



## Maternal obesity 3

# Influence of maternal obesity on the long-term health of offspring

Keith M Godfrey\*, Rebecca M Reynolds\*, Susan L Prescott, Moffat Nyirenda, Vincent W V Jaddoe, Johan G Eriksson, Birit F P Broekman

In addition to immediate implications for pregnancy complications, increasing evidence implicates maternal obesity as a major determinant of offspring health during childhood and later adult life. Observational studies provide evidence for effects of maternal obesity on her offspring's risks of obesity, coronary heart disease, stroke, type 2 diabetes, and asthma. Maternal obesity could also lead to poorer cognitive performance and increased risk of neurodevelopmental disorders, including cerebral palsy. Preliminary evidence suggests potential implications for immune and infectious-disease-related outcomes. Insights from experimental studies support causal effects of maternal obesity on offspring outcomes, which are mediated at least partly through changes in epigenetic processes, such as alterations in DNA methylation, and perhaps through alterations in the gut microbiome. Although the offspring of obese women who lose weight before pregnancy have a reduced risk of obesity, few controlled intervention studies have been done in which maternal obesity is reversed and the consequences for offspring have been examined. Because the long-term effects of maternal obesity could have profound public health implications, there is an urgent need for studies on causality, underlying mechanisms, and effective interventions to reverse the epidemic of obesity in women of childbearing age and to mitigate consequences for offspring.

### Introduction

Maternal obesity before and during pregnancy is widely recognised to have immediate implications in terms of pregnancy complications, including gestational diabetes, pre-eclampsia, and delivery of large-for-gestational-age infants.<sup>1</sup> Recognition that developmental effects can have long-term consequences on offspring health and wellbeing has led to attention being focused on the potential for maternal obesity to be one of the influences contributing to the “developmental origins of health and disease”.<sup>2</sup> The high prevalence of maternal obesity associated with the global obesity epidemic means that determination of any such long-term effects is now an urgent priority.<sup>3</sup>

Although to control for potentially confounding variables remains a challenge in human observational studies, extensive experimental work in rodents and non-human primates has demonstrated that maternal obesity induced by dietary intervention leads to obesity, diabetes, raised blood pressure, fatty liver, and behaviour changes in offspring.<sup>4</sup> These studies have shown that maternal obesity can permanently alter various metabolic control processes in fetuses, including the hypothalamic response to leptin and subsequent regulation of appetite and pancreatic  $\beta$ -cell physiology.<sup>4</sup> Mechanisms are probably multifactorial, but could include maternal metabolic changes, such as changes in glucose and fatty acids,<sup>5</sup> altered maternal hypothalamic–pituitary–adrenal axis activity,<sup>6</sup> and changes in placental function and inflammation.<sup>7</sup>

In this Series paper, we review the evidence linking maternal obesity with long-term consequences for offspring. We focus on body composition, cardiometabolic, allergic, immune, infectious, and neurobehavioural

outcomes, and discuss altered epigenetic processes as a probable major mechanism underlying long-term effects of maternal obesity on offspring.

### Body composition and cardiometabolic outcomes

An accumulating body of evidence suggests that maternal pre-pregnancy obesity and excessive gestational weight gain are associated with an increased risk of obesity in offspring during childhood.<sup>8–11</sup> Although the initial focus was on severe maternal obesity, the results of several studies<sup>12–15</sup> over the past decade suggest that higher maternal pre-pregnancy BMI across the full spectrum is associated with greater childhood adiposity and an adverse body-fat distribution. Excessive gestational weight gain is also associated with an increased childhood BMI and fat mass estimated by dual-energy x-ray absorptiometry.<sup>15–20</sup> Although both maternal pre-pregnancy obesity and excessive gestational weight gain seem to be associated with increased blood pressure, adverse lipid profiles, and insulin resistance in offspring,<sup>12,16,20,21</sup> some evidence suggests that these associations are largely mediated by childhood BMI.<sup>12,16</sup>

Alongside studies focused on outcomes in children, the results of several studies<sup>22–29</sup> have suggested that a high maternal pre-pregnancy BMI and gestational weight gain are associated with an increased BMI in offspring during adolescence and adulthood. A study of 2432 Australians showed that greater maternal gestational weight gain was associated with a higher BMI (on average 0.3 kg/m<sup>2</sup> [95% CI 0.1–0.4] higher for each 0.1 kg per week greater gestational weight gain) in offspring at age 21 years.<sup>29</sup> These associations were independent of maternal BMI before the pregnancy. Similarly, a study<sup>23</sup> among 1400 mother–offspring pairs

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This is the third in a Series of four papers about maternal obesity

\*These authors contributed equally

MRC Lifecourse Epidemiology Unit and NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK (Prof K M Godfrey PhD); Endocrinology Unit, University/BHF Centre for Cardiovascular Science, University of Edinburgh, Queen's Medical Research Institute, Edinburgh, Scotland, UK (R M Reynolds PhD); School of Paediatrics and Child Health, and Telethon Kids Institute, University of Western Australia, Perth, WA, Australia (S L Prescott PhD); London School of Hygiene & Tropical Medicine, London, UK (M Nyirenda PhD); College of Medicine, University of Malawi, Blantyre, Malawi (M Nyirenda); Departments of Epidemiology and Pediatrics, Erasmus University Medical Center, Rotterdam, Netherlands (V W V Jaddoe PhD); Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland (J G Eriksson PhD); Folkhälsan Research Center, Helsinki, Finland (J G Eriksson); Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A\*STAR), Singapore,

Singapore (B F P Broekman PhD); Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore (B F P Broekman); and National University Health System, Singapore, Singapore (B F P Broekman)

Correspondence to: Prof Keith M Godfrey, University of Southampton and MRC Lifecourse Epidemiology Unit, University Hospital Southampton, Tremona Road, Southampton SO16 6YD, UK [kmg@mrc.soton.ac.uk](mailto:kmg@mrc.soton.ac.uk)

in Jerusalem showed that increased maternal pre-pregnancy BMI was associated with increased offspring BMI at age 30 years (an increase of 1.8 kg/m<sup>2</sup> in offspring BMI per increase of one SD in maternal pre-pregnancy BMI). In the study, the associations of maternal pre-pregnancy BMI with cardiovascular risk were fully explained by adult BMI in offspring.<sup>23</sup> Findings from the Helsinki Birth Cohort Study suggest that maternal BMI is positively associated with offspring BMI at age 60 years.<sup>30,31</sup> Across the range of maternal BMI, a higher BMI was associated with a less favourable body composition in the offspring at a mean age of 62 years.<sup>31</sup> Similar to the studies in children, no consistent associations of maternal BMI with other cardiovascular risk factors were present among adults. Inconsistencies could be due to study design and availability of measurements and confounding factors.

