, most of the studies collected maternal BMI data from self-reported height and weight, whereas those that measured height and weight varied between collecting data at pregravid time points and collecting at first prenatal visit (first trimester). Rajappan et al.[28] (2017) noted that the time from pregravid measures to conception in their participants could be up to a year, leading to potential deviation from precise BMI at conception. The best possible data, although fraught with its own logistical difficulties, would be collected from the point of first missed menstrual period. Currently, the easiest and most available data are collected at first prenatal visit, which occurs with relative consistency in most developed countries by 10 weeks gestation.[51]

There was significant study-to-study variability in the use of the established WHO BMI categories.[52] Two of the reviewed studies did not identify a category of underweight BMI.[26,30] Gutvirtz et al.[30] categorized participant groups as obese (≥30 kg/m^2) or nonobese (<30 kg/m^2), combining the overweight and nonobese categories. Gutierrez et al.[31] found that participants whose BMIs were categorized as overweight also showed increased offspring respiratory infection risk; therefore, collapsing overweight and optimal BMI categories by Gutvirtz et al.[30] may have weakened the observed associations. The

use of national cohort catalogs and databases may help to mitigate the variability in clinical measures, consolidate findings, and offer access to more consistent data to conduct future epidemiologic studies.[53]

In terms of the outcome of childhood respiratory infection, 3 studies used caregiver and maternal reports to assess incidence of LRTIs and, more specifically, pneumonia.[25,26,28] This allowed researchers to capture any illnesses that did not necessitate hospitalization. The remaining 4 studies focused exclusively on hospitalization as the outcome of interest; thus, milder cases that would have been handled in clinics or ambulatory centers would have been missed. In future studies, the inclusion of these lower-acuity cases in analyses would provide a more comprehensive landscape of respiratory infection vulnerability, severity, and incidence between populations.

In terms of follow-up time, the longest follow-up time was 18 years; however, this study terminated participant follow-up upon first hospitalization. Future studies should consider investigating repeated service use as a measure of severity and vulnerability to infection in children born to women with high BMI; this would strengthen any potential associations. Bentley et al.[54] (2018) found a significant association of caesarean delivery, earlier gestational age, and formula feeding with repeated infection-related hospitalization in children up to age 5 years. Given the relationship between high maternal BMI and these perinatal factors[55] and the subsequent role in childhood respiratory morbidity,[18] investigating obesity during pregnancy as an independent variable in repeated respiratory infection hospitalizations of children should be explored.

CONCLUSIONS

The authors of this review set out to investigate the current human literature on the association between maternal BMI and offspring respiratory infections throughout childhood. The key findings align with the growing evidence that maternal BMI may have independent and profound consequences on respiratory infection risk across childhood. Given that only a very limited number of primary publications met the search criteria, in this review, the authors also identify a significant gap in the research space and encourage more primary investigations of linkages between maternal BMI and offspring respiratory infections. The limited but strong associations serve to highlight that this significant gap in the literature has important implications in clinical practice and public health policy, where emerging evidence suggests that childhood infections predispose individuals to long-term infection vulnerability.[56,57] Thus, every effort should be made to further explore this relationship as a first step in preventing long-term lung damage and the longer-term burden of respiratory disease.

ACKNOWLEDGMENTS

The authors would like to acknowledge the funders that supported the work including the Lung Health Foundation and the Canada Chairs Program.

Declaration of interest: none.

CREDIT AUTHOR STATEMENT

Anastasia V. Warmington: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing — original draft, Writing — review & editing. Dawn M.E. Bowdish: Conceptualization, Supervision, Writing — review & editing. Diana Sherifali: Conceptualization, Resources, Supervision, Writing — review & editing. Deborah M. Sloboda: Conceptualization, Supervision, Writing — review & editing.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.focus.2024.100234.

