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Sex-dependent associations between maternal prenatal stressful life events, BMI trajectories and obesity risk in offspring: The Raine Study

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ABSTRACT

Background: There is a high and growing prevalence of childhood obesity which increases the risk of adult obesity and adverse physical and mental health outcomes in adulthood. Experimental and clinical data suggest that the early life environment, particularly prenatal stress, may program development of obesity in the offspring. But few studies have assessed the associations between prenatal maternal stress and rapid (ascending) weight gain, which is the strongest predictor of adult obesity and metabolic disease. Experimental data indicate that the associations may be sex dependent, but the sex-dependent association between prenatal stress and growth in the human offspring during childhood and adolescence is largely unexplored. The aim of this study is to investigate the association between prenatal exposure to stressful life events and childhood obesity in the offspring and whether maternal smoking during pregnancy and breastfeeding mediate this.

Method: Participants from a large prospective population-based Australian pregnancy cohort study (The Raine Study, n=2868) were closely and frequently followed from prenatal life (18 weeks gestation) through to adolescence. Maternal stressful life events were prospectively recorded at 18 and 34 weeks and childhood BMI (categorized into six z-score trajectories) was measured from 3 to age 14 years. We studied the prospective association between maternal exposure to stressful life events and BMI *z*-score trajectories in 2056 offspring (1082 boys). Mothers prospectively reported stressful life events at 18- and 34-weeks' gestation using a standardized and validated 10-point questionnaire. Age- and gender-specific *z*-scores for BMI were obtained from height and weight at age 3, 5, 8, 10 and 14 years using standardized methods. Latent class group analysis identified six distinct trajectory classes of BMI z-score. Multinomial logistic regression was used to examine the associations between maternal stressful life events and gender-specific BMI *z*-score trajectories as well as risk of overweight/obesity at each age point. Mediation analyses were also conducted to model the indirect associations through maternal smoking during pregnancy and breastfeeding.

Results: Of the 2056-included offspring, 1322 (64.3%) were exposed to at least one maternal stressful life event during early gestation and 1203 (58.5%) were exposed in late gestation. In boys, exposure to stressful life events in early but not late gestation was significantly associated with ascending (accelerated) weight-gain (ages 3–14 years) (adjusted odds ratio (aOR): 1.25, 95% CI: 1.02, 1.52) and increased risk of overweight (aOR: 1.18, 95% CI: 1.00, 1.39) aged 10 years. No similar associations were observed in girls. We observed that 29.2% of the association between more maternal stressful life events and obesity in male offspring was mediated by breastfeeding for less than 6 months. Likewise, up to 35% of the association between more maternal stressful life events and obesity in male offspring was mediated by maternal smoking during the index pregnancy.

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Conclusion: Prenatal stress in early gestation is directly associated with accelerated childhood weight gain (assessed by childhood BMI z-score trajectories) and risk of obesity in adolescent boys, but not girls and breastfeeding and maternal smoking significantly mediates this association.

1. Introduction

The worldwide obesity epidemic is a burgeoning health and economic burden [1,52]. Childhood obesity confers short-term health risks and strongly predicts adult obesity which contributes to the global burden of non-communicable disease [23,46]. Hence, understanding the determinants of childhood and adult obesity is a public health concern.

Although the tendency to accumulate fat is largely determined by genetic factors [9] as well as environmental/socio-economic risk factors [16,39], increasing evidence indicates that *in utero* exposures to stress and stress hormones may have long-term effects on offspring obesity and metabolic health [20]. Experimental studies in rodents have consistently reported that maternal stress (as restraint) leads to significantly increased caloric intake and body weight/adiposity in the offspring which persists into adulthood [32,36,38]. Human studies are very limited, but suggest that maternal stress (such as a natural disaster) increases the risk of obesity in infancy [29] which continues throughout childhood until age 15 years [6,10,11,35]. Similarly, bereavement or divorce during or prior [26] to pregnancy [34] and multiple stressful life events [4,19] have been associated with obesity in childhood and adulthood. Finally, previous reports from the Raine cohort in Western Australia showed a significant association between maternal stressful life events in pregnancy and offspring adiposity from age 8 through to 20 years [4]. However, results are not consistent and one study reports no effect of self-report of anxiety, depression or stress at 30 weeks' gestation on overweight or obesity in girls or boys age 7 years [28] and yet another reports that self-perceived stress in 36 weeks' gestation had no association with BMI z-scores in girls or boys children aged $\leq$ 5 years [31].

A limitation of many previous studies assessing maternal psychological stress and offspring body mass index (BMI) is that potential effects on BMI have only been assessed at a single time point during childhood. Furthermore, no previous studies have prospectively measured maternal stress using a standardized instrument and repeated trajectories of BMI z-scores throughout childhood and adolescence. Because rapid (ascending) weight-gain is the strongest predictor of adult obesity and metabolic and cardiovascular disease in later life [37], the trajectories of growth during childhood and adolescence are likely to be of greater clinical significance than BMI at a single time point.

Experimental data in rodents demonstrate that prenatal maternal stressors are associated with greater body weight in males but not in females, however, this remains largely unexplored in humans. Similarly, experimental data in rodents have demonstrated the importance of the timing of maternal stress exposure. These studies have shown that prenatal stress (as maternal restraint) in late but not early gestation is associated with greater body weight in the offspring when compared to non-exposed controls rats exposed to prenatal stress in early gestation [2,36,44].

There is strong evidence from human studies that maternal psychological stress is associated with delayed onset of breastfeeding, less frequent feedings and lower milk volume [14] and that breastfeeding is protective against childhood obesity [24]. Thus, breastfeeding may be an important mediator in the association between prenatal stress and BMI. Similarly, a large population-based prospective cohort study (n=71,757) demonstrated that mothers who reported high levels of stress in pregnancy were more likely to smoke [25], and there is strong evidence from human studies that maternal smoking during pregnancy is associated with an increased risk of overweight and obesity in the offspring [40]. This evidence suggests that maternal smoking during pregnancy is a potential mediator for the association between maternal stress and offspring BMI, but this has not previously been investigated.