Findings from registration-based, register-based, and retrospective cohort studies in Helsinki implicate maternal obesity in pregnancy as an important determinant of the risk of cardiovascular morbidity and mortality in offspring.<sup>30</sup> A further study of birth records from 37709 individuals in the UK showed that a high (ie >30 kg/m<sup>2</sup>) maternal BMI was associated with an increased risk of premature all-cause mortality (hazard ratio [HR] 1.35, 95% CI 1.17–1.55) and hospital admissions for cardiovascular events in adult offspring (1.29, 1.06–1.57).<sup>32</sup> These associations were independent of socioeconomic status and current age. Similar findings have been reported in participants in the Helsinki Birth Cohort Study<sup>33</sup> who were born between 1934 and 1944 and followed up between the years 1971 and 2010. Associations between cardiovascular disease, coronary heart disease, type 2 diabetes, and stroke in offspring and maternal obesity were apparent. For cardiovascular disease, findings were similar for men (per kg/m<sup>2</sup> HR 1.022, 95% CI 1.003–1.041) and women (1.035, 1.005–1.066), but for type 2 diabetes the association was stronger in women (1.082, 1.036–1.130) than men (1.015, 0.981–1.050). The association of maternal BMI with coronary heart disease was significant among male offspring only (trend per kg/m<sup>2</sup> HR 1.031, 95% CI 1.009–1.054), whereas the association with stroke was significant among female offspring only (1.059, 1.019–1.101).<sup>33</sup>

Several studies have been done to identify periods of maternal weight during pregnancy that are crucial for childhood outcomes. A study<sup>17</sup> done in 5000 UK mother–offspring pairs showed that gestational weight gain in the first 14 weeks of pregnancy was positively associated with offspring adiposity at age 9 years. Likewise, a study<sup>16</sup> among 6000 Dutch mother–offspring dyads showed that early-pregnancy weight gain was associated with an adverse cardiometabolic profile (OR 1.20, 95% CI 1.07–1.35) in childhood; this finding was independent of maternal weight gain before pregnancy and of weight gain in later pregnancy. These studies suggest that maternal weight gain in early

pregnancy, when maternal fat accumulation forms a large component of gestational weight gain,<sup>34</sup> could be a crucial period for the development of an adverse childhood cardiovascular risk profile. Thus, maternal pre-pregnancy obesity and gestational weight gain, especially in early pregnancy, could influence the risks of adiposity and adverse cardiovascular risk from childhood to adulthood.

### Allergic and atopic outcomes

The global rise in maternal obesity has been implicated in the parallel rising burden of asthma, allergic disease, and other early immune diseases, with speculation that this burden could be among the multisystem consequences of obesity-related inflammation for offspring (table 1). A meta-analysis<sup>46</sup> of 14 studies and 108 321 mother–child pairs showed that maternal overweight or obesity in pregnancy was associated with increased risks of childhood asthma or wheeze ever (odds ratio [OR] 1.31, 95% CI 1.16–1.49) and current asthma or wheeze (1.21, 1.07–1.37), independent of offspring BMI. High maternal gestational weight gain was also associated with increased odds of current asthma or wheeze (OR 1.02 per 1 kg increase, 95% CI 1.01–1.02) in offspring, but not associated with asthma or wheeze ever (1.04, 0.97–1.11). Follow-up of the Danish National Birth Cohort<sup>38</sup> showed that the impact of maternal obesity was largely limited to asthma and wheezing: maternal obesity did not increase the risk of eczema, sensitisation (sensitisation to aeroallergens was largely assessed), or hay fever, suggesting tissue-specific effects. This finding is consistent with evidence that allergic diseases result from both systemic immune dysregulation and tissue-specific effects during crucial stages of development.

Although pathways linking maternal obesity to offspring allergic and atopic outcomes are multifactorial, the contribution of reduced microbial diversity—and particularly intestinal dysbiosis—has emerged as a central risk factor. Changing microbial exposure has been long implicated in the substantial increase in early-onset inflammatory non-communicable disease, such as allergy and asthma, but the importance of these complex microbiological ecosystems is becoming increasingly apparent in the physiological, immunological, and metabolic dysregulation of obesity.<sup>47</sup> Emerging evidence suggests the multisystem effects of declining microbial diversity begin in utero, including through epigenetic influences.<sup>48</sup>

Thus, an aberrant gut microbiome, which is known to be associated with maternal obesity, provides an additional mechanism for both immune and metabolic consequences on the developing fetus.<sup>49</sup> Preliminary evidence in human beings suggests that dietary manipulation of the maternal microbiome in pregnancy with prebiotic fibre has beneficial effects for both offspring immune function and metabolism.<sup>50</sup> In animal models, this intervention can