REFERENCES

1. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet.* 2012;379(9832):2151–2161. https://doi.org/10.1016/S0140-6736(12)60560-1.
2. McDermott KWS, Freeman W J. *Overview of Pediatric Emergency Department Visits*. Healthcare Cost and Utilization Project *(HCUP). Statistical Briefs, 2018.* 2015. https://www.ncbi.nlm.nih.gov/books/NBK526418/. Accessed May 24, 2024.
3. Satia I, Cusack R, Greene JM, O'Byrne PM, Killian KJ, Johnston N. Prevalence and contribution of respiratory viruses in the community to rates of emergency department visits and hospitalizations with respiratory tract infections, chronic obstructive pulmonary disease and asthma. *PLoS One.* 2020;15(2):e0228544. https://doi.org/10.1371/journal.pone.0228544.
4. Matienzo N, Youssef MM, Comito D, et al. Respiratory viruses in pediatric emergency department patients and their family members. *Influenza Other Respir Viruses.* 2021;15(1):91–98. https://doi.org/10.1111/irv.12789.
5. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet.* 2010;376(9743):826–834 /9/4. https://doi.org/10.1016/S0140-6736(10)61380-3.
6. Gern JE, Rosenthal LA, Sorkness RL, Lemanske RF Jr.. Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol.* 2005;115(4):668–674 quiz 675. https://doi.org/10.1016/j.jaci.2005.01.057.
7. Nafstad P, Magnus P, Jaakkola JJ. Early respiratory infections and childhood asthma. *Pediatrics.* 2000;106(3):E38. https://doi.org/10.1542/peds.106.3.e38.
8. Duijts L, Reiss IK, Brusselle G, de Jongste JC. Early origins of chronic obstructive lung diseases across the life course. *Eur J Epidemiol.* 2014;29(12):871–885. https://doi.org/10.1007/s10654-014-9981-5.
9. Dharmage SC, Erbas B, Jarvis D, et al. Do childhood respiratory infections continue to influence adult respiratory morbidity? *Eur Respir J.* 2009;33(2):237–244. https://doi.org/10.1183/09031936.00062907.