The aim of this study was to measure the prospective association between maternal exposure to stressful life events during both early and late gestation and BMI z-score trajectories from ages 3 to 14 years in the offspring, to measure sex differences and to measure whether maternal smoking during pregnancy and breastfeeding mediate this association.

2. Methods

The Raine Study is a prospective longitudinal cohort formed from a pregnancy cohort in Western Australia, designed to measure the relationships between early life events and subsequent health and behavior [48]. The study recruited almost 3000 women, mainly white (93%) (Generation-1, Gen-1) between their 16th and 20th gestational week (GW) in the period from May 1989 to November 1991 (average recruitment at GW18). The 2868 children (Generation 2, Gen-2) (1414/1454: girls/boys) born to 2804 mothers (Gen-1) were retained to form The Raine Study [48]. Eligibility criteria included; English speaking pregnant women (between 16-20 weeks gestation) living in Western Australia, not intending to leave the state, and expecting to deliver at a tertiary maternity hospital (King Edward Memorial Hospital, Perth WA). The cohort was assessed at recruitment and throughout gestation, and the offspring were assessed at birth and then at 2–3 year intervals. At each follow-up extensive clinical and health/lifestyle questionnaire data (diet, physical activity, drug, smoking, alcohol, prescription medicines, and sexual activity) were collected [48].

Childhood BMI z-scores and trajectories from 3 to 14 years. Wearing minimal clothing and without shoes, participants were weighed with a Wedderburn Chair Scale (nearest 100 g), and height was measured with a Holtain Stadiometer (nearest 0.1 cm). BMI was calculated as: $\left[\frac{Weight,\ kg}{(height,\ m)x\ (height,\ m)}\right]$, at ages 3, 5, 8, 10 and 14 years. Age-and sex-specific normalized BMI *z*-scores were calculated using the United States of America Centers for Disease Control and Prevention (CDC) 2000 growth references for assessments from ages 3 to 14 years (Box-Cox transformation [48]).

In the present study we are using previously calculated BMI trajectories and the calculation of these has been described previously [47]. In brief, multilevel mixed-effects linear regression for estimating developmental trajectories was applied. The model is a latent growth curve model assuming a continuous, multivariate normal distribution of intercept and slope parameters within the population. The Latent Class Group Analysis (LCGA) uses finite mixture models to estimate discrete groupings of trajectory parameters estimated using maximum likelihood, and thus accounts for the varying pathways to overweight and obesity in childhood [33,50]. A categorical variable was determined describing the trajectories of the age-and sex-specific normalized BMI *z*-score from 3 to 14 years for each of the offspring (SAS, macro PROC TRAJ). A series of models using all available data estimating two to eight latent trajectory classes with linear and quadratic terms for each group was systematically fitted and compared using the Bayesian Information Criterion (BIC) statistic. The choice of the number of groups was therefore guided by the goal of analysis and confirmation of model adequacy based on posterior probability diagnostics. Model validity was confirmed by replicating the latent class solution by random split-half sampling. Subjects were assigned to the trajectory group for which they had the highest probability of membership (Fig. 1). A six-class model was selected as best describing the trajectories of BMI *z*-scores, consisting of '*Very Low*' (3.9%) displaying a slight linear increase in very low scores; '*Low*' (22.2%) displaying below average scores; '*Average*'

(33.9%) displaying average scores following a slight initial decrease; '*Ascending*' (7.0%) with below average BMI z-scores at year 3, which increased to above average BMI *z*-scores during childhood with some leveling off into adolescence; '*Moderate High*' (26.7%) displaying slightly increasing, above average scores over childhood, leveling to scores in the overweight range (> 85th percentile); and a '*High*' (6.3%) class displaying consistently high scores in the overweight range (> 95th percentile).

Maternal Stressful Life Events. We used a 10-item questionnaire based on the 67-item Stressful Life Event Inventory developed by Tennant and Andrews for an Australian population [49]. In brief, the complete Tennant inventory was derived from established scales [27] and includes a wide range of stressful life events. Dimensions include health concerns, loss and bereavement, family conflicts and social relations, friends and relatives, educational concerns, job security, moving to a new house, finance and legal issues. In order to apply the Tennant inventory to stressful life events in pregnant women, the Raine Study created a 10-item inventory which included at least one item from each dimension. To allow women to include stressful events that were not included in the 10-item scale, an option to report "other problems" was created for this cohort. Stressful life events included death of a close relative, death of a close friend, separation or divorce, marital problems, problems with children, own involuntary job loss, partner's involuntary job loss, money problems, pregnancy concerns, residential moves and other events (unspecified). At 18 gestational weeks, mothers were asked to record stressful life events experienced since confirmation of their pregnancy and at 34 gestational weeks they were asked about events in the preceding 4 months, to ensure that the same event was not reported twice. The response to each item in the questionnaire was recorded as "yes/no" once, in accordance with previous studies to maximize recall. Separate continuous variables including the total number of maternal stressful life events reported at gestation weeks 18 and 34 were created weighting each event equally.