	Study details	Sample	Country	Major findings
Dumas et al, <sup>35</sup> 2016	Analyses of children of participants in the Nurses' Health Study II: physician-diagnosed asthma and allergies assessed by questionnaires	12 963 children age 9–14 years	USA	Maternal pre-pregnancy overweight (OR 1.19, 95% CI 1.03–1.38) and obesity (1.34, 1.08–1.68) associated with asthma in offspring
Pike et al, <sup>36</sup> 2013	Mothers and children from the Southampton Women's Survey: childhood follow-up visits at 6, 12, 24, and 36 months, skin prick tests at 6 years	940 children with available data in the first 6 years	UK	Greater maternal BMI and fat mass associated with increased transient wheeze (RR 1.10 [95% CI 1.03–1.18] per 5 kg/m <sup>2</sup> , p=0.006; 1.11 [1.02–1.21] per 10 kg/m <sup>2</sup> , p=0.01), but not with persistent wheeze or asthma; maternal adiposity not associated with offspring atopy or exhaled nitric oxide
Guerra et al, <sup>37</sup> 2013	Multicentre, longitudinal, population-based study of two INMA (Infancia y Medio Ambiente) birth cohorts in Sabadell and Gipuzkoa, Spain: wheeze data obtained through interviewer-administered parental questionnaires	1107 mother-child pairs assessed up to age 14 months	Spain	Maternal pre-pregnancy obesity increased risk of frequent (RR 4.18, 95% CI 1.55–11.3) but not infrequent (1.05, 0.55–2.01) wheezing in offspring; children of obese mothers more likely to have frequent wheezing than children of healthy-weight mothers (11.8% vs 3.8%; p=0.002)
Harpsoe et al, <sup>38</sup> 2013	Mother-child pairs from the Danish National Birth Cohort: information from the 16th week of pregnancy and at offspring age 6 months, 18 months, and 7 years	38 874 mother-child pairs assessed up to age 7 years	Denmark	Risk of severe asthma in offspring at age 7 years was increased with maternal pre-pregnancy BMI $\geq 35$ (adjusted OR 1.87, 95% CI 0.95–3.68) and gestational weight gain $\geq 25$ kg (1.97, 1.38–2.83); maternal BMI and gestational weight gain were not associated with eczema or hay fever
Watson et al, <sup>39</sup> 2013	Prospective study of Europeans and Polynesians from northern New Zealand: home assessments in pregnancy and at offspring age 18 months	369 18-month-old infants	New Zealand	Changes in subcutaneous fat during pregnancy were associated with prevalence of infant wheeze: wheeze prevalence was 19.2% when the difference in mothers' skinfolds between months 4 and 7 of pregnancy decreased by $\geq 10$ mm, and 41.7% where the difference increased by $\geq 10$ mm
Patel et al, <sup>40</sup> 2012	Adolescents from the prospective 1986 Northern Finland Birth Cohort	6945 adolescents (age 15–16 years) assessed for asthma symptoms	Finland	High maternal pre-pregnancy BMI was a significant predictor of wheeze in adolescents (increase per kg/m <sup>2</sup> for wheeze ever 2.8%, 95% CI 0.5–5.1; and for current wheeze 4.7%, 1.9–7.7)
Lowe et al, <sup>41</sup> 2011	Data linkage of the Swedish Medical Birth Registry, Swedish Prescribed Drug Register, and Swedish Inpatient Registry: asthma medication use in offspring from age 6–8 years and 8–10 years	89 783 children born to 129 239 mothers in Stockholm between 1998 and 2009	Sweden	Higher maternal BMI was consistently associated with an increased risk of asthma in the child, both in terms of medicine use and hospital admission; risk of use of asthma medication increased for maternal BMI of 30–34.9 (OR 1.40, 95% CI 1.16–1.68) and $\geq 35$ (1.57, 1.15–2.15)
Scholten et al, <sup>42</sup> 2010	Birth cohort participating in the Prevention and Incidence of Asthma and Mite Allergy study: sensitisation and bronchial hyper-responsiveness determined at 8 years in offspring	3963 children and their mothers	Netherlands	Maternal overweight before pregnancy increased risk of childhood asthma at 8 years (OR 1.52, 95% CI 1.05–2.18) in children with atopic heredity but not in children without a predisposition (0.86, 0.60–1.23); there was no association with sensitisation or bronchial hyper-responsiveness
Kumar et al, <sup>43</sup> 2010	Boston Birth Cohort (started in 1998): prospective follow-up to a mean age of 3.0 years (SD 2.4) with study visits aligned with the paediatric primary care schedule	1191 children	USA	Children of obese mothers had an increased risk of recurrent wheezing (OR 3.51, 95% CI 1.68–7.32); maternal obesity was not associated with eczema or food allergy
Haberg et al, <sup>44</sup> 2009	Population-based cohort study: Norwegian Mother and Child Study	33 192 children born between 1999 and 2005	Norway	Risk of wheeze increased linearly with maternal BMI in pregnancy, and was 3.3% higher (95% CI 1.2–5.3) in children with mothers who were obese during pregnancy than in those whose mothers had BMIs in the healthy ranges
Reichman et al, <sup>45</sup> 2008	Population-based study: main outcome—diagnosis of asthma in child by age 3 years reported by mothers	1971 children born in large US cities in 1998–2000	USA	Children with obese mothers were more likely to have an asthma diagnosis by age 3 years (OR 1.52, 95% CI 1.18–1.93)

OR=odds ratio. RR=relative risk.

**Table 1: Studies linking maternal obesity with asthma in offspring**

prevent the development of an allergic asthma phenotype in the offspring—an effect directly mediated by the short-chain fatty acid (SCFA) metabolites produced by microbial fermentation of dietary fibre.<sup>51</sup> In addition to their effects on metabolism, glucose homeostasis, and appetite regulation, SCFAs also have powerful anti-inflammatory effects—both in local tissues and systemically through regulatory T-cell induction.<sup>50,51</sup> Notably, they have tissue-specific effects in the lung.<sup>51</sup> Moreover, preliminary evidence from human studies shows that high SCFA (acetate) concentrations in pregnancy correlate with fewer

doctor visits for cough and wheeze in their offspring.<sup>51</sup> A systematic review<sup>52</sup> showed suggestive evidence that western-style fast-food diets linked to obesity might increase asthma risk, whereas a Mediterranean diet (high in fish, fruits, nuts, and vegetables) might be protective against wheeze and asthma in childhood. This finding leads us to speculate that maternal diet could alter microbiome-derived SCFA concentrations, with effects on offspring immune responses and tissue function.

