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ORIGINAL ARTICLE

Modifiable risk factors in the first 1000 days for subsequent risk of childhood overweight in an Asian cohort: significance of parental overweight status

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BACKGROUND/OBJECTIVE: Many studies have identified early-life risk factors for subsequent childhood overweight/obesity, but few have evaluated how they combine to influence risk of childhood overweight/obesity. We examined associations, individually and in combination, of potentially modifiable risk factors in the first 1000 days after conception with childhood adiposity and risk of overweight/obesity in an Asian cohort.

METHODS: Six risk factors were examined: maternal pre-pregnancy overweight/obesity (body mass index (BMI) $\geqslant 25\ kg\ m^{-2}$), paternal overweight/obesity at 24 months post delivery, maternal excessive gestational weight gain, raised maternal fasting glucose during pregnancy ($\geqslant 5.1\ mmol\ l^{-1}$), breastfeeding duration < 4 months and early introduction of solid foods (< 4 months). Associations between number of risk factors and adiposity measures (BMI, waist-to-height ratio (WHtR), sum of skinfolds (SSFs), fat mass index (FMI) and overweight/obesity) at 48 months were assessed using multivariable regression models.

RESULTS: Of 858 children followed up at 48 months, 172 (19%) had none, 274 (32%) had 1, 244 (29%) had 2, 126 (15%) had 3 and 42 (5%) had $\geqslant 4$ risk factors. Adjusting for confounders, significant graded positive associations were observed between number of risk factors and adiposity outcomes at 48 months. Compared with children with no risk factors, those with four or more risk factors had s.d. unit increases of 0.78 (95% confidence interval 0.41–1.15) for BMI, 0.79 (0.41–1.16) for WHtR, 0.46 (0.06–0.83) for SSF and 0.67 (0.07–1.27) for FMI. The adjusted relative risk of overweight/obesity in children with four or more risk factors was 11.1 (2.5–49.1) compared with children with no risk factors. Children exposed to maternal pre-pregnancy (11.8 (9.8–13.8)%) or paternal overweight status (10.6 (9.6-11.6)%) had the largest individual predicted probability of child overweight/obesity.

CONCLUSIONS: Early-life risk factors added cumulatively to increase childhood adiposity and risk of overweight/obesity. Early-life and preconception intervention programmes may be more effective in preventing overweight/obesity if they concurrently address these multiple modifiable risk factors.

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INTRODUCTION

Recent findings have highlighted the importance of pre-conceptional health and nutrition on later offspring health.[1,2] Mounting evidence also suggests that the first 1000 days of life, spanning from conception to age 24 months, represents a crucial period for the development of later overweight/obesity and hence an opportunity for prevention.[3] A number of potentially modifiable risk factors spanning this important window, such as parental obesity,[4,5] excessive gestational weight gain (GWG),[6,7] maternal smoking during pregnancy,[8,9] gestational glycemia[10,11] and short breastfeeding duration,[12,13] have been positively associated with risk of subsequent childhood overweight or obesity. However, most prior studies have assessed these risk factors individually only; few have evaluated how they combine to influence risk of childhood overweight/obesity. To better understand their potential public health impact, these risk factors should be evaluated in combination, rather than one at a time. Gillman and Ludwig[14] reported that a combination of four modifiable risk factors (excessive GWG, smoking during pregnancy, breastfeeding < 12 months and infant sleep < 12 h per day) predicted an obesity prevalence of 28% at 7–10 years, compared with 4% in children who had none of those risk factors. Similar findings were observed in a UK mother–offspring cohort, which reported that children with four or five risk factors (pre-pregnancy obesity, excessive GWG, smoking during pregnancy, breastfeeding < 1 month and low maternal vitamin D) were at higher risk of developing obesity at 4 and 6 years, compared with children who had none.[15] However, neither of these studies included

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information on paternal overweight/obesity or maternal fasting glucose (FPG) in their analyses. Both risk factors have been shown to impair subsequent metabolic health of offspring[16,17] and are potentially modifiable through behavior change intervention.[3,18] Including paternal overweight/ obesity and maternal FPG in our analysis simultaneously allows comparison of their independent contributions to the offspring's risk for subsequent overweight/ obesity.

We are not aware of any similar studies conducted in Asian populations, whose susceptibility to obesity and metabolic disease differs from that of Europeans.[19] Among school-going children in Singapore, the prevalence of overweight/obesity has risen steadily from 1.4% in 1976 to 11% in 2013.[20] Therefore, studies on the relation between the combined effects of early-life risk factors on child overweight/obesity and direct measures of adiposity in Asian populations are needed to inform clinical practice and public health policies. Such information is increasingly important in Western countries as well, given current and future immigration patterns in those settings.