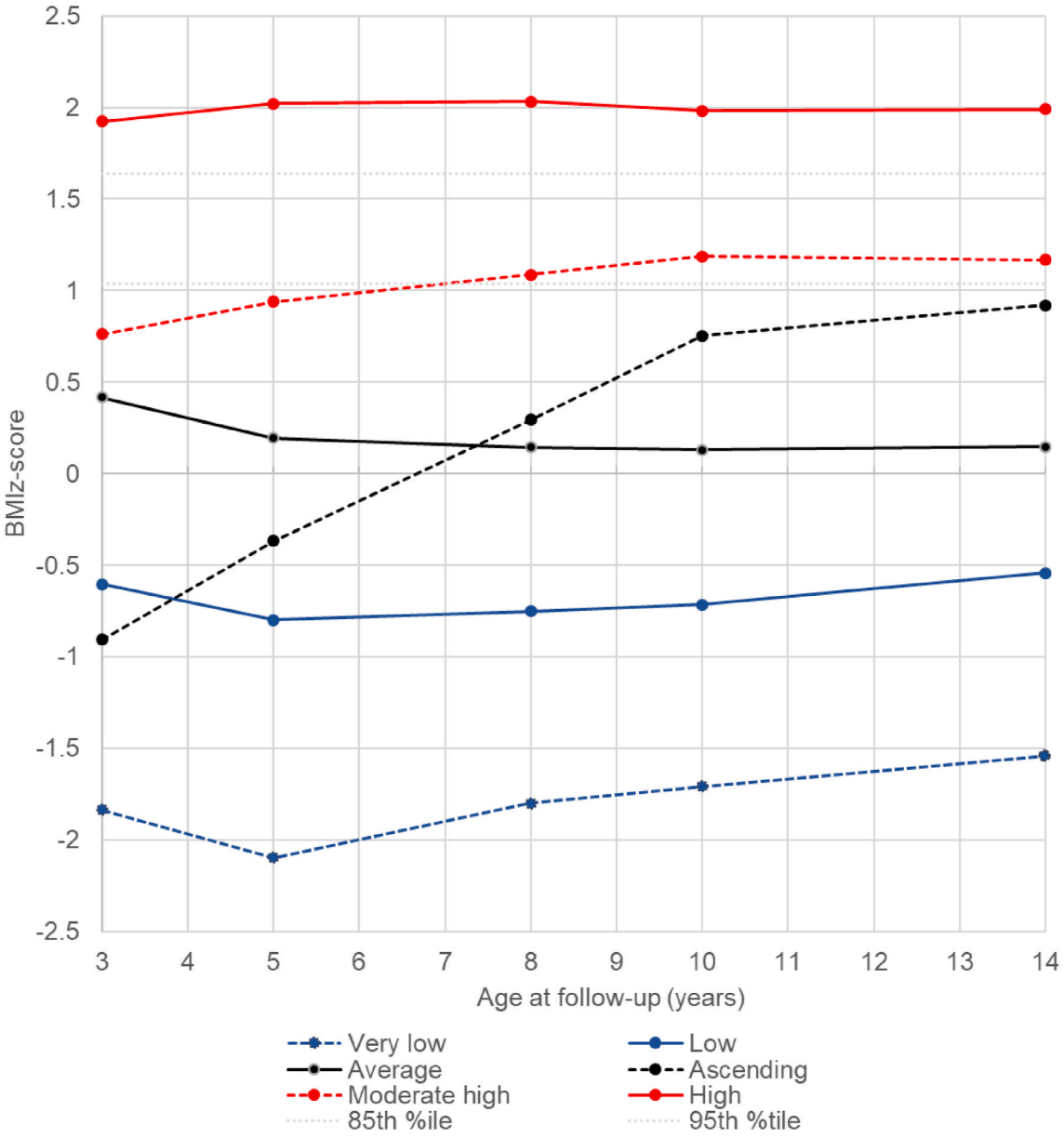


Fig. 1. BMI z-score trajectories in a six-class model following latent class group analysis. Follow-up points are age in years and y-axis indicates BMI z-scores. The 85th and 95th percentile in BMI z-scores are indicated with dotted lines.

2.1. Statistical approach

Descriptive data for exposures, co-variates and outcomes were computed. Continuous data were summarized using medians and interquartile ranges (IQRs), and categorical data were summarized using frequency distributions.

First, a multinomial logistic regression model was used to calculate the odds ratio (OR) and 95% confidence intervals (CI) for the association between maternal stressors (timing [early and late gestation] and number as an independent continuous variable) and the child BMI z-trajectory patterns generated from the trajectory model described above using the class "*average, consistent growth*" as the reference.

Second, the same regression approach was used to calculate the odds ratio (OR) and 95% CI for the association between maternal stressors (timing [early and late gestation] and number, independent continuous variable) and childhood overweight/obesity, with a separate model for each age and with sex stratification, using normal weight (BMI *z*-score $<$ 1.04) as the reference group. Overweight and obesity were categorized according to the criteria from the CDC as: overweight (1.04 $\leq$ z-score$<$1.64) and obese (z-score $\geq$ 1.64) [7].

All models were stratified by sex, introducing an interaction term for the offspring sex. All associations were assessed by separately examining the effects of early gestational stressful life event exposures (reported at 18 weeks) and late gestational exposures (reported at 34 weeks). Models addressing effects of stressful life event in late gestation (34 weeks) were mutually adjusted for events reported in early gestation (introduced as a continuous variable).

All estimates are reported as crude and main model based on complete case analysis. The main models were adjusted for potential confounders including maternal [age (continuous), pre-pregnancy BMI (continuous), pregnancy weight gain (continuous), parity (dichotomized 0 or $\geq$ 1) and proxies of socio-economic status (SES) [total household annual income: dichotomized to reflect a minimum income level ($<$ $24,000 p.a. or $\geq$ $24,000 p.a.) according to the Australian Government guidelines at the time of the pregnancies (1989–1991), education (none or trade certificate, profession registration, college diploma, university degree, other) and marital status (never married/single, married/de facto, separated/divorced or widowed)]]. Causal directed acyclic graphs were used to explore different causal scenarios between the maternal psychological stress exposure and BMI trajectories to reduce conditional associations and confounding bias [46].