Collectively these findings underscore the complex interplay between evolving metabolic and immune

responses and how these responses can be modified by maternal nutrition, adiposity, and microbial diversity to alter susceptibility to inflammatory diseases across the life course.<sup>53</sup>

### Other immune and infectious-disease-related outcomes

Whether maternal obesity increases susceptibility of offspring to other immune and infectious-disease-related outcomes has been less well studied, but is important to consider in view of the rising prevalence of obesity in low-income and middle-income countries,<sup>54</sup> where the burden of infection during pregnancy and childhood is high. With dampened maternal immunity to tolerate the semi-allogeneic offspring, pregnancy represents a period of increased susceptibility to infection, and maternal obesity further increases this risk.<sup>55</sup> Studies in rodent models of maternal obesity demonstrate worse outcomes in offspring in response to bacterial infection and experimentally induced autoimmunity.<sup>56,57</sup>

In human beings, maternal obesity also affects the maturation and development of the neonate's immune system, with adverse influences on the frequency and function of key innate and adaptive immune cells measured in umbilical cord blood.<sup>58</sup> Infants born in high-income countries also have different proportions of circulating immune cells and innate immune responses from those born in low-income and middle-income countries, but little is known about the contributions of maternal nutritional state versus other exposures (eg, infections) to these differences.<sup>59</sup> The difference could, however, have important effects on susceptibility to pathogens, responses to vaccines, and development of immuno-pathological disorders, such as asthma and allergy.<sup>60</sup> Obesity is a recognised risk factor for severe viral infections,<sup>61</sup> and, in pregnant women who are obese, prenatal exposure to a range of infections (such as influenza, toxoplasmosis, rubella, cytomegalovirus infection, and herpes simplex virus infection) could have consequences for the offspring, including cardiometabolic and neurobehavioural diseases. Whether maternal obesity further increases susceptibility to vertical transmission of pathogens is unknown, although susceptibility could plausibly increase indirectly through exacerbation of the already altered maternal endocrine, immune, and metabolic milieu, and inflammatory status associated with maternal adiposity.<sup>62,63</sup>

Another important consideration is whether therapies used to treat maternal infection could have adverse impacts on offspring's risk of later disease, through increasing maternal adiposity. Protease inhibitors, antiretrovirals used to prevent mother-to-child transmission of HIV, are associated with adverse maternal metabolic side-effects, including changes in maternal body composition, such as increased central adiposity, together with associated dyslipidaemia, insulin

resistance, type 2 diabetes, and mitochondrial toxicity, which could have long-term effects on infants exposed to these drugs.<sup>64</sup> Detailed studies will be required to establish the long-term effects, and to determine optimal regimens to reduce any adverse outcomes.

### Neurocognitive and behavioural outcomes in offspring

Despite the potential public health importance, few cohort studies have been done to examine associations between maternal obesity and detailed neurodevelopmental outcomes in offspring (table 2). Some human data have shown that higher pre-pregnancy weight is associated with poorer cognitive outcomes in offspring, and higher (but not excessive) weight gain during pregnancy has been associated with better cognitive outcomes.<sup>73,74</sup> However, published data do not allow for definitive conclusions to be drawn about the potential effects of pre-pregnancy adiposity on offspring's cognitive development. Most studies showed moderate inverse associations with both early and later performance on cognitive standardised assessments or reading and mathematics scores.<sup>75</sup> A study<sup>76</sup> published in 2015 showed a possible temporary increase in cognitive outcomes on a standardised assessment at 6 months. However, associations with maternal reports of cognitive performance were inconsistent in other large cohort studies.<sup>65</sup>

Maternal obesity has also been associated with behavioural and emotional problems in offspring.<sup>65,69</sup> A meta-analysis<sup>70</sup> and longitudinal study<sup>69</sup> showed an increased risk for autism spectrum disorders in children of mothers with obesity before or during pregnancy or with excessive gestational weight gain; other investigations suggested a particularly robust association for excessive gestational weight gain.<sup>68</sup> In three large European cohort studies, the association between pre-pregnancy obesity and attention deficit hyperactivity disorder was inconsistent, and absent when adjusted in full-sibling comparisons.<sup>66,76</sup> Fewer studies have been done to investigate the association of maternal obesity with affective disorders, and no studies in the past 10 years have been focused on the link with anxiety, psychotic, or eating disorders. Only one qualitative review<sup>77</sup> has been published on pre-pregnancy obesity and schizophrenia, which suggested an association, although maternal schizophrenia was not taken into account. Although past studies had contradictory results relating maternal obesity to cerebral palsy in offspring,<sup>78</sup> a more recent study<sup>65</sup> published in 2014 showed positive associations, even after multiple adjustments.

A major limitation of these studies is the difficulty in differentiating intrauterine effects from residual confounding. One way to explore this issue is to compare effect sizes of maternal obesity versus paternal obesity. However, even with maternal effect sizes, other influences are clearly also associated with both obesity

and neurodevelopment, such as maternal intelligence, socioeconomic status, breastfeeding, maternal mental health, maternal diet, and other postnatal lifestyle influences. Other possible reasons for contradictory findings are differences in methods, sampling biases, differing ages at which outcomes are measured, and