10. Bui DS, Walters HE, Burgess JA, et al. Childhood respiratory risk factor profiles and middle-age lung function: a prospective cohort study from the first to sixth decade. *Ann Am Thorac Soc.* 2018;15(9):1057–1066. https://doi.org/10.1513/AnnalsATS.201806-374OC.
11. Ashraf S, Islam M, Unicomb L, et al. Effect of improved water quality, sanitation, hygiene and nutrition interventions on respiratory illness in Young children in rural Bangladesh: a multi-arm cluster-randomized controlled trial. *Am J Trop Med Hyg.* 2020;102(5):1124–1130. https://doi.org/10.4269/ajtmh.19-0769.
12. Brakema EA, van Gemert FA, van der Kleij RMJJ, et al. COPD's early origins in low-and-middle income countries: what are the implications of a false start? *npj Prim Care Respir Med.* 2019;29(1):6. https://doi.org/10.1038/s41533-019-0117-y.
13. Li HY, Gao TY, Fang W, et al. Global, regional and national burden of chronic obstructive pulmonary disease over a 30-year period: estimates from the 1990 to 2019 Global Burden of Disease Study. *Respirology.* 2023;28(1):29–36. https://doi.org/10.1111/resp.14349.
14. Kollmann TR, Kampmann B, Mazmanian SK, Marchant A, Levy O. Protecting the newborn and Young infant from infectious diseases: lessons from immune ontogeny. *Immunity.* 2017;46(3):350–363. https://doi.org/10.1016/j.immuni.2017.03.009.
15. Hanson M, Aagaard-Hansen J. Developmental Origins of Health and Disease: towards a combined bio-social life-course perspective. *Acta Paediatr.* 2021;110(8):2306–2309. https://doi.org/10.1111/apa.15905.
16. Creanga AA, Catalano PM, Bateman BT. Obesity in pregnancy. *N Engl J Med.* 2022;387(3):248–259. https://doi.org/10.1056/NEJMra1801040.
17. Serrano-Lomelin J, Hicks A, Kumar M, et al. Patterns of respiratory health services utilization from birth to 5 years of children who experienced adverse birth outcomes. *PLoS One.* 2021;16(2):e0247527. https://doi.org/10.1371/journal.pone.0247527.
18. McGillick EV, Lock MC, Orgeig S, Morrison JL. Maternal obesity mediated predisposition to respiratory complications at birth and in later life: understanding the implications of the obesogenic intrauterine environment. *Paediatr Respir Rev.* 2017;21:11–18. https://doi.org/10.1016/j.prrv.2016.10.003.
19. Forno E, Young OM, Kumar R, Simhan H, Celedón JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. *Pediatrics.* 2014;134(2):e535–e546. https://doi.org/10.1542/peds.2014-0439.
20. Gaillard R, Felix JF, Duijts L, Jaddoe VWV. Childhood consequences of maternal obesity and excessive weight gain during pregnancy. *Acta Obstet Gynecol Scand.* 2014;93(11):1085–1089. https://doi.org/10.1111/aogs.12506.
21. MacDonald KD, Vesco KK, Funk KL, et al. Maternal body mass index before pregnancy is associated with increased bronchodilator dispensing in early childhood: a cross-sectional study. *Pediatr Pulmonol.* 2016;51(8):803–811. https://doi.org/10.1002/ppul.23384.
22. Eising JB, Uiterwaal CSPM, van der Ent CK. Maternal body mass index, neonatal lung function and respiratory symptoms in childhood. *Eur Respir J.* 2015;46(5):1342–1349. https://doi.org/10.1183/13993003.00784-2014.
23. Liu S, Zhou B, Wang Y, Wang K, Zhang Z, Niu W. Pre-pregnancy maternal weight and gestational weight gain increase the risk for childhood asthma and wheeze: an updated meta-analysis. *Front Pediatr.* 2020;8:134. https://doi.org/10.3389/fped.2020.00134.
24. Thomas BH, Ciliska D, Dobbins M, Micucci S. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews Evid Based Nurs.* 2004;1(3):176–184. https://doi.org/10.1111/j.1524-475X.2004.04006.x.
25. Håberg SE, Stigum H, London SJ, Nystad W, Nafstad P. Maternal obesity in pregnancy and respiratory health in early childhood. *Paediatr Perinat Epidemiol.* 2009;23(4):352–362. https://doi.org/10.1111/j.1365-3016.2009.01034.x.
26. Chen CH, Wen HJ, Chen PC, et al. Prenatal and postnatal risk factors for infantile pneumonia in a representative birth cohort. *Epidemiol Infect.* 2012;140(7):1277–1285. https://doi.org/10.1017/S0950268811001890.
27. Cameron CM, Shibl R, McClure RJ, Ng SK, Hills AP. Maternal pregravid body mass index and child hospital admissions in the first 5 years of life: results from an Australian birth cohort. *Int J Obes (Lond).* 2014;38(10):1268–1274. https://doi.org/10.1038/ijo.2014.148.
28. Rajappan A, Pearce A, Inskip HM, et al. Maternal body mass index: relation with infant respiratory symptoms and infections. *Pediatr Pulmonol.* 2017;52(10):1291–1299. https://doi.org/10.1002/ppul.23779.
29. Videholm S, Silfverdal SA, Reniers G. Maternal weight and infections in early childhood: a cohort study. *Arch Dis Child.* 2019;104(1):58–63. https://doi.org/10.1136/archdischild-2017-314628.
30. Gutvirtz G, Wainstock T, Landau D, Sheiner E. Maternal obesity and offspring long-term infectious morbidity. *J Clin Med.* 2019;8(9):8. https://doi.org/10.3390/jcm8091466.
31. Gutierrez MJ, Nino G, Hong X, Wang X. Maternal pre-pregnancy weight and early life lower respiratory tract infections in a low-income urban minority birth cohort. *Sci Rep.* 2021;11(1):9790. https://doi.org/10.1038/s41598-021-88360-y.
32. Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord.* 1998;22(12):1164–1171. https://doi.org/10.1038/sj.ijo.0800741.
33. Institute of Medicine (US) and National Research Council (U.S.) Committee to Reexamine IOM Pregnancy Weight Guidelines. In: Rasmussen KM, Yaktine AL, eds. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: National Academies Press (U.S.), 2009 https://pubmed.ncbi.nlm.nih.gov/20669500/. Accessed May 24, 2024.
34. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 548: weight gain during pregnancy. *Obstet Gynecol.* 2013;121(1):210–212. https://doi.org/10.1097/01.aog.0000425668.87506.4c.
35. International statistical classification of diseases and related health problems (ICD). WHO. https://www.who.int/standards/classifications/classification-of-diseases. Updated January 2022. Accessed May 24, 2024.
36. Subhan FB, Shulman L, Yuan Y, et al. Association of pre-pregnancy BMI and gestational weight gain with fat mass distribution and accretion during pregnancy and early postpartum: a prospective study of Albertan women. *BMJ Open.* 2019;9(7):e026908. https://doi.org/10.1136/bmjopen-2018-026908.
37. Gluckman PD, Hanson MA, Buklijas T. A conceptual framework for the developmental origins of health and disease. *J Dev Orig Health Dis.* 2010;1(1):6–18. https://doi.org/10.1017/S2040174409990171.
38. Segovia SA, Vickers MH, Gray C, Reynolds CM. Maternal obesity, inflammation, and developmental programming. *BioMed Res Int.* 2014;2014:418975. https://doi.org/10.1155/2014/418975.
39. Madan JC, Davis JM, Craig WY, et al. Maternal obesity and markers of inflammation in pregnancy. *Cytokine.* 2009;47(1):61–64. https://doi.org/10.1016/j.cyto.2009.05.004.
40. Challier JC, Basu S, Bintein T, et al. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta.* 2008;29(3):274–281. https://doi.org/10.1016/j.placenta.2007.12.010.
41. Jayabalan N, Nair S, Nuzhat Z, et al. Cross talk between adipose tissue and placenta in obese and gestational diabetes mellitus pregnancies via exosomes. *Front Endocrinol.* 2017;8:239. https://doi.org/10.3389/fendo.2017.00239.
42. Wilson RM, Marshall NE, Jeske DR, Purnell JQ, Thornburg K, Messaoudi I. Maternal obesity alters immune cell frequencies and responses in umbilical cord blood samples. *Pediatr Allergy Immunol.* 2015;26(4):344–351. https://doi.org/10.1111/pai.12387.
43. Wilson RM, Messaoudi I. The impact of maternal obesity during pregnancy on offspring immunity. *Mol Cell Endocrinol.* 2015;418(0 2):134–142. https://doi.org/10.1016/j.mce.2015.07.028.
44. Sureshchandra S, Wilson RM, Rais M, et al. Maternal pregravid obesity remodels the DNA methylation landscape of cord blood

