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Parental Smoking during Pregnancy and Offspring Cardio-Metabolic Risk Factors at ages 17 and 32

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Abstract

Objective—To examine the association of maternal and/or paternal smoking during pregnancy with offspring cardio-metabolic risk (CMR) factors at adolescence and early adulthood, taking into account socio-demographic, medical and lifestyle characteristics of parents and offspring, as well as offspring common genetic variation.

Methods—We used a population-based cohort of all 17 003 births in Jerusalem during 1974–76, with available archival data on parental and birth characteristics. Measurements at age 17 were assessed at military induction examinations for 11 530 offspring. 1440 offspring from the original 1974–1976 birth cohort were sampled using a stratified sampling approach, and were interviewed and examined at age 32. Parental smoking during pregnancy (i.e. maternal, paternal and any parent) was primarily defined dichotomously (any number of cigarettes smoked daily by mother or father during pregnancy vs. non-smokers). Additionally, smoking was assessed by quantity of cigarettes smoked daily. Linear regression models were used to evaluate the associations of parental smoking during pregnancy with various offspring CMR factors, after controlling for potential confounders and for genetic variation in candidate genes.

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Results—Prevalence of exposure to parental smoking in-utero (i.e. smoking of any parent) was 53.2% and 48.4% among the 17 years old and 32 years old samples, respectively. At age 17, smoking of at least one parent during pregnancy was significantly associated with weight (B=1.39), height (B=0.59), BMI (B=0.32) and pulse rate (B=−0.78) (p-values<0.001). At age 32, parental smoking, adjusted for covariates, was associated with 2.22 kg higher mean offspring weight, 0.95 cm higher mean offspring height, 0.57 kg/m2 higher BMI, and 1.46 cm higher waist-circumference (p-values≤0.02). Similar results, reflecting a dose response, were observed when maternal and paternal smoking were assessed by number of cigarettes smoked daily.

Conclusions—This prospective study demonstrates a potential long-term adverse effect of parental smoking during pregnancy on offspring health and calls for increasing efforts to promote smoking cessation of both parents before pregnancy.

Keywords

cohort study; smoking; pregnancy; obesity; risk factors

Introduction

Active and passive cigarette smoking are major risk factors for multiple clinical conditions, such as cardiovascular disease, cancer, chronic lung disease, and mortality[1,2]. Hence, cigarette smoking is a major public health concern globally. Despite the known harmful effects of cigarette smoking on the health of mothers and their children, it is estimated that 22 to 34 percent of American women of reproductive age smoke cigarettes[3]. Smoking during pregnancy is one of the most important modifiable risk factors associated with adverse pregnancy outcomes. The negative impact of cigarette smoking on fetal health is well established and cigarette smoking has been associated with numerous adverse perinatal outcomes[4,5]. Low birth weight (LBW) (<2500 grams) is the best-studied complication of smoking during pregnancy. Women who smoke are 1.5 to 3.5 times more likely to have a LBW infant with increasing risk as cigarette consumption increases[6]. It has been estimated that at least 20% percent of LBW and small for gestational age infants are attributed to tobacco exposure during pregnancy[7]. Exposure to passive smoking during pregnancy also appears to have adverse effects on the fetus, child, and adult offspring[8,9], including increased rate of stillbirth, and reduced mean birth weight[9].

Additionally, parental smoking during pregnancy is associated with long-term offspring health risks. Associations of parental smoking with offspring cardiovascular risk factors have been demonstrated mostly in pre-pubertal children[10,11]. Only few studies have examined these associations in adolescents and adults and most of them were retrospective[12–15]. Prior studies have focused mostly on maternal smoking, rather than paternal smoking, and the associations of maternal smoking with offspring obesity[16,17] and blood pressure[18]. Evidence regarding the associations of parental smoking with other cardio-metabolic risk (CMR) traits is sparse[19–21].

It has been suggested that the long-term effects of both paternal and maternal smoking on offspring health are related to effects on the intrauterine environment as well as to postnatal characteristics that are associated with CMR[22–24].