	Population	Design	Country	Follow-up	Overweight or obesity assessments in mother	OR of neurodevelopment disorders
Brion et al, <sup>65</sup> 2011	British Avon Longitudinal Study (n=5000), UK, and Generation R Study (n=2500), Netherlands	Two cohorts	UK, Netherlands	Behavioural problems—eg, attention deficit—measured at 47 months (UK) and 36 months (Netherlands) by parental reports	Pre-pregnancy overweight (ie, BMI of 25–29.9)	Maternal pre-pregnancy overweight not associated with an increased risk of attention deficit problems (or other emotional or internalising problems) in offspring in either cohort
Chen et al, <sup>66</sup> 2014	Population-based cohort study with data from national and regional registers (n=673 632, including 272 790 full, biological siblings)	Cohort	Sweden	From age 3 years until diagnosis of ADHD, death, or emigration	Pre-pregnancy overweight (ie, BMI of 25–29.9) or obesity (ie, BMI ≥30)	Risk of ADHD in offspring was associated with pre-pregnancy overweight (OR 1.23, 95% CI 1.18–1.27) and obesity (1.64, 1.57–1.73); increase was not significant in siblings discordant for maternal pre-pregnancy overweight or obesity (0.98, 0.83–1.16 for overweight; 1.15, 0.85–1.56 for obesity)
Crisham et al, <sup>67</sup> 2013	Longitudinal population-based study (n=6 221 001, including 8798 diagnoses of cerebral palsy)	Cohort	USA	Neonates followed up until age 5 years for assessment of cerebral palsy	Pre-pregnancy obesity (ie, BMI ≥30) and morbid obesity (ie, BMI ≥40)	Risk of cerebral palsy in offspring was associated with pre-pregnancy obesity (OR 1.72, 95% CI 1.25–2.35) and morbid obesity (3.79, 2.35–6.10)
Gardner et al, <sup>68</sup> 2015	Stockholm Youth Cohort, a population-based study (n=333 057, including 6420 participants with autism spectrum disorder and 1156 matched siblings)	Cohort	Sweden	4–21 years	Pre-pregnancy overweight (ie, BMI 25–29.9) and obesity (ie, BMI ≥30), and excessive gestational weight gain (according to Institute of Medicine)	Autism spectrum disorders in offspring were associated with pre-pregnancy overweight (OR 1.31, 95% CI 1.21–1.41) and obesity (1.94, 1.72–2.17); excessive gestational weight gain non-significantly associated with increase in autism spectrum disorders in matched sibling analyses (1.48, 0.93–2.38)
Jo et al, <sup>69</sup> 2015	Infant Feeding Practices Study II, a nationally distributed longitudinal study (n=1311)	Cohort	USA	6 years	Severe pre-pregnancy obesity (ie, BMI >35.0)	Severe pre-pregnancy obesity associated with increase in offspring of diagnosis of autism spectrum disorders or development delay disorders (OR 3.13, 95% CI 1.10–8.94) and ADHD by maternal report (4.55, 1.80–11.46)
Li et al, <sup>70</sup> 2016	Meta-analysis of four population-based studies (n=129 733, including 924 cases of autism spectrum disorder [Canada]; n=517, including 315 cases of autism spectrum disorder [USA]; n=4800, including 100 cases of autism spectrum disorder [USA]; n=92 909, including 419 cases of autism spectrum disorder [Norway]) and one case-cohort study (n=62, including 14 cases of autism spectrum disorder [USA])	Population-based cohort studies and one case-control study	Canada, USA, Norway	1–17 years (Canada); 4–5 years (USA); 2 years (USA); 4–13.1 years (Norway); 2–5 years (USA)	Pre-pregnancy obesity (ie, BMI ≥30 or pre-pregnancy weight ≥90 kg) and obesity during pregnancy	Pre-pregnancy and pregnancy obesity associated with a pooled adjusted increase in autism spectrum disorders in offspring (OR 1.47, 95% CI 1.24–1.74)
Pan et al, <sup>71</sup> 2014	Retrospective study of South Carolina Medicaid Program (n=83 901, including 100 cases of any cerebral palsy and 53 cases of confirmed cerebral palsy—ie, at least two diagnoses)	Cohort	USA	5–8 years	Severe (ie, BMI of 35–39.9) or morbid (ie, BMI ≥40) obesity at birth	Severe obesity associated with increase in any (OR 2.00, 95% CI 1.00–4.01) and confirmed (1.22, 0.38–3.81) cerebral palsy in offspring; morbid obesity associated with increase in any (2.95, 1.45–5.97) and confirmed (3.03, 1.09–8.37) cerebral palsy in offspring
Rodriguez, <sup>72</sup> 2010	Population-based prospective pregnancy-offspring study (n=1714)	Cohort	Sweden	5 years	Pre-pregnancy overweight (ie, BMI of 25–29.9) and obesity (ie, BMI ≥30)	Pre-pregnancy overweight associated with increase in ADHD by teacher ratings OR 1.92 (95% CI 1.21–3.05) and non-significant increase in high inattention symptom score by maternal ratings (1.11, 0.77–1.59) in offspring; pre-pregnancy obesity associated with increase in ADHD symptoms in offspring as assessed by teacher ratings (2.05, 1.06–3.95) but not by maternal ratings (1.05, 0.61–1.79)

We included only studies published in the past 6 years in which ORs were reported. OR=odds ratio. ADHD=attention deficit hyperactivity disorder.

**Table 2: Studies of neurodevelopmental disorders in offspring of women with overweight or obesity before or during pregnancy**

differences in defining obesity and outcomes. In some studies, retrospective self-reports of pre-pregnancy weight or maternal reports of offspring outcomes were used, which could be less reliable.<sup>73,76</sup>

In human studies, confirmation of causation and identification of mechanisms linking maternal obesity with offspring neurodevelopment are difficult. However, studies in rodents and non-human primates have identified three potential pathways: high concentrations of nutrients, including fatty acids and glucose; high concentrations of hormones such as leptin and insulin; and inflammatory mediators, including interleukins and tumour necrosis factor.<sup>65,78</sup> These factors cross the placenta and can influence fetal neuroendocrine development, neuronal proliferation, and brain development.<sup>65,78</sup> Many dynamic factors have a role, with complex interactions between maternal environment, placental pathophysiology, and fetal epigenetic changes. Animal studies showed that obesity during pregnancy can change brain homeostasis and offspring behaviour through epigenetic mechanisms, including those implicated in the serotonin and dopamine pathways, lipid peroxidation, and corticosteroid-receptor expression.<sup>79,80</sup> Even parental lifestyle factors before and at conception could have transgenerational effects as a result of epigenetic reprogramming at fertilisation.<sup>81</sup>