In order to further understand potential mechanisms underlying the association between maternal stressful life events and BMI-z score trajectories and obesity, the potential mediating (indirect) effects of maternal smoking during pregnancy [yes/no (reference)] and breastfeeding [$<$ 6 months/$\geq$ 6 months (reference)] were investigated separately in additional sub-analyses. Mediation analyses were conducted by using nonparametric estimation methods to model the indirect association between exposures [stressful life events (early, late and total gestation)] and outcomes [BMI z-scores, BMI z-score trajectories] through changes in the mediating variable (breastfeeding or maternal smoking assessed separately). In the mediation analyses, a pathway is specified a *priori*, wherein stressful life events influence the mediator, which in turn affects the outcome of interest. The model assumes no unmeasured confounding or effect modification between the included elements. Outcomes and mediating variables were treated as ordinal variables. The proportion mediated describes the average magnitude of the indirect association between exposure (maternal stressful life events) and the outcome through changes in the mediating variable relative to the average total association. Nonparametric bootstrapping with 100 simulations was applied to obtain accurate p values of the estimates of the total effects, direct effects, as well as median effects in the *lavaan* package in R. All analyses were conducted using SAS (v9.4) (Cary, NC, USA) and the R software package (v3.6.1) (R Development Core Team, https://cran.r-project.org/). A p-value $<$ 0.05 was considered statistically significant.

The Raine Study was approved by the University of Western Australia Human Research Ethics Committee and written informed consent was obtained from all participants prior to enrollment. The study is reported according to the STROBE (Strengthening the Reporting of Observational Studies) guidelines and checklist.

3. Results

Of 2868 mother-offspring pairs, we were unable to classify 471 BMI *z*-score trajectories due to missing data and excluded 341 who had missing maternal stressful life event data and/or confounder information leaving 2056 pairs (1082/974: sons/daughters) with complete information for the main analyses. Excluded mother-offspring pairs had similar parity prior to index pregnancy, pregnancy weight gain and exposure to stressful life events, but were slightly younger at recruitment than the included mother-offspring pairs (not shown in tables).

Mothers of boys and girls had similar age, parity (at the time of the index pregnancy), socio-economic status (income, education and marital status), pre-pregnancy BMI, pregnancy weight gain and they reported similar exposures to maternal stressful life events. As expected, boys were significantly larger at birth (weight and height) than girls ($p < 0.001$) but were breastfed with similar prevalence (Table 1).

Of the 2056-included children, 1322 (64.3%) were exposed to at least one maternal stressful life event during early gestation and 1203 (58.5%) during late gestation. The distribution of exposure to maternal stressful life events was similar for male and female offspring in early gestation (male: female/64.9%:63.7%; $p_{difference} = 0.563$), but in late gestation exposure to stressful life events was more prevalent among boys (male: female/61.2%:55.5%; $p_{difference} = 0.010$) (Table 1).

The distribution of the six-class BMI z-score trajectory model during childhood/adolescence was similar for males and females in each class ($p = 0.362$) (Table 1). The proportion of overweight/obese was respectively, 18.2, 18.3, 20.8, 25.8 and 25.0% at the 3, 5, 8, 10 and 14 year follow-ups (Fig. 2), and sex-distribution was similar at all ages ($p < 0.380$). The proportion of overweight and obese children in the present study is similar to contemporary Australian normative values for this age group [population of Australia children aged 5–14 years overweight (17%) or obese (7.7%)] [3].

The results of the multinomial logistic regression analyses of associations between exposures to maternal stressful life events (introduced as a continuous variable) and individual BMI z-score trajectories during childhood for male and female offspring are displayed in Table 2. The consistent (average) growth BMI z-score trajectory was chosen as the reference group given that all the participants had relatively stable and consistent BMI growth through early childhood relative to the other growth curves. From ages 3 to 14 years, each increment increase in exposure to maternal stressful life events in early gestation was significantly associated with ascending weight-gain in boys (adjusted odds ratio (aOR): 1.25, 95% CI: 1.02, 1.52), but not in girls (aOR (ascending): 0.90, 95% CI: 0.72, 1.12). No statistically significant associations between exposure to maternal stressful life events in late gestation and individual BMI z-score trajectories (ages 3 to 14 years) in the offspring were detected and estimates for ascending weight gain were of the same magnitude and direction for boys (aOR: 1.18, 95% CI: 0.93, 1.50) and girls (aOR: 1.18, 95% CI: 0.93, 1.49) (Table 2).

The results of the multinomial logistic regression analyses of associations between exposure to maternal stressful life events and individual point BMI z-score at ages 3, 5, 8, 10 and 14 years are presented in Table 3. Exposure to maternal stressful life events in early but not late gestation was associated with an increased risk of overweight in boys (aOR: 1.18, 95% CI: 1.00, 1.39) aged 10 years, and similar estimates (direction and magnitude) were detected at 14-years (without reaching statistical significance). There were no statistically significant associations between exposure to maternal stressful life events and individual BMI z-scores in female offspring regardless of the timing of exposure (Table 3).

Table 1
Participant characteristics of 2056 mothers and their offspring.