In our study, we aimed to assess the effect of maternal and/or paternal smoking during pregnancy on a range of cardio-metabolic risk factors at age 17 and 32, taking into account various socio-demographic, medical and lifestyle characteristics of the parents and the offspring, as well as common genetic variation in offspring.

Methods

The Jerusalem Perinatal Study (JPS), a population-based birth cohort, recorded data on all 17 003 births to residents of Jerusalem, between the years 1974 and 1976. Details regarding data collection methods were described previously[25]. Briefly, available data consisted of demographic, socioeconomic, medical conditions of the mother during current and previous pregnancies, and offspring birth weight, abstracted either from birth certificates or maternity ward logbooks. Parental smoking status as well as additional information on lifestyle and pregnancy-related and medical characteristics, such as gestational age, height and pre-pregnancy weight, end of pregnancy weight and gynecological history, was collected by interviews of mothers on the first or second day postpartum. Through data linkage with the Israeli military draft records, information from medical examinations at age 17, was obtained for approximately 70% of the JPS cohort[26] (82% of male offspring, and 54% of female offspring, totaling 11 530 individuals). The adequacy of the linkage was ascertained by comparing offspring's sex, date of birth and several other demographic characteristics. Military induction medical examinations included measurements of standing height (without shoes to the nearest centimeter), body weight (with indoor light clothes, to the nearest kilogram) and pulse rate. Blood pressure was measured in the right arm, in sitting position, with a mercury sphygmomanometer. The proportion of the birth cohort with military induction data was lower for females, as a result of exemption from military service of women due to religious practice.

The JPS Family Follow-Up study includes a sample of 1440 offspring from the original 1974–1976 birth cohort, who were interviewed and examined between 2007 and 2009[27]. The sampling frame for the follow-up study included singletons and term (gestational age≥36 weeks) births without congenital malformations. Both low (≤2500 grams) and high (≥4000 grams) birth weight offspring as well as over-weight and obese mothers (BMI≥27) were over-sampled given the focus of the research on maternal and offspring body size. Standard procedures and training protocols were used to measure standing height, body weight, waist circumference (at the midpoint between the lower ribs and iliac crest in the midaxillary line) and blood pressure (measured three consecutive times in the right arm in sitting position following five minute rest). Blood samples at fasting (at least 8 hours of fasting) were taken using standard procedures. Samples were immediately spun and biochemical measurements were assayed in plasma, including insulin and glucose levels, total cholesterol, HDL-C and triglycerides[27]. Genomic DNA was extracted at Hebrew University using the salting-out method; and, high throughput genotyping was performed at the University of California, San Francisco using an Illumina, Inc., BeadArray™. Available genotypic data included 1384 SNPs from 180 candidate genes selected based on molecular pathways associated with CMR-related traits.

Study variables

We examined the associations of parental smoking during pregnancy with offspring cardio-metabolic outcomes at age 17 (n = 11 530) and 32 (range 30–35) years (n = 1440). Information on smoking was obtained from postpartum interviews of the mothers in response to the question: “Do you and/or your husband smoke cigarettes?” and was categorized into the following 4 groups: Never smoked; quit before this pregnancy; quit during this pregnancy; smoking now. Smoking was defined as any number of cigarettes smoked per day by the parent. To define smoking during pregnancy, we grouped those quitting before this pregnancy with parents who never smoked (i.e. non-smokers) and those quitting during this pregnancy with current smokers (i.e. smokers). In the models, exposure to parental smoking during pregnancy was primarily assessed by three separate explanatory variables: 1) maternal smoking (yes/no); 2) paternal smoking (yes/no); and 3) smoking of at least one parent (i.e. any smoker; yes/no). Additionally, we assessed maternal and paternal smoking by quantity of cigarettes smoked daily, grouped into intervals of 10 cigarettes (i.e. 0 (non-smoker), 1 (1–10 cigarettes smoked daily), 2 (11–20), 3 (21–30), 4 (31–40) and 5 (over 40 cigarettes).