Maternal obesity has many pathophysiological features in common with gestational diabetes, a disorder increasingly associated with evidence of mild cognitive impairment in offspring.<sup>75</sup> For maternal obesity, the paucity of evidence emphasises a need for large-scale studies with more detailed cognitive and behavioural phenotyping in different cultures and ethnicities. Future studies should be done to examine whether maternal diet or obesity is more important for programming of neurodevelopmental outcomes, and should include comprehensive assessments of diet and direct measurements of adiposity. Furthermore, underlying mechanisms should be studied in people with biomarkers including genetic and epigenetic modifications.

### Epigenetic modifications: a potential underlying mechanism

Epigenetic processes are emerging as an important mechanism through which the memory of developmental exposures is held, with pathophysiological consequences for various organs and systems. Epigenetic modifications have been proposed as a key causal mechanism linking maternal adiposity and outcomes in offspring.<sup>82</sup> Furthermore, evidence is now emerging that epigenetic processes can act over three or more generations and through the paternal line.<sup>83</sup> Epigenetic modifications result in alterations in gene function in the absence of changes to the DNA sequence. The epigenetic marks that mediate this process include DNA methylation, post-translational modification of histones,

and non-coding RNAs. DNA methylation occurring predominantly at cytosines in cytosine–guanine (CpG) dinucleotides is the most widely studied. Table 3 summarises the evidence linking maternal obesity in human beings with offspring DNA methylation.

Global methylation techniques have been used in several studies to explore associations between maternal obesity and offspring DNA methylation (table 3). Although the findings are not consistent, three cohort studies showed associations between maternal BMI and offspring DNA methylation at birth<sup>87,88</sup> and at age 3 years.<sup>85</sup> Notably, in the largest and most robust study,<sup>88</sup> the methylation differences were noted only with comparisons of obese versus healthy BMIs and not when overweight and healthy-weight BMIs were compared. The reasons why are unknown, but this observation could partly explain the negative findings in other studies in which analyses have been done across a range of maternal BMI measurements.<sup>84,86</sup> The observation of differentially methylated CpG sites in the peripheral blood of 2–25-year-old siblings born to obese mothers before and after bariatric surgery with associated weight loss<sup>95</sup> is also consistent with the hypothesis that maternal obesity affects offspring DNA methylation.

When a candidate-gene approach has been used, associations between maternal adiposity and DNA methylation at imprinted genes<sup>91–93</sup> or in several genes involved in metabolism<sup>90–94</sup> have been reported. Of particular interest is the observation that *AHRR* DNA methylation is 2.1% higher in offspring of obese mothers than in those of healthy-weight mothers;<sup>94</sup> robust links are now established between maternal smoking during pregnancy and *AHRR* methylation in offspring, and there is much evidence that maternal smoking is associated with long-term effects on offspring adiposity.<sup>15</sup> The observations raise the possibility that *AHRR* DNA methylation could be involved in the link between maternal obesity and offspring adiposity. Evidence also suggests that maternal glycaemia is involved in causal pathways influencing epigenetic regulation of leptin in offspring.<sup>96</sup>

### Methodological considerations

Fixed genetic variants shared by mother and offspring are important confounders of proposed links between metabolic factors associated with maternal obesity and offspring outcomes, as are shared postnatal influences on diet and lifestyle behaviours<sup>97</sup> and microbiome-related mechanisms.<sup>98</sup> However, abdominal fat depots already differ at birth between groups with different risks of later metabolic disease,<sup>99</sup> and at least some of the effects of maternal obesity are probably mediated through prenatal environmental mechanisms. Further delineation of maternal effect modifiers will aid the development of interventions to improve offspring health, as will understanding of the underlying

mechanisms and related biomarker signatures of these processes. Alongside providing insights into the fundamental processes and additional risk factors, such biomarker signatures will provide immediate outcome

or adherence measures for interventions, and enable identification of postnatal effect modifiers and stratification of infants for targeting of postnatal interventions.