	Total sample (n=2056)	Boys (n=1082)	Girls (n=974)	P-value*
	Median (25th; 75th ‰)/N (%)			
Maternal characteristics of Generation 1 (mothers) at the index pregnancy				
Age at pregnancy (years)	28 (24; 32)	28 (24; 32)	28 (24; 32)	0.474
Nulliparous[a]	1 086 (52.8)	572 (52.9)	514 (52.8)	0.966
Maternal smoking[a]	493 (24.0)	238 (22.0)	255 (26.2)	0.026
Pre-pregnancy BMI (kg/m^2)	21.5 (19.8; 23.8)	21.4 (19.7; 23.9)	21.5 (19.9; 23.8)	0.593
Socio-economic status				
Low household income[b]	840 (40.9)	445 (41.1)	395 (40.6)	0.792
Highest level of education				
None	1 002 (48.7)	534 (49.3)	468 (48.0)	0.392
Trade certificate	175 (8.5)	80 (7.4)	95 (9.8)	
Profession registration	201 (9.8)	102 (9.4)	99 (10.2)	
College diploma	346 (16.8)	188 (17.4)	158 (16.2)	
University degree	231 (11.3)	120 (11.1)	111 (11.4)	
Other	101 (4.9)	58 (5.4)	43 (4.4)	
Marital status				
Never married or single	219 (10.7)	113 (10.4)	106 (10.9)	0.884
Married or de facto	1 773 (86.2)	937 (86.6)	836 (85.8)	
Separated or divorced	61 (3.0)	31 (2.9)	30 (3.1)	
Widowed	3 (0.1)	1 (0.1)	2 (0.2)	
Pregnancy factors of Generation 1 (mothers)[a]				
Pregnancy weight gain (kg)	8.5 (6.5; 11.0)	8.6 (6.6; 11.0)	8.5 (6.4; 11.0)	0.186
Stressful life event (≥ 1 event)				
Early gestation	1 322 (64.3)	702 (64.9)	620 (63.7)	0.563
Late gestation	1 203 (58.5)	662 (61.2)	541 (55.5)	0.010
Generation 2 (offspring) characteristics				
Birth length (cm)	49 (48; 50.5)	49.5 (48; 51)	49 (47; 50)	<0.001
Birth weight (g)	3385 (3045; 3698)	3455 (3105; 3780)	3300 (2990; 3625)	<0.001
Breastfed	1 745 (90.7)	927 (91.6)	818 (89.7)	0.150
< 6 months	697 (39.9)	370 (39.9)	327 (40.0)	0.979
≥ 6 months	1 048 (60.1)	557 (60.1)	491 (60.0)	
BMI z-score trajectory (3 to 14 years)				
Very low	81 (3.9)	43 (4.0)	38 (3.9)	0.362
Low	457 (22.2)	256 (23.7)	201 (21.6)	
Average (consistent growth)	697 (33.9)	358 (33.1)	339 (34.8)	
Ascending	144 (7.0)	75 (6.9)	69 (7.1)	
Moderate high	548 (26.7)	275 (25.4)	273 (28.0)	
Very high	129 (6.3)	75 (6.9)	54 (5.6)	

*Differences by offspring sex compared using Pearson's chi squared test (categorical variables) or two-independent-samples *t*-test (continuous variables).

[a] At the index pregnancy.

[b] Average annual family income level per annum below AUD 24,000 reflecting the minimum income level in 1989–1991, according to the Australian Government guidelines.

Mediation analyses showed that more maternal stressful life events in early gestation but not late gestation was associated with less breastfeeding (<6 months), which explained overweight in boys at age 10 (29.2% attributed to breastfeeding < 6 months) and 14 years (17.2% attributed breastfeeding < 6 months). In contrast no mediating effect of breastfeeding on the association between maternal stressful life events (any time during pregnancy) and overweight in girls was detected. More maternal stressful life events in early gestation but not late gestation was also associated with maternal smoking during pregnancy which explained overweight in boys at age 10 by 35.3% and 14 years by 21.5% (Table 4). No mediating effects of maternal smoking or breastfeeding on the association between maternal stressful life events and BMI z-score trajectories were detected (results not shown).

4. Discussion

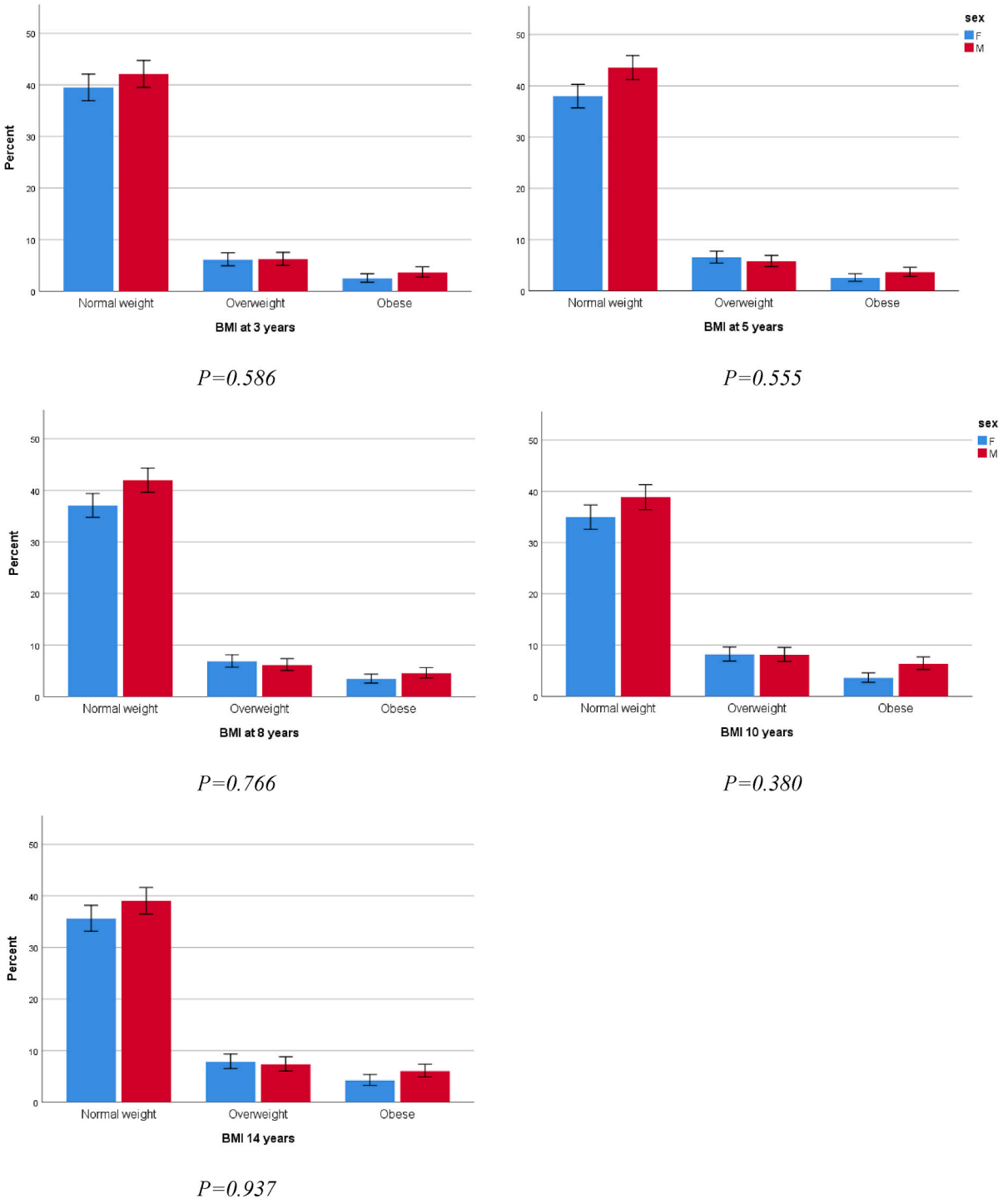
This is the first prospective study quantifying effects of maternal stressful life events and BMI z-score trajectories and risk of obesity in the offspring from 3-years to adolescence by sex. Our results indicate that prenatal exposure to stressful life events in early but not late gestation is associated with accelerated weight-gain (from ages 3 to 14 years) and increased risk of obesity (at age 10 years) in male adolescent offspring. No similar association was observed in female offspring. Our findings that maternal stressors exert sex-specific effects on childhood overweight and obesity, add to the growing evidence that prenatal programming may exert sex-specific effects on the offspring.