Using data from a prospective mother-offspring Asian cohort in Singapore, we aimed to examine the associations of six potentially modifiable risk factors in combination (maternal pre-pregnancy and paternal overweight, excessive GWG, raised FPG during pregnancy, duration of any breastfeeding <4 months and early solid food introduction) with adiposity and overweight/obesity at age 48 months. We hypothesized a positive and graded association between the number of these risk factors and child adiposity and risk of overweight/obesity.

MATERIALS AND METHODS

Study population

The Growing Up in Singapore Towards healthy Outcomes study has been previously described in detail.[21] Briefly, pregnant women in their first trimester were recruited from two major public maternity hospitals in Singapore (KK Women's and Children's Hospital and National University Hospital) between June 2009 and September 2010. Of 3751 women screened, 2034 met eligibility criteria (detailed in Soh *et al.*[21]), 1247 were recruited and 1170 had singleton deliveries (Supplementary Figure 1). Informed written consent was obtained from the women and the study was approved by the National Healthcare Group Domain Specific Review Board and SingHealth Centralized Institutional Review Board.

Maternal and paternal data

Socio-demographic data (age, self-reported ethnicity, education level and parity) were obtained at recruitment. Pregnant women underwent a 2 h, 7 g oral glucose tolerance test after an overnight fast at 26–28 weeks of gestation, as detailed previously.[10] Women diagnosed with gestational diabetes, based on World Health Organization's criteria (FPG $\geqslant 7.0$ mmol l^{-1} or 2 h glucose $\geqslant 7.8$ mmol l^{-1}), were placed on a diet and/or treated with insulin; these women were included in the analysis. Gestational age was assessed by trained ultrasonographers at the first dating scan after recruitment, and reported in completed weeks.

Maternal pre-pregnancy weight was self-reported at study enrollment. Measurements of weight and height for mothers (during pregnancy) and fathers (at 24 months post delivery) were obtained using SECA 803 Weighing Scale and SECA 213 Stadiometer (SECA Corp., Hamburg, Germany). These measurements were used to calculate body mass index (BMI, in kg m^{-2}) and GWG (in kg). GWG was calculated as the difference between final measured weight before delivery and pre-pregnancy weight.

Childhood data

Mothers were asked about infant milk feeding (as detailed previously[22]) and the age at which their child had been introduced to solid foods using interviewer-administered questionnaires. At 12 months, energy intake was derived using either a 24 h recall or a food diary. At 24 months, mothers were asked the average number of hours per day their child spent playing/ exercising outdoors using interviewer-administered questionnaires.

At 48 months, measurements of weight, height, waist circumference and four skinfold thicknesses (triceps, biceps, subscapular and suprailiac) were obtained, as detailed previously.[23] Anthropometric training and standardization sessions were conducted every 3 months; reliability was estimated by inter-observer technical error of measurement and coefficient of variation (Supplementary Table 1). Fat mass was measured in a subset of children ($n=274$) whose parents provided written consent when approached, using air displacement plethysmography (BOD POD, Life Measurement, Inc., Concord, CA, USA). These measurements were used to calculate BMI, sum of skinfolds (SSFs, in mm), waist-to-height ratio (WHtR) and fat mass index (FMI, in kg m^{-2}). Sex-specific BMI *z*-scores were calculated using the local Singapore[24] and World Health Organization[25] references. Overweight/obesity was defined as sex-specific BMI >85th percentile of the local Singapore reference.

Risk factors

We selected four risk factors that have been empirically demonstrated to be independently associated with higher childhood adiposity in our cohort: pre-pregnancy BMI (ppBMI),[26] GWG,[26] gestational hyperglycemia[10] and breastfeeding duration.[27] We also selected two other risk factors that have previously been associated with childhood obesity: paternal BMI[28] and timing of solid food introduction.[29] Maternal smoking during pregnancy was not included as a risk factor, owing to low prevalence in our study sample (2%), and was unrelated to child adiposity in previous analyses.[30] Risk factor definitions were maternal pre-pregnancy overweight/obesity: ppBMI $\geqslant 25$ kg m^{-2}; paternal overweight/obesity: BMI $\geqslant 25$ kg m^{-2}; excessive GWG: Institute of Medicine 2009 guidelines;[31] raised FPG during pregnancy: FPG $\geqslant 5.1$ mmol l^{-1} (International Association of the Diabetes and Pregnancy Study Groups criteria[32]); duration of any breastfeeding: <4 months; and early introduction of solid foods: <4 months.[29] Risk factor scores were computed by calculating the cumulative number of risk factors for each individual, as described in previous studies.[14,15]