The primary outcome variables measured at age 17 were weight [kg], height [cm], body-mass index (BMI, calculated by dividing weight by squared height [kg/m^2]) (continuous), pulse rate (PR [bpm]), systolic blood pressure (SBP) and diastolic blood pressure (DBP [mm Hg]). The following cardio-metabolic outcomes were measured at age 32: weight, height, BMI, waist circumference (WC, mean of two consecutive measurements [cm]), PR, SBP and DBP (mean of three consecutive measurements), glucose [mg/dL], insulin (mean of two repeated measures [μU/mL], log-transformed (base 10) due to asymmetrical distribution), low-density lipoprotein cholesterol (LDL-C [mg/dL], high-density lipoprotein cholesterol (HDL-C [mg/dL]) and total cholesterol [mg/dL] and triglycerides (TG [mg/dL], log-transformed (base 10) due to asymmetrical distribution). All outcomes were treated as continuous variables.

All models were adjusted for offspring gender and ethnicity. Adjustment for ethnicity in the analyses examining cardio-metabolic outcomes measured at age 17 was based on mother’s country of birth (categorized as: Israel, other West Asia, North Africa and Europe/America and other industrialized countries). In the analyses examining outcomes at age 32, availability of more detailed information on ethnicity in this subcohort enabled us to follow an approach suggested by Thomas and Witte[28], in which ethnicity was adjusted for by covariates reflecting nine major ethnicity strata based on country of origin of all four grandparents[27].

In all analyses we addressed potential confounders at time of birth reflecting the early environment (i.e. pre- and peri-natal periods). Potential confounders were: (1) average parental age at child birth (years, continuous); (2) socioeconomic status (SES) based on father’s occupation at time of birth (grouped into three categories: low, medium, high); (3) average parental years of education at time of birth (years, continuous); (4) maternal medical condition (dichotomous, based on whether the mother had ever suffered from any of the following diseases: diabetes, hypertension, heart disease and toxemia); 5) birth weight (grams, continuous); and (6) maternal pre-pregnancy BMI (mppBMI; kg/m^2, continuous).

To deal with a limited number of missing values for average parental age or average parental years of education (<2%) we either used information on only one parent when available or imputed the data based on the mean. Missing data for mppBMI (6% and 3% in the age 17 and age 32 analyses, respectively) were imputed as the mean. Results of analyses using imputed data for missing values and those obtained by excluding missing values were essentially identical and therefore the reported analyses included imputed data for missing values.

In the analyses examining the associations with cardio-metabolic outcomes measured at age 32, we could further address potential confounders at young adulthood (age 32). Potential confounders were: (1) smoking status (current smoker vs. never smoked or smoked in the past); (2) physical activity (grouped into 2 categories; 1 - moderate or vigorous physical activity that lasts at least 20 minutes, three or more times a week, 0 - less or no activity; and (3) years of education (continuous). The expected positive associations of physical activity with HDL-cholesterol and years of education, and the negative association with current smoking observed in our data provide support for the validity of these variables.

Genetic Scores

Genetic scores were created based on established methodology used to create composite scores to study the influence of the additive effect of genetic variations on given relationships [29–31]. A similar approach was also applied in two previous studies conducted in JPS [32,33]. Using 1384 SNPs from 180 CMR-related genes among offspring, we created genetic scores that were predictive of the cardio-metabolic outcomes, to be used as precision variables. Separate genetic scores were created for the different CMR traits by fitting linear regression models individually for each of the 1384 SNPs with each separate outcome. The final scores were constructed as the mean predicted value of these outcomes calculated across all relevant SNPs for each individual.

Statistical analyses

Analyses were carried out using the SPSS version 20.0 statistical package (SPSS, Inc., Chicago, Illinois) and Stata 10.0 (StataCorp, College Station TX).

Linear regression models were used to investigate the associations of maternal or paternal smoking, independent of each other, with cardio-metabolic outcomes measured at age 17 and at age 32, after controlling for potential confounders.