Childhood obesity is a harbinger for adult obesity [23,45] and short- and long-term physical and mental health [12,41]. Our findings suggest a novel potential driver of childhood obesity in boys is early pregnancy maternal stress. This is supported by experimental data in rodents, demonstrating that maternal stressors are associated with greater body weight in males, but not in females [44]. To date this area remains largely unexplored in humans, in support of our finding, one previous study reports a small non-significant tendency of overweight in boys, but not girls associated with maternal stressor in gestational week 30 [28]. A prospective human study during the Dutch Famine reported that maternal malnutrition was associated with childhood obesity, but only in male offspring, supporting our findings about sex specific effects of prenatal stressors [43]. Further, in the Raine Study it has previously been reported that overall prenatal stressors were significantly associated with adult BMI from age 8 increasing through to 20 years. However, although that study is based on the same cohort as the present study, authors considered a different age group and did not consider whether stressor were in the early or late gestational period or whether these associations differed by sex [4]. Finally, another longitudinal study reports that self-perceived maternal postnatal stress at 1 year only increased obesity in girls but not boys aged ≤ 5 years [31]. However, this study only measured gender differences in postnatal and not prenatal stress. Prenatal stress has the potential to confer direct physiological effects on the developing fetus whilst postnatal stress is likely to be mediated by behavioral factors such as parenting style and mother-child interactions.

In this present study we report that timing of exposure to maternal stressors in early gestation, but not late, affects the risk of accelerated growth and obesity in the offspring. Preclinical observations in rodents indicate that timing of prenatal stress is important [2,36], and one previous human study has reported that both pre- and post-natal stress were positively associated with BMI at 54 months [18]. Further studies in humans are needed to validate whether BMI is associated with the timing of prenatal stress.

The underlying mechanisms driving the association we find between maternal stressful life events and accelerated childhood increase in BMI, and risk of obesity in boys are uncertain. Preclinical data indicate that maternal stressors elevate circulating glucocorticoids which cross the placenta into fetal circulation, which may cause endocrine dysregulation and influence the development of the hypothalamic-pituitary-adrenocortical axis, and metabolism in later life [13]. Although these mechanisms are not expected to be exclusive to boys, findings from experimental studies support the plausibility of an association between prenatal psychological stress and obesity in later life [5,15,30,42]. These studies demonstrate that administration of glucocorticoids during pregnancy programs greater obesity in the offspring in later life [5,15,30,42]. Human studies also indicate that maternal circulating glucocorticoids in mid-to-late gestation (26–38 weeks) are positively associated with BMI z-scores in offspring at age 3 years [21].

We observed that 29.2% of the association between more maternal



Definition of overweight and obesity is based on the Centers for Disease Control and Prevention definition of overweight as: 1.04≤ BMI *z*-score < 1.64 (85th-95th percentile) and obesity as a BMI *z*-score ≥ 1.64 (≥95th percentile)

Fig. 2. Proportion of normal [BMI z-score < 1.04 (85th percentile)] and overweight/obese [BMI z-score ≥ 1.04 (85th percentile)] Gen-2 offspring during follow-up overall and stratified by sex.

stressful life events and obesity in male offspring was mediated by breastfeeding for less than 6 months. Breast milk contains numerous protective nutrients and anti-inflammatory components [51] and the World Health Organization recommends that breastfeeding is initiated within 1 h after birth and continued for at least 6 months to secure optimal maternal and newborn health [53]. There is strong evidence from human studies that being breastfed is protective against childhood obesity [24] and that longer duration of breastfeeding is more protective [24]. Maternal stress is associated with delayed onset of breastfeeding, less frequent feedings and lower milk volume [14]. Thus, our novel observation that less breastfeeding may be a mediator of the association between maternal stress and male offspring obesity may indicate novel

Table 2
Odds Ratio (OR) and 95% confidence intervals (CIs) from the multi-nominal logistic regression analyses of stressful life events (continuous) and BMI trajectories in childhood (3 to 14 years), stratified by sex. Consistent growth is the reference group.