Statistical analysis

Child adiposity data (BMI, WHtR, SSF and FMI) were log-transformed and standardized to *z*-scores with a mean of 0 and SD of 1, which reduced the skewness and non-normality. Linear regression models were fitted with risk factor scores as a continuous predictor, or a categorical predictor using children with no risk factors as the reference. Parameter estimates were back-transformed to their original units, by multiplying them by the observed s.d. of the corresponding logged adiposity data, followed by exponentiation to the base 10. Logistic regression models were used to estimate probabilities of child overweight for different risk factor combinations. Poisson regression models with robust variance were used to estimate the relative risk of child overweight for each number of risk factors, with no risk factors as the reference. All models were adjusted for maternal education level, height, parity and ethnicity, along with child sex and actual age at measurement to improve precision. As these risk factors may be considered as markers of the child's postnatal environment, the models were further adjusted for energy intake at 12 months and child physical activity level at 24 months (<1, 1 to <2 or $\geqslant 2$ h per day). Potential effect modification by ethnicity and sex was assessed by including multiplicative interaction terms with the risk factor scores in the fully adjusted model.

Several sensitivity analyses were conducted; first, as self-reported pre-pregnancy weight may have limited validity, we re-ran the analyses using maternal overweight at booking (mean 8.7 ± 2.8 weeks of gestation) as a risk factor instead. Second, three risk factor categorizations were changed: ppBMI and paternal BMI $\geqslant 30$ kg m^{-2} ($n=66$ and 165, respectively) and FPG during pregnancy $\geqslant 5.6$ mmol l^{-1} ($n=10$), according to National Institute of Health Care and Excellence 2015 guidelines.[33] Third, child overweight was re-categorized according to International Obesity Task Force[34] ($n=56$) and World Health Organization[25] ($n=10$) cutoffs. Lastly, missing values for any risk factors and/or covariates were imputed by multiple imputation, using the Markov-chain Monte Carlo technique generated from 20 imputed datasets. All analyses were performed using Stata 13 software (StataCorp LP, College Station, TX, USA).

RESULTS

Of 1170 infants delivered, 73.3% ($n=858$) were followed up at 48 months (Supplementary Figure 1). Between subjects with and without ($n=312$) follow-up data, no significant differences were observed in maternal and child characteristics, with the exception

of breastfeeding duration and child physical activity (Supplementary Table 2). Among those followed up, maternal characteristics differed by ethnicity, including age, education level, parity, height and proportion with pre-pregnancy overweight, excessive GWG, raised FPG during pregnancy and short breastfeeding duration (Table 1). Compared with Chinese mothers, Malay mothers had lower educational attainment, were younger, shorter, more likely to be overweight, had excessive GWG and less likely to breastfeed $\geqslant 4$ months (Table 1).

Compared with Chinese children, Malay children had the highest BMI (16.1 vs 15.3 kg m^{-2}), SSF (17.1 vs 16.0 mm) and WHtR (0.50 vs 0.48), whereas Indian children had the highest FMI (4.2 vs 3.7 kg m^{-2}) at 48 months. One hundred and seventy-two children (19%) had no risk factors, 274 (32%) had 1, 244 (29%) had 2, 126 (15%) had 3 and 42 (5%) had 4 or more risk factors (Supplementary Table 3). Children with no risk factors were more likely to be of Chinese ethnicity and born to mothers with higher educational attainment, while children with four or more risk factors were more likely to be of Malay ethnicity and born to mothers with lower educational attainment (Supplementary Table 4).

After adjusting for potential confounders, graded increases in BMI (Figure 1a), BMI *z*-score (Figures 1b and c), WHtR (Figure 1d), SSF (Figure 1e) and FMI (Figure 1f) were observed with increasing risk factor score. The linear trends were highly significant ($P_{trend} < 0.001$) for all adiposity outcomes: 0.21 (95% confidence interval: 0.14–0.28) s.d. unit per additional risk factor for BMI, 0.19 (0.12–0.26) s.d. unit for WHtR, 0.12 (0.05–0.19) s.d. unit for SSF and 0.14 (0.02–0.25) s.d. unit for FMI. Children with four or more risk factors had increases of 0.78 (0.41–1.15) s.d. units for BMI, 0.79 (0.41–1.16) s.d. units for WHtR, 0.46 (0.06–0.83) s.d. units for SSF and 0.67 (0.07–1.27) s.d. units for FMI compared with those with no risk factors; this corresponded to differences of 1.1 kg m^{-2} for BMI, 1.1 for WHtR, 1.1 mm for SSF and 1.3 kg m^{-2} for FMI. The relative risk (95% confidence interval) of child overweight was 1.5 (1.3–1.7) per additional risk factor, after adjusting for potential confounders. Children with four or more risk factors had the highest RR (11.1 (2.5–49.1)) compared with children who had none (Figure 1g). Further analyses showed that graded increases in adiposity and overweight risk with increasing risk factor score persisted even when maternal ppBMI was included as a covariate, rather than a risk factor in the model (Table 2), thereby supporting the observed additive effect. No interactions were observed between ethnicity and risk factor score, nor between child sex and risk factor score, for any of the outcomes.