Maternal and paternal smoking were introduced into the models either separately (i.e. including both maternal and paternal smoking) or as smoking of at least one parent. At both ages (17 and 32) we constructed two models: 1) adjusted for gender and ethnicity, and 2) further adjusting for the aforementioned potential confounders at birth and at time of outcome measurement. In the analyses using outcomes measured at age 32 in addition to potential confounders, model 2 included also outcome-specific genetic score. To assess dose response, model 2 was repeated with maternal and paternal smoking defined by number of cigarettes smoked daily.

All analyses examining cardio-metabolic outcomes at age 32 used inverse probability weighting to account for the stratified sampling. Additionally, individuals who reported taking BP-lowering medication (n=11), lipid-lowering medication (n=13) or medication to treat diabetes (n=13) were excluded from the corresponding analyses.

This study was approved by the Institutional Review Board of the Hadassah-Hebrew University Medical Center and the University of Washington Human Subject Review Committee. All participants provided informed consent.

Results

Maternal, and offspring socio-demographic and offspring cardio-metabolic characteristics at age 17 and age 32 are listed in tables 1a and 1b, respectively.

Table 2 presents results of linear regression models examining the associations of maternal, paternal and any parent smoking with offspring cardio-metabolic outcomes at age 17. The coefficients in the table indicate the mean difference in cardio-metabolic outcome according to parental smoking status. After adjusting for potential confounders, maternal smoking and paternal smoking, independent of each other, were positively associated with offspring weight, height and BMI ($p<0.01$) and negatively associated with offspring PR ($p<0.01$) at age 17 (Table 2, Model 2). The coefficients of the associations between maternal smoking and anthropometric measures were at least 2-fold greater than those of paternal smoking. For example, compared to offspring of non-smoking parents, weight of offspring whose mothers had smoked during pregnancy was 1.71 kg higher at age 17 while weight of offspring of smoking fathers was 0.80 kg higher (Table 2, Model 2). When examining the effect of smoking of any parent (i.e. maternal, paternal or both) on cardio-metabolic outcomes at age 17, parental smoking was positively associated with weight, height and BMI ($p<0.001$) and negatively associated with PR ($p<0.001$). Our data show an increase of 1.39 kg in offspring weight, 0.59 cm in height, 0.32 kg/m^2 in BMI and decrease of 0.78 heart bpm at age 17, in offspring of at least one smoking parent, as compared to offspring of non-smoking parents (Table 2, Model 2). To further examine dose response, associations of maternal and paternal smoking with offspring CMR outcomes measured at age 17, independent of each other and of potential confounders, were also assessed by quantity of cigarettes smoked daily (grouped into intervals of 10 cigarettes). Results showed a clear significant dose response for each additional 10 cigarettes smoked daily by both parents. The effect sizes of the associations of maternal smoking with offspring PR ($B=-0.332\pm0.13$, $p=0.015$), height (0.280 ± 0.091, $p=0.002$), weight (1.019 ± 0.143, $p<0.001$) and BMI (0.287 ± 0.045, $p<0.001$) were larger than those observed for paternal smoking: PR (-0.224 ± 0.072, $p=0.002$), height (0.200 ± 0.048, $p<0.001$), weight (0.353 ± 0.075, $p<0.001$) and BMI (0.067 ± 0.024, $p=0.005$).

Table 3 presents results of associations between parental smoking and offspring cardio-metabolic outcomes at age 32. Offspring of at least one smoking parent had higher weight ($B=2.22$, $p=0.004$; i.e. mean weight for offspring of at least one smoking parent was higher by 2.22 kg as compared to that of offspring of nonsmoking parents), height ($B=0.95$, $p=0.01$), BMI ($B=0.57$, $p=0.02$) and WC ($B=1.46$, $p=0.02$). These associations were

independent of characteristics at birth and at age 32 as well as of offspring common genetic variation (Table 3, Model 2). Association of at least one smoking parent with glucose was significant in the minimally adjusted model (B=1.89, p=0.04, model 1), yet was attenuated to the null in the fully adjusted model (model 2). No significant associations were demonstrated between parental smoking and offspring PR, insulin, lipids and lipoproteins at age 32. When assessed separately, there were significant associations between maternal smoking and glucose levels and between paternal smoking and offspring weight, height, BMI and WC. Analyses examining maternal and paternal smoking as number of cigarettes smoked daily yielded a similar picture. Each additional 10 cigarettes smoked daily by father were positively associated with offspring weight (0.089±0.031, p=0.005), height (0.033±0.016, p=0.035) and BMI (0.022±0.010, p=0.030), but not with WC. The associations between maternal smoking by number of cigarettes and offspring cardio-metabolic traits tended to be smaller.