	Boys (n=1082)		Girls (n=974)		Sex difference (P-value$_{interaction}$)	
BMI growth trajectory	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]
Early gestation						
Very low	0.72 (0.52; 0.99)	0.66 (0.47; 0.93)	0.97 (0.74; 1.27)	0.96 (0.72; 1.28)	0.159	0.150
Low	0.93 (0.81; 1.07)	0.89 (0.78; 1.03)	0.93 (0.80; 1.07)	0.94 (0.81; 1.09)	0.927	0.927
Average (consistent growth)	Reference	Reference	Reference	Reference	Reference	Reference
Ascending	1.19 (0.99; 1.43)	1.25 (1.02; 1.52)	0.94 (0.76; 1.16)	0.90 (0.72; 1.12)	0.097	0.094
Moderate high	1.05 (0.92; 1.19)	1.01 (0.88; 1.15)	0.98 (0.86; 1.11)	0.95 (0.84; 1.09)	0.473	0.545
High	1.05 (0.86; 1.28)	1.02 (0.82; 1.27)	0.96 (0.76; 1.21)	0.95 (0.74; 1.21)	0.565	0.738
Late gestation[b]						
Very low	1.13 (0.81; 1.56)	1.07 (0.77; 1.50)	0.85 (0.59; 1.21)	0.86 (0.60; 1.22)	0.584	0.656
Low	1.06 (0.90; 1.24)	1.03 (0.87; 1.22)	1.06 (0.90; 1.25)	1.09 (0.92; 1.29)	0.992	0.947
Average (consistent growth)	Reference	Reference	Reference	Reference	Reference	Reference
Ascending	1.14 (0.90; 1.44)	1.18 (0.93; 1.50)	1.21 (0.96; 1.52)	1.18 (0.93; 1.49)	0.709	0.631
Moderate high	1.14 (0.97; 1.33)	1.10 (0.94; 1.29)	1.12 (0.97; 1.30)	1.08 (0.93; 1.26)	0.705	0.706
High	1.17 (0.92; 1.48)	1.08 (0.84; 1.40)	1.25 (0.97; 1.60)	1.19 (0.92; 1.55)	0.912	0.832

[a] Model adjusted for maternal {age, pre-pregnancy BMI, pregnancy weight gain, socioeconomic status [total household annual income: dichotomized to reflect a minimum income level (< $24,000 p.a. or ≥ $24,000 p.a.) according to the Australian Government guidelines at the time (1989–1991), highest level of education (none or trade certificate/profession registration/college diploma/university degree/other) and marital status (single, married/de-facto, separated/divorced, widowed)]} and parity (dichotomized 0 or ≥ 1).
[b] Models in LATE GESTATION adjusted for stressful life events reported in EARLY GESTATION.

Table 3
Odds Ratio (OR) and 95% confidence intervals (CIs) from the multi-nominal logistic regression analyses of stressful life events (continuous) and overweight/obesity[a] in childhood (3 to 14 years), stratified by sex.

		Boys (n=1082)		Girls (n=974)		Sex difference (P-value$_{interaction}$)	
		Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]
Early gestation							
3-years	Overweight	1.02 (0.84; 1.25)	1.02 (0.83; 1.25)	0.96 (0.79; 1.16)	0.96 (0.79; 1.18)	0.627	0.737
	Obese	1.13 (0.90; 1.43)	1.11 (0.87; 1.43)	1.06 (0.81; 1.38)	1.05 (0.79; 1.41)	0.696	0.767
5-years	Overweight	1.01 (0.84; 1.20)	0.98 (0.82; 1.19)	1.08 (0.93; 1.26)	1.06 (0.90; 1.26)	0.544	0.347
	Obese	1.01 (0.82; 1.26)	0.98 (0.77; 1.24)	1.01 (0.79; 1.29)	0.99 (0.77; 1.28)	0.964	0.838
8-years	Overweight	1.08 (0.91; 1.27)	1.09 (0.91; 1.29)	0.94 (0.80; 1.12)	0.90 (0.75; 1.07)	0.275	0.308
	Obese	0.96 (0.79; 1.18)	0.94 (0.76; 1.17)	0.90 (0.71; 1.13)	0.90 (0.70; 1.16)	0.656	0.901
10-years	Overweight	1.18 (1.01; 1.37)	1.18 (1.00; 1.39)	0.93 (0.79; 1.11)	0.91 (0.76; 1.09)	0.048	0.069
	Obese	1.07 (0.89; 1.28)	1.04 (0.86; 1.27)	1.04 (0.83; 1.31)	1.04 (0.81; 1.33)	0.873	0.882
14-years	Overweight	1.18 (0.99; 1.41)	1.17 (0.98; 1.40)	1.06 (0.90; 1.26)	1.06 (0.89; 1.27)	0.392	0.585
	Obese	1.25 (1.04; 1.50)	1.18 (0.96; 1.46)	1.16 (0.94; 1.44)	1.20 (0.95; 1.50)	0.637	0.742
Late gestation[c]							
3-years	Overweight	0.94 (0.74; 1.19)	0.91 (0.72; 1.16)	1.11 (0.90; 1.37)	1.08 (0.88; 1.34)	0.441	0.386
	Obese	1.32 (1.03; 1.71)	1.25 (0.95; 1.65)	1.29 (0.97; 1.72)	1.28 (0.95; 1.74)	0.827	0.988
5-years	Overweight	1.05 (0.85; 1.29)	0.98 (0.79; 1.22)	1.00 (0.84; 1.21)	0.94 (0.78; 1.14)	0.984	0.854
	Obese	1.20 (0.95; 1.53)	1.11 (0.86; 1.42)	0.90 (0.67; 1.22)	0.87 (0.64; 1.19)	0.181	0.232
8-years	Overweight	0.95 (0.78; 1.16)	0.90 (0.73; 1.12)	1.14 (0.96; 1.36)	1.08 (0.90; 1.30)	0.427	0.398
	Obese	1.20 (0.97; 1.48)	1.11 (0.89; 1.40)	0.86 (0.65; 1.14)	0.79 (0.59; 1.06)	0.063	0.086
10-years	Overweight	0.97 (0.80; 1.17)	0.94 (0.77; 1.14)	1.15 (0.96; 1.37)	1.09 (0.91; 1.31)	0.713	0.677
	Obese	1.06 (0.86; 1.31)	0.98 (0.78; 1.22)	1.04 (0.80; 1.35)	0.98 (0.74; 1.28)	0.861	0.981
14-years	Overweight	0.98 (0.79; 1.22)	0.98 (0.79; 1.23)	1.23 (1.02; 1.48)	1.18 (0.98; 1.43)	0.281	0.237
	Obese	1.04 (0.83; 1.30)	0.93 (0.72; 1.20)	1.17 (0.93; 1.49)	1.11 (0.86; 1.42)	0.634	0.307