Table 1. Socio-demographic and clinical characteristics of study participants according to ethnicity

	Chinese (n = *485)*	*Malay* (n = *217)*	*Indian* (n = *156)*	P-*value*[a]
Maternal age (years)	31.9 ± 4.7[b]	29.0 ± 5.5[c]	30.2 ± 4.8	< 0.001
Maternal education level				< 0.001
< 12 Years	144 (30)[b]	148 (68)	43 (28)	
⩾ 12 Years	339 (70)	67 (32)[c]	112 (72)	
Parity				0.007
Primiparous	243 (50)	90 (41)	58 (37)	
Multiparous	242 (50)	127 (59)	98 (63)[c]	
Maternal height (cm)	159 ± 6	157 ± 6[c]	157 ± 5[c]	< 0.001
Pre-pregnancy overweight				< 0.001
No	341 (76)	95 (47)	59 (41)	
Yes	107 (24)	105 (53)[c]	84 (59)[c]	
Paternal overweight				0.01
No	195 (54)	69 (41)	43 (43)	
Yes	168 (46)	98 (59)[c]	57 (57)	
Raised FPG during pregnancy				0.006
No	442 (97)	187 (92)	125 (91)	
Yes	15 (3)	17 (8)	12 (9)[c]	
Excessive GWG				< 0.001
No	286 (65)	94 (48)	77 (55)	
Yes	156 (35)	102 (52)[c]	64 (45)	
Any BF < 4 months				< 0.001
No	229 (57)	57 (33)	64 (54)	
Yes	171 (43)	115 (67)[c]	54 (46)	
Early introduction to solids				0.003
No	444 (99)	176 (95)	124 (95)	
Yes	4 (1)	9 (5)[c]	6 (5)[c]	
Gestational age (weeks)	38.4 ± 1.3	38.0 ± 1.3[c]	38.1 ± 2.1[c]	0.007
Child gender				0.65
Male	235 (48)	97 (45)	75 (48)	
Female	250 (52)	120 (55)	81 (52)	
Child energy intake at 12 months (kcal)	734 ± 187	806 ± 242	784 ± 205	< 0.001
Child physical activity at 24 months				0.04
< 1 h per day	268 (61)	137 (65)	73 (49)	
1 to < 2 h per day	123 (28)	52 (25)	54 (36)	
⩾ 2 h per day	49 (11)	22 (10)	23 (15)	
BMI at 48 months	15.3 ± 1.4	16.1 ± 2.2[c]	15.6 ± 2.3	< 0.001
SSF at 48 months	16.0 ± 3.8	17.1 ± 6.6[c]	16.9 ± 6.9	< 0.001
WHR at 48 months	0.48 ± 0.03	0.50 ± 0.04[c]	0.49 ± 0.05	< 0.001
FMI at 48 months	3.7 ± 1.1	4.0 ± 1.3	4.2 ± 1.7[c]	0.02

Abbreviations: BF, breastfeeding; BMI, body mass index; FMI, fat mass index; GWG, gestational weight gain; SSF, sum of skinfolds; WHR, waist-to-height ratio. [a]*P*-value across three ethnic groups were determined with the use of a χ^2-analysis (categorical) or one-factor analysis of variance (continuous). [b]Mean ± s.d. or *n* (%). [c]$P < 0.05$ compared with Chinese (determined with the use of a χ^2- analysis (categorical) or two-sample *t*-test).