monocytes disrupting their inflammatory program. *J Immunol.* 2017;199(8):2729–2744. https://doi.org/10.4049/jimmunol.1700434.
45. Song Y, Yu Y, Wang D, et al. Maternal high-fat diet feeding during pregnancy and lactation augments lung inflammation and remodeling in the offspring. *Respir Physiol Neurobiol.* 2015;207:1–6. https://doi.org/10.1016/j.resp.2014.12.003.
46. Heyob KM, Mieth S, Sugar SS, et al. Maternal high-fat diet alters lung development and function in the offspring. *Am J Physiol Lung Cell Mol Physiol.* 2019;317(2):L167–L174. https://doi.org/10.1152/ajplung.00331.2018.
47. Griffiths PS, Walton C, Samsell L, Perez MK, Piedimonte G. Maternal high-fat hypercaloric diet during pregnancy results in persistent metabolic and respiratory abnormalities in offspring. *Pediatr Res.* 2016;79(2):278–286. https://doi.org/10.1038/pr.2015.226.
48. Enninga EAL, Jang JS, Hur B, et al. Maternal obesity is associated with phenotypic alterations in fetal immune cells by single-cell mass cytometry. *Am J Reprod Immunol.* 2021;85(3):e13358. https://doi.org/10.1111/aji.13358.
49. Gonzalez-Espinosa LO, Montiel-Cervantes LA, Guerra-Márquez A, Peñaflor-Juárez K, Reyes-Maldonado E, Vela-Ojeda J. Maternal obesity associated with increase in natural killer T cells and CD8+ regulatory T cells in cord blood units. *Transfusion.* 2016;56(5):1075–1081. https://doi.org/10.1111/trf.13481.
50. Sureshchandra S, Mendoza N, Jankeel A, Wilson RM, Marshall NE, Messaoudi I. Phenotypic and epigenetic adaptations of cord blood CD4+ T cells to maternal obesity. *Front Immunol.* 2021;12:617592. https://doi.org/10.3389/fimmu.2021.617592.
51. Lockwood C, Magriples U. Prenatal care: initial assessment. UptoDate. https://www.uptodate.com/contents/prenatal-care-initial-assessment. Updated May 2024. Accessed May 24, 2024.
52. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000;894 i-253 https://pubmed.ncbi.nlm.nih.gov/11234459/. Accessed May 24, 2024.
53. Bergeron J, Massicotte R, Atkinson S, et al. Cohort profile: research advancement through cohort cataloguing and harmonization (ReACH). *Int J Epidemiol.* 2021;50(2):396–397. https://doi.org/10.1093/ije/dyaa207.
54. Bentley JP, Burgner DP, Shand AW, Bell JC, Miller JE, Nassar N. Gestation at birth, mode of birth, infant feeding and childhood hospitalization with infection. *Acta Obstet Gynecol Scand.* 2018;97(8):988–997. https://doi.org/10.1111/aogs.13371.
55. Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG.* 2006;113(10):1126–1133. https://doi.org/10.1111/j.1471-0528.2006.00989.x.
56. de Steenhuijsen Piters WAA, Watson RL, de Koff EM, et al. Early-life viral infections are associated with disadvantageous immune and microbiota profiles and recurrent respiratory infections. *Nat Microbiol.* 2022;7(2):224–237. https://doi.org/10.1038/s41564-021-01043-2.
57. Achten NB, van Rossum AMC, Bacharier LB, Fitzpatrick AM, Hartert TV. Long-term respiratory consequences of early-life respiratory viral infections: a pragmatic approach to fundamental questions. *J Allergy Clin Immunol Pract.* 2022;10(3):664–670. https://doi.org/10.1016/j.jaip.2021.12.005.