[a] Based on the Centers for Disease Control and Prevention definition of overweight as: 1.04≤ BMI z-score < 1.64 (85th-95th percentile) and obesity as a BMI z-score ≥ 1.64 (≥95th percentile).
[b] Model adjusted for maternal {age, pre-pregnancy weight, pregnancy weight gain, socioeconomic status [total household annual income: dichotomized to reflect a minimum income level (< $24,000 p.a. or ≥ $24,000 p.a.) according to the Australian Government guidelines at the time (1989–1991), highest level of education (none or trade certificate/profession registration/college diploma/university degree/other) and marital status (single, married/de-facto, separated/divorced, widowed)]} and parity (dichotomized 0 or ≥ 1).
[c] Models in LATE GESTATION adjusted for stressful life events reported in EARLY GESTATION.

interventions encouraging breastfeeding that may potentially prevent childhood obesity in offspring.

We observed that up to 35% of the association between more maternal stressful life events and obesity in male offspring was mediated by maternal smoking during the index pregnancy. There is strong evidence from human studies that maternal smoking during pregnancy is associated with an increased risk of overweight and obesity in the offspring [40]. A large population-based prospective cohort study (n=71,757) has shown that maternal smoking is more prevalent among mothers who reported higher levels of stress during pregnancy, measured as depression and anxiety [25]. This suggests that maternal smoking during pregnancy is a potential mediator for the association of maternal psychological stress and offspring BMI, but this has not previously been investigated. Our findings suggest that reducing maternal stress might help mothers reduce levels of smoking which would then confer substantial health benefits for the offspring.

Strengths of this study include, large sample size and detailed prospective data collected using standardized questionnaires measuring maternal stressful life events during both early and late gestation. This minimized the possibility of recall bias. Further strengths include

Table 4
Mediation of breast feeding and maternal smoking during pregnancy on the association between maternal psychological stress and overweight in offspring[a].

Sex	Timing of exposure	Mediator	Age (years)	Parameter	Effect, β (SE)	Proportion mediated (%)
Male	Early gestation	Breastfeeding [< 6 months/≥ 6 months (reference)]	10	Total effect	0.078 (0.046)	29.2
				Effect not mediated by breastfeeding	0.055 (0.046)	
				Effect mediated by breastfeeding	0.023 (0.014)	
			14	Total effect	0.122 (0.047)	17.2
				Effect not mediated by breastfeeding	0.101 (0.048)	
				Effect mediated by breastfeeding	0.021 (0.011)	
		Maternal smoking during pregnancy [yes/no (reference)]	10	Total effect	0.078 (0.046)	35.3
				Effect not mediated by maternal smoking	0.051 (0.050)	
				Effect mediated by maternal smoking	0.028 (0.016)	
			14	Total effect	0.122 (0.047)	21.5
				Effect not mediated by maternal smoking	0.096 (0.051)	
				Effect mediated by maternal smoking	0.026 (0.014)	
Female	Late gestation	Maternal smoking during pregnancy [yes/no (reference)]	14	Total effect	0.104 (0.036)	24.4
				Effect not mediated by maternal smoking	0.078 (0.038)	
				Effect mediated by maternal smoking	0.025 (0.014)	

[a] Conducted by using nonparametric estimation methods to model the indirect association between exposures [stressful life events (early and late gestation)] and outcomes BMI z-scores (only significant mediation shown here), BMI z-score trajectories (not significant and not shown here)] through changes in the mediating variable.

prospectively collected measures of potential confounders and mediators which minimized information and selection bias. The longitudinal collection of childhood BMI at multiple ages in both male and female offspring, and the normalization of BMI to sex and age-specific z-scores, as well as the application of BMI z-score trajectories, are a major strength of this study.

There are some limitations, obesity is a multifactorial outcome and socio-economic status and genetic factors play major roles in the development of obesity [9,17]. Our analyses were adjusted for the mother's pre-pregnancy weight and weight gain during pregnancy, as well as several well-defined proxies of socio-economic status (income, education and marital status). However, we cannot exclude the influence of unmeasured pre- and postnatal factors, for example we did not measure pubertal stage in the offspring which could be an important confounder. In addition, there are numerous potential mechanisms by which maternal factors may influence the offspring via non-biological (e.g. psychological and psychosocial) mechanisms relating to offspring food insecurity, physical activity and diet. It is not possible to account for all these factors. In addition, women may vary in their response to stressful events and measures of perceived stress severity which individually quantify the womens perception about the stressfulness of life may have been more relevant as these would be influenced by the sum of all events. We performed many analyses in the present study, which may have led to an increased risk of false positive type I errors.

4.1. Perspectives

Maternal stressful life events in early gestation may have adverse implications for ascending weight-gain and increased risk of childhood obesity in male offspring, with consequent adverse short and long-term health implications. Further studies are needed to understand the mechanisms underlying these associations.

5. Conclusion

Exposure to prenatal stressful life events in early gestation is directly associated with ascending childhood weight gain (assessed by childhood BMI z-score trajectories) and risk of obesity in adolescent boys, but not girls. Obesity in boys carries extensive adverse long-term health implications. Further studies are needed to confirm these associations and better understand the underlying mechanisms.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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