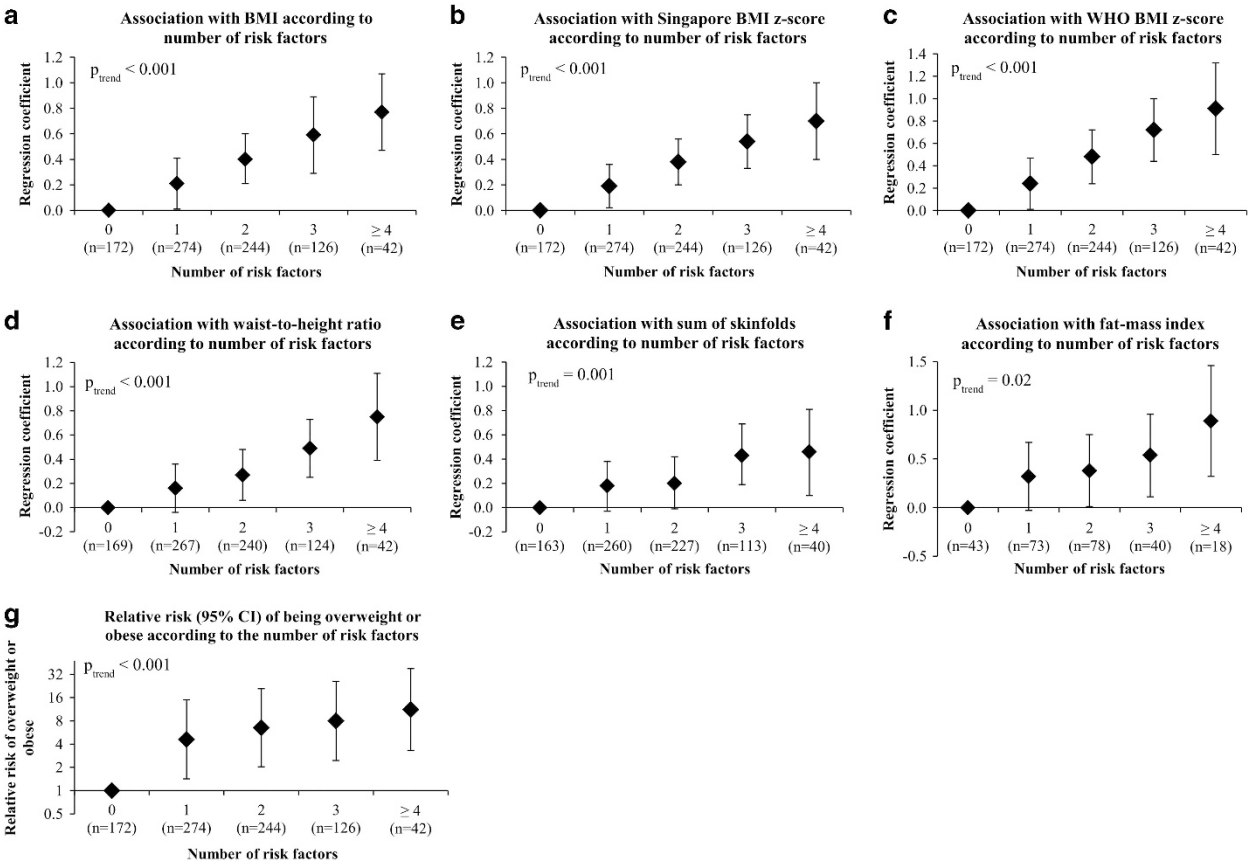

Figure 1. Associations with (**a**) BMI, (**b**) BMI *z*-score (Singapore reference), (**c**) World Health Organization (WHO) BMI *z*-score, (**d**) WHtR, (**e**) SSFs, (**f**) FMI (subset $n = 274$) and (**g**) relative risk of overweight or obese at 48 months, according to number of risk factors. All models were adjusted for maternal education level, height, parity, child daily physical activity level, total energy intake and ethnicity. (**a**, **d**–**f**) Additionally adjusted for child sex and actual age at measurement. Data points represent regression coefficients (**a**–**f**) or relative risk (**g**) estimates; error bars represent 95% confidence intervals.

Figure 2 shows the adjusted predicted probability of child overweight/obesity for each risk factor, as well as different risk factor combinations. Children exposed to maternal pre-pregnancy or paternal overweight status had predicted probabilities of overweight/obesity of 11.8 (9.8–13.8)% and 10.6 (9.6–11.6)%, respectively, which were the largest relative to the other individual risk factors. Risk factor combinations involving maternal pre-pregnancy or paternal overweight showed similar graded increases in estimated probability of child overweight/obesity, and these estimates were further amplified when risk factor combinations included both maternal pre-pregnancy and paternal overweight (Figure 2).

Sensitivity analyses showed that the observed associations were robust to replacing pre-pregnancy overweight with booking overweight (Supplementary Table 5), re-categorization of three risk factors (Supplementary Table 6), re-categorization of child overweight according to International Obesity Task Force or World Health Organization cutoffs (Supplementary Table 7) and multiple imputation for missing risk factors and/or covariates (Supplementary Table 6), which is reassuring with respect to potential for measurement or selection bias.