	Population	Design	Country	Tissue	Method	Findings
<b>Global methylation techniques</b>						
Michels et al, <sup>84</sup> 2011	Epigenetic birth cohort (319 neonates with 316 placentas)	Cohort	USA	Cord blood, placental tissue	Global methylation with a LINE-1 bisulphite pyrosequencing assay (Zymo Research, Orange, CA, USA)	No associations between maternal pre-pregnancy BMI and global methylation in either tissue
Herbstman et al, <sup>85</sup> 2013	Northern Manhattan Mothers & Newborns Study of the Columbia Center for Children's Environmental Health (n=279 neonates, 165 of whom were available at 3 year follow-up)	Cohort	USA	Cord blood, peripheral blood at 3 years	Global DNA methylation with MethyLamp Global DNA Methylation Quantification Kit (Epigentek Group, Farmingdale, NY, USA)	Pre-pregnancy BMI negatively predictive of DNA methylation in both cord and 3 year blood
Morales et al, <sup>86</sup> 2014	Avon Longitudinal Study of Parents and Children cohort (n=88 term neonates, plus 170 term neonates in replication study population)	Cohort	UK	Cord blood	GoldenGate Cancer Panel I Array (Illumina, San Diego, CA, USA); validation with PyroMark MD Pyrosequencing System (Qiagen, Hilden, Germany) in replication cohort	No associations between maternal pre-pregnancy BMI and differentially methylated DNA at any CpG site in either cohort
Liu et al, <sup>87</sup> 2014	Boston Birth Cohort (n=309 black—African American and Haitian—term neonates)	Cohort	USA	Cord blood	HumanMethylation27 BeadChip (Illumina)	The methylation levels of 20 CpG sites were associated with maternal BMI; one site (ZCCHC10) remained significantly associated with maternal BMI after correction for multiple comparisons (p=0.04)
Sharp et al, <sup>88</sup> 2015	Accessible Resource for Integrated Epigenomics Studies (ARIES), a subset of Avon Longitudinal Study of Parents and Children (n=1018)	Cohort	UK	Cord blood	HumanMethylation 450 K (Illumina)	Compared with neonatal offspring born to healthy-weight mothers, 28 and 1621 CpG sites were differentially methylated in offspring of obese and underweight mothers, respectively. A positive association, in which higher methylation was associated with BMI outside the healthy range, was noted in 78.6% of the 28 sites associated with obesity
Guenard et al, <sup>89</sup> 2013	50 siblings aged 2 years 8 months to 24 years 11 months, 25 of whom were born before maternal bariatric surgery and 25 born after	Case-control	Canada	Peripheral blood	Genome-wide methylation analysis with HumanMethylation450 BeadChip (Illumina, San Diego, CA, USA)	5698 differentially methylated genes between offspring born before and after maternal bariatric surgery (main differences in genes involved in inflammatory and immune pathways)
<b>Candidate-gene approach</b>						
Gemma et al, <sup>90</sup> 2009	88 neonates: 57 with appropriate weight for gestational age, 17 small for gestational age, and 14 large for gestational age	Cohort	Argentina	Umbilical cord	PPARGC1A promoter: after bisulphite treatment of umbilical cord genomic DNA, a real-time methylation-specific PCR was used to determine the promoter methylation status in selected CpGs	Positive correlation between maternal BMI and PPARGC1A promoter methylation in umbilical cord (Pearson correlation coefficient r=0.41; p=0.0007)
Hoyo et al, <sup>91</sup> 2012	438 participants in Newborn Epigenetics Study	Cohort	USA	Cord blood	Bisulphite sequencing	Lower methylation at the IGF2 differentially methylated region was associated with increased plasma IGF2 concentrations, an association that was stronger in infants born to obese women than in those born to non-obese women; increased IGF2 concentrations were significantly associated with higher birthweight (p=0.0003)
Soubry et al, <sup>92</sup> 2013	79 neonates from the Newborn Epigenetics Study cohort	Cohort	USA	Cord blood	Bisulphite sequencing	Increase in DNA methylation at the H19 (but not IGF2) differentially methylated regions among neonates born to obese mothers compared with those born to non-obese mothers
Soubry et al, <sup>93</sup> 2015	92 neonates from the Newborn Epigenetics Study cohort	Cohort	USA	Cord blood	Bisulphite pyrosequencing	Obesity in mothers was associated with an increase in methylation at the PLAGL1 differentially methylated region ( $\beta$ coefficient 2.58, SE 1.00; p=0.01) and a decrease at the MEG differentially methylated region (3.42, 1.69; 0.04)
Burris et al, <sup>94</sup> 2015	531 infants from Programming Research in Obesity, Growth Environment and Social Stress cohort	Cohort	Mexico	Cord blood	AHRR DNA methylation by bisulphite sequencing	AHRR DNA methylation was positively associated with maternal BMI (p=0.0009) and was 2.1% higher in offspring of obese mothers than in those of mothers with a BMI <27, which represented a third of the SD differences in methylation

**Table 3: Human studies linking maternal obesity with DNA methylation changes in offspring**

Although the available data are consistent with the hypothesis that maternal obesity affects changes in DNA methylation in offspring at birth, whether these changes affect development of later adverse outcomes in offspring remains unclear. The observation that the methylation changes at birth were also present at 3 year follow-up<sup>85</sup> provides some evidence that the methylation changes can persist. This finding, together with the observation of persistence of epigenetic marks associated with obesity across childhood and adolescence,<sup>100</sup> raises the possibility that epigenetic analysis could provide useful biomarkers of disease risk across the lifespan. These findings need to be interpreted with caution, however. Few studies have included attempts to replicate or validate findings in a replication cohort<sup>86</sup> or in comparison with published data,<sup>88</sup> and few have examined whether relations are similar in male and female offspring. That many DNA-methylation patterns are tissue-specific and cell-specific is well established,<sup>101</sup> so the relevance of findings from DNA extracted from cord or peripheral blood leucocytes remains unclear. However, evidence also suggests that, for several non-imprinted genes, levels of DNA methylation measured in blood are equivalent to those in buccal cells, despite the fact that these cell types arise from different germ layers (mesoderm and ectoderm, respectively).<sup>102</sup>

#### Panel: Key points for future research

- Comprehensive experimental research is required into the epigenetic and other mechanisms linking maternal obesity to long-term outcomes in offspring. This molecular research will enable development of novel biomarkers and assist in design of new intervention studies.
- Detailed information is needed about the specific maternal lifestyle (eg, physical activity, smoking, other environmental stressors), nutritional, and metabolic exposures that underpin effects of maternal obesity on outcomes in offspring. These findings need to be combined with information about whether there are crucial periods during development when such exposures have their effects and whether any outcomes are sex-specific.
- Alongside mechanistic research, sophisticated observational studies are needed to obtain further insight into the multiple causalities of the observed associations. Such study designs include parent-offspring longitudinal cohorts, sib-pair analyses, and the use of genetic variants and haplotypes as instrumental variables.
- There is a paucity of intervention studies focused on remediation of maternal obesity before and during pregnancy, or on moderation of the effects of maternal obesity on offspring. With a deeper understanding of the underlying mechanisms, new interventions need to be designed and tested, with long-term follow-up of offspring.

Although DNA extracted from blood leucocytes has been used in most studies as a reflection of processes occurring in the fetus,<sup>84–88,91–94</sup> the heterogeneity in sample population, study size, and the inconsistency between methodological approaches make comparison of studies challenging. Further, methodological considerations—particularly if complex tissues such as the placenta, which contains mixed cell types, each with a distinct methylation pattern are used—could cause problems for data interpretation.