DISCUSSION

By using risk factor categorizations defined *a priori*, we observed graded associations of an increasing risk factor score with higher child adiposity and overweight/obesity. Children with four or more risk factors showed an 11-fold increased risk of overweight/obesity compared to children with no risk factors, along with 1.1 mm and 1.3 kg m^{-2} increases in SSF and FMI, respectively. These associations remained after adjusting for potential confounders, child physical activity level, total energy intake, and after various sensitivity analyses. To our knowledge, ours is the first study to evaluate the combined effects of early-life risk factors on direct measures of adiposity in an Asian cohort.

Our findings are in line with those from cohort studies in the United States[14] and United Kingdom.[15] In Project Viva, a sevenfold difference in predicted obesity prevalence was observed between 7- and 10-year-old children with four risk factors and those with none.[14] In the Southampton Women's Survey, a fourfold difference in relative risk of overweight at 4 and 6 years was observed between children with four or five risk factors and those with none. Each risk factor assessed in our study is potentially modifiable through behavior change intervention. For example, interventions to limit GWG,[35] promote breastfeeding duration[36] and educate mothers regarding timing of solid food introduction[37] have had some success. A recent randomized clinical trial has demonstrated the ability of an exercise intervention in reducing the incidence of gestational diabetes and improving glucose metabolism during pregnancy.[18] Prevention of maternal pre-pregnancy overweight is often encouraged, but few interventions have successfully achieved persistent reductions in parental BMI and we are aware of no randomized controlled trials that have assessed the effects of BMI-focused preconception interventions on pregnancy and infant outcomes.[38] Interventions that aim to address other early-life risk factors concurrently may, however, amplify their individual positive effects on preventing childhood overweight/obesity.

Table 2. Estimated regression coefficients and relative risk (95% CIs)

Number of risk factors	*BMI*[a]		*SG BMI z-score*[b,c]		*WHO BMI z-score*[b,d]	
	B *(95% CI)*	P-*value*	B *(95% CI)*	P-*value*	*B (95% CI)*	P-*value*
0	Ref	—	Ref	—	Ref	—
1	0.14 (−0.05, 0.33)	0.15	0.14 (−0.02, 0.31)	0.11	0.19 (−0.05, 0.43)	0.12
2	0.28 (0.08, 0.48)	0.01	0.27 (0.09, 0.44)	0.002	0.42 (0.17, 0.66)	0.001
3	0.39 (0.14, 0.65)	0.003	0.34 (0.11, 0.56)	0.003	0.43 (0.12, 0.74)	0.01
⩾4	0.45 (0.01, 0.89)	0.04	0.38 (0.001, 0.76)	0.05	0.67 (0.04, 1.30)	0.04
β-Trend	0.14 (0.06, 0.23)	< 0.001	0.13 (0.05, 0.20)	0.001	0.17 (0.07, 0.28)	0.001

Number of risk factors	*WHtR*[a]		*SSF*[a]		*FMI*[a,e]	
	B *(95% CI)*	P-*value*	B *(95% CI)*	P-*value*	B *(95% CI)*	P-*value*
0	Ref	—	Ref	—	Ref	—
1	0.12 (−0.08, 0.33)	0.22	0.08 (−0.12, 0.28)	0.45	0.19 (−0.18, 0.56)	0.31
2	0.27 (0.06, 0.48)	0.01	0.18 (−0.03, 0.39)	0.09	0.38 (0.04, 0.73)	0.03
3	0.31 (0.05, 0.58)	0.02	0.38 (0.11, 0.65)	0.01	0.52 (0.04, 1.00)	0.04
⩾ 4	0.73 (0.20, 1.26)	0.01	0.37 (−0.11, 0.85)	0.13	0.75 (−0.10, 1.51)	0.05
β-Trend	0.13 (0.05, 0.22)	0.002	0.08 (0.00, 0.16)	0.05	0.16 (0.02, 0.29)	0.02

Number of risk factors	*Overweight by Singapore reference*[b]		*Overweight by IOTF reference*[b]		*Overweight by WHO reference*[b]	
	Relative risk (95% CI)	P-*value*	*Relative risk (95% CI)*	P-*value*	*Relative risk (95% CI)*	P-*value*
0	Ref	—	Ref	—	Ref	—
1	1.62 (0.73–3.59)	0.23	2.46 (0.74–8.21)	0.14	4.24 (0.56–32.31)	0.16
2	2.53 (1.15–5.56)	0.02	4.40 (1.34–14.45)	0.02	7.01 (1.00–51.70)	0.05
3	2.49 (1.07–5.84)	0.04	4.83 (1.42–16.42)	0.01	8.62 (1.15–64.48)	0.03
⩾4	2.92 (1.09–7.87)	0.03	5.48 (1.44–20.89)	0.01	5.21 (0.58–47.15)	0.14
β-Trend	1.31 (1.04, 1.63)	0.02	1.43 (1.09, 1.90)	0.01	1.36 (1.06, 1.76)	0.02

Abbreviations: BMI, body mass index; CI, confidence interval; FMI, fat mass index; IOTF, International Obesity Task Force; SG, Singapore; SSF, sum of skinfolds; WHO, World Health Organization; WHtR, waist-to-height ratio.Estimated regression coefficients and relative risk (95% CIs) of the associations between number of modifiable risk factors (paternal overweight, excessive GWG, BF < 4 months, raised glucose during pregnancy and early introduction of solid foods) with child adiposity and overweight/obesity risk at 48 months, independent of maternal pre-pregnancy BMI. [a]Adjusted for maternal pre-pregnancy BMI, education level, height, parity, child sex, daily physical activity level, total energy intake, ethnicity and actual age at measurement. [b]Adjusted for maternal pre-pregnancy BMI, education level, height, parity, child daily physical activity level, total energy intake and ethnicity. [c]BMI *z*-score calculated using local Singapore reference. [d]BMI *z*-score calculated using WHO reference. [e]FMI measured in a subset of infants ($n = 274$).

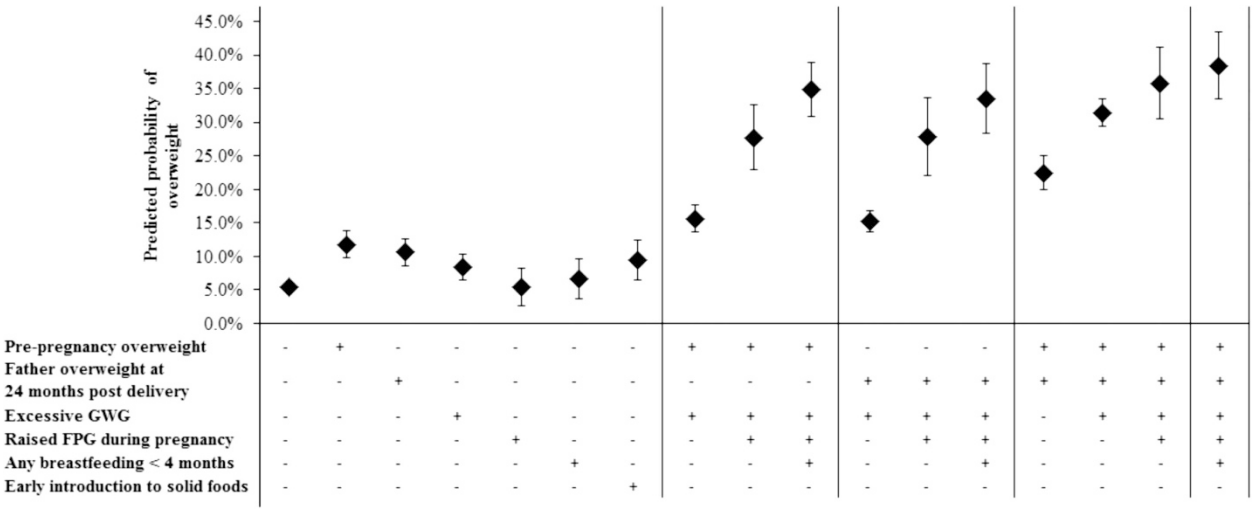

Figure 2. Predicted probability of overweight or obese at 48 months according to different risk factor combinations. '+' indicates presence of risk factor, '–' indicates absence of risk factor. All models were additionally adjusted for maternal education level, height, parity, child daily physical activity level, total energy intake and ethnicity.

These risk factors are known to be interlinked and may stem from maternal overweight; assortive mating would induce correlations between maternal and paternal BMI.[39] In addition, maternal overweight or excessive GWG are known to increase the risk of gestational hyperglycemia.[40] In some settings, overweight or hyperglycemic women are more likely to be referred for planned cesarean delivery,[41,42] which reduces the likelihood of initiation and maintenance of breastfeeding.[43] Nevertheless, our observations of graded increases in adiposity and overweight risk with increasing risk factor score persisted independently of maternal ppBMI, thereby supporting the observed additive effect.