Whether the reported associations between maternal obesity and epigenetic processes are causal in relation to later outcomes is unknown, as is whether they are merely a response to the maternal obesogenic environment, or are secondary to the changes in growth that occur in a fetus exposed to maternal obesity in utero. Obesity is also associated with changes in intestinal microbiota, and epigenetic changes can be induced by gut microbiome metabolites such as SCFAs. Obesity-associated changes in intestinal microbiota have implications for infant microbiome development, with consequences for outcomes later in childhood.<sup>103</sup> Postnatal colonisation of the microbiome in offspring has been linked to changes in the hypothalamic–pituitary–adrenal axis, connecting brain function and intestinal bacteria.<sup>104</sup> Studies showed associations between changes in the microbiome and neurodevelopment disorders in which inflammation is implicated, such as autism spectrum disorders and attention deficit hypersensitivity disorder.<sup>105</sup> These observations suggest that the microbiome could be a further mechanism linking maternal obesity with later outcomes in the offspring.

Studies to test for causal effects of maternal obesity on offspring epigenetics in human beings are difficult; however, by using associations with paternal obesity as a negative control, the demonstration that epigenetic modifications are more strongly associated with maternal than paternal obesity<sup>88</sup> provides some support for the hypothesis that the associations of maternal obesity with offspring methylation are due to an intrauterine mechanism. The experimental demonstration that paternal diet before conception can have lasting effects on offspring outcomes through epigenetic processes does, however, add further complexity to an already complex situation.<sup>81</sup> Furthermore, many of the techniques used to investigate global DNA-methylation changes are limited in coverage of the human epigenome. For example, the Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA, USA) array used in many studies<sup>88,95</sup> covers only around 1.7% of all CpG sites in the genome and so far there has been little consideration of non-CpG methylation or 5-hydroxymethylation.<sup>106</sup> More studies are needed of the interaction of epigenetic changes with changes in the genome—data suggest that around a quarter of the variation in neonatal methylomes arises from fixed genetic variants, with the remainder from gene–environment interactions.<sup>107</sup>



### Search strategy and selection criteria

We systematically reviewed MEDLINE, Embase, and the Cochrane library with the search terms “maternal obesity”, “pre-conception”, “pregnancy”, “intergenerational”, and “offspring” or “infant” or “child” in combination with the terms “fetal programming”, “epigenetic”, “methylation”, “disease”, “immunity”, “cardiovascular”, “type 2 diabetes”, “infection”, “HIV”, “malaria”, “proinflammatory”, “cognition”, “school performance”, “psychopathology”, “mental health”, “ADHD”, “autism”, “affective disorders”, “anxiety disorders”, “eating disorders”, “psychotic disorders”, and “cerebral palsy” for articles published in English between Jan 1, 1980, and Dec 31, 2015. We selected large cohort and case-control studies that were judged relevant, with a focus on studies done in the past 10 years in human beings, but did not exclude commonly referenced and highly regarded older publications. We also included relevant references from the reference lists of articles identified by our search strategy.

### Conclusion

Although initial research linking developmental influences with major non-communicable disorders in later life focused on the effects of fetal undernutrition, increasing evidence suggests that exposure to maternal obesity also leads to an increased risk of disease in offspring. Observational studies have provided evidence for associations between maternal obesity and an increase in their offspring’s risk of obesity, coronary heart disease, stroke, type 2 diabetes, and asthma. Emerging evidence suggests that maternal obesity could be associated with poorer cognition in offspring and an increased risk of neurodevelopmental disorders, including cerebral palsy. With the exception of small studies of women with obesity who had bariatric surgery between pregnancies, there is a paucity of controlled intervention studies in which maternal obesity is reversed and the consequences for offspring are examined. However, the offspring of women who are obese and lose weight before pregnancy have reduced risk of obesity,<sup>108</sup> and insights from experimental studies support a causal effect of maternal obesity on offspring outcomes in later life. Mechanistic insights also support causal effects of maternal obesity on offspring mediated through changes in epigenetic processes and perhaps through alterations in the offspring’s gut microbiome. The panel lists key points for further research.

Greater insight is needed into the mechanisms acting in the mother, through which maternal obesity and excess nutrient supply increase risk for future metabolic disease. Pre-pregnancy obesity predisposes the mother to gestational diabetes, hypertension, and pre-eclampsia, which can affect placental function and fetal energy metabolism. Additionally, obesity in pregnancy is associated with complex neuroendocrine, metabolic,

immune, and inflammatory changes, which probably affect fetal hormonal exposure and nutrient supply.<sup>6,109</sup>

The observations linking maternal obesity with lifelong consequences for offspring have profound public health implications. More than 60% of women are either overweight or obese at conception in the USA,<sup>110</sup> and the prevalence of overweight and obesity in women of childbearing age is increasing worldwide, which will increase the population of children exposed to an obese intrauterine environment and thus perpetuate the cycle of increasing obesity and chronic-disease burden. Public health measures that will rapidly reverse the epidemic of maternal obesity seem implausible at present; in their absence, breaking the cycle of maternal and offspring obesity requires a new generation of intervention studies based on more detailed analysis of observational studies and designed with a better understanding of the underpinning mechanisms acting in the mother and their offspring.

#### Contributors

Each author drafted parts of the Series paper, which were subsequently integrated by KMG and RMR. The final version of the manuscript was corrected as necessary and approved by all authors.

#### Declaration of interests

KMG reports reimbursement for speaking at Nestlé Nutrition Institute conferences. He has patents pending for phenotype prediction, predictive use of CpG methylation, and maternal nutrition composition. SLP reports speaker fees, board member honoraria, and travel costs from the Nestlé Nutrition Institute and Danone; speaker fees and reimbursement of travel costs by ALK Abello; and consulting fees from Bayer, all outside the submitted work. The other authors declare no competing interests.

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