The risk factors assessed are socially patterned and reflect socio-economic inequalities in the population; children with none of the studied risk factors were more likely to be from a higher socio-economic background, while children with four or more risk factors were more likely to be from a disadvantaged background. Risk factors such as parental overweight, shorter breastfeeding duration and early solid food introduction are known to be more prevalent in low socio-economic status groups.[22] Children with multiple risk factors may also be living in an 'obesogenic' family environment established by their parents. Earlier studies have described the fathers' role in their child's feeding practices,[44] fathers' parenting style on their child's BMI[45] and the father's positive influence on their child's physical activity involvement.[46] A recent systematic review had found that early-life interventions effective at preventing childhood overweight focused on family-level behavior changes.[3] Findings from a randomized controlled trial also showed positive effects of a 'responsive parenting' intervention on reducing rapid infancy weight gain and early childhood overweight risk.[47] Taken together, the evidence suggests that early-life interventions aimed at addressing childhood obesity should target not just mothers before and during pregnancy, but fathers as well, with meaningful and practical lifestyle guidance at the family-level.

It is noteworthy that parental overweight showed the largest association with child overweight. The positive relation between maternal ppBMI and child adiposity is widely recognized.[48] Maternal ppBMI represents the mother's nutritional status prior to conception and may reflect a genetic contribution to offspring adiposity. Our finding that paternal BMI is a significant risk factor of child overweight confirms the study of Freeman *et al*,[49] which reported an overweight or obese father, but a healthy-weight mother, significantly increased the odds of child obesity. The influence of paternal obesity on subsequent offspring obesity could be driven by a persistent unhealthy paternal lifestyle, contributing to an obesogenic family environment, as well as inheritance of obesity susceptibility genetic variants.[50] Recent animal studies by Fullston *et al*.[51] and Carone *et al*.[52] have described how paternal exposure to high-fat diet affects the metabolic function of offspring into late adulthood,[51] which may be partly explained by epigenetic alterations to sperm caused by diet-induced obesity.[52] More recently, Soubry *et al*.[53] reported how children of obese fathers showed altered methylation levels at multiple genes involved in normal human growth and development, compared with children of non-obese fathers. This evidence, along with ours, suggests that paternal health is an important consideration when identifying offspring at risk for childhood overweight/obesity.

Strengths of our study include its prospective design, which is crucial for assessing the relationship between early-life risk factors and subsequent childhood overweight. We are aware of no similar studies previously conducted in Asian populations, and even those in Western populations have not considered paternal overweight/obesity or maternal FPG during pregnancy. Our study also has the advantage of several measures of adiposity, including BMI, WHtR, skinfolds and fat mass. Limitations of our study include the fact that some cohort children were not followed up and differences between included and excluded children might conceivably have biased our findings. Maternal pre-pregnancy weight was self-reported during study enrollment, which may be affected by recall limitation. However, our data showed a strong correlation between self-reported pre-pregnancy weight and measured booking weight ($\rho = 0.96$) and sensitivity analyses using booking overweight as a risk factor showed similar observations. Paternal BMI was obtained at 24 months post delivery, rather than at pre-pregnancy. Nonetheless, BMI in adults is known to track strongly over time; fathers who were overweight at 24 months post-delivery were likely to have been overweight at pre-pregnancy as well.

Although other potentially modifiable risk factors for child overweight have been reported before (infant sleep duration,[14] maternal smoking during pregnancy[14,15] and maternal vitamin D[15]), they had no association with child overweight/obesity in our cohort;[30,54] hence, we did not include them in our analysis. In addition, although birthweight is known to be associated with childhood overweight/obesity,[55] we did not include it as a risk factor because it is not directly modifiable through behavior change intervention. We were unable to account for childhood dietary patterns that may reflect exposure to an obesogenic environment. Our observed associations accounted for the child's energy intake at 12 months, although we are aware that this may not be representative of their diet at later ages. There is an ongoing debate regarding the causal effect of some risk factors, such as breastfeeding duration or age at introduction of solid foods, on childhood obesity; such risk factors may act merely as markers of the postnatal environment.[56,57] As ours is an observational study, it is not possible to determine whether the associations observed are causal. Finally, our study lacked other obesity-related measures such as insulin, triglycerides and C-peptide, which would be helpful in understanding the long-term health implications of our findings.

In conclusion, our findings should help understand the contribution of multiple modifiable risk factors towards development of childhood overweight/obesity, especially in Asian populations. Interventions to prevent childhood obesity may be more effective if conducted early in life or during pre-conception.[58] Novel approaches during the first 1000 days of life may help prevent obesity and its long-term adverse consequences.

CONFLICT OF INTEREST

Keith M Godfrey, Yap Seng Chong and Yung Seng Lee have received reimbursement for speaking at conferences sponsored by companies selling nutritional products. Keith M Godfrey and Yap Seng Chong are part of an academic consortium that has received research funding from Abbot Nutrition, Nestec and Danone. All other authors declare no conflict of interest.

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