To further illustrate the findings, we used estimates from linear regressions adjusted for confounders presented in tables 2 and 3 to predict adjusted means for offspring weight and BMI by parents smoking (Figure 1). For example, adjusted mean weight at age 17 was 63.2 kg for offspring of non-smoking parents compared to 64.6 kg for offspring of at least one smoking parent. At age 32, adjusted weights were 68.3 kg and 70.5 kg for offspring of non-smoking and smoking parents, respectively.

Discussion

Summary of findings

This study investigated the associations between parental smoking during pregnancy with a range of offspring cardio-metabolic risk factors in adolescence and early adulthood. We demonstrated that at age 17 maternal and paternal smoking were independently and positively associated with offspring weight, height and BMI and negatively associated with PR. At age 32, smoking of at least one parent was positively associated with offspring weight, BMI and WC, independent of potential confounders and genetic scores. These associations also showed a significant dose response at both time points when maternal and paternal smoking was assessed by number of cigarettes smoked daily, validating the findings based on the dichotomous smoking variables. We extend previous studies by assessing the associations with both maternal and paternal smoking during pregnancy, dichotomously and as number of cigarettes smoked daily, by examining a wide range of long term cardio-metabolic risk factors at two points of time: adolescence and early adulthood, and by taking into account various characteristics reflecting the pre-peri- and post-natal environment, including measures of lifestyle at young adulthood, as well as offspring common genetic variation.

Associations with offspring adiposity

Our findings that maternal smoking was positively associated with offspring adiposity are in accordance with other studies. Most studies have demonstrated this association in early childhood[34], but the association has also been reported in adolescents[35] and young adults[16]. These findings were also verified by two metaanalyses[17,36]. Evidence regarding the impact

of paternal smoking on offspring adiposity is sparse and inconsistent. Several studies report a positive association of paternal smoking during pregnancy with childhood adiposity, albeit weaker than for maternal smoking[37]; however, a recent study failed to show an association of paternal smoking with growth characteristics at age 4[10]

Associations with offspring BP

No associations were observed in our cohort for maternal, paternal or parental smoking and BP levels at ages 17 and 32. Few studies have shown a positive association between parental smoking and offspring BP, mainly in childhood[38,39], while others have not[18,24].

Associations with offspring fasting glucose and insulin

Parental smoking, adjusted for all covariates, was not associated with offspring glucose levels. Yet, maternal smoking assessed separately was positively associated with fasting glucose. Data on the associations between parental smoking and offspring levels of glucose and insulin are scarce. Horta et al., using a Brazilian cohort, did not observe associations between maternal smoking and offspring glucose levels[20]. In a British cohort, maternal smoking was related to higher offspring glucose levels at age 45, yet, this association did not remain significant after further adjustment for adult adiposity[40]. In our study, adjusting for current offspring BMI had a minimal effect on the findings (data not shown).

Associations with offspring fasting lipids and lipoproteins

We did not find an association between parental smoking and offspring fasting lipids and lipoproteins levels. An association between maternal smoking and offspring total cholesterol was demonstrated in one study including 350 offspring[14]. However, this association was not observed in the large Brazilian cohort study[20].

Associations with offspring pulse rate

We demonstrated a negative association between both maternal and paternal smoking and PR levels measured during adolescence. This association was not observed in adulthood. An increase in heart rate, as an indirect marker of adrenergic drive, has been shown in patients with metabolic syndrome[41] and is receiving attention as a potential cardiovascular risk factor[42]. However, a recent study did not show an association, positive or negative, between maternal smoking and offspring PR in young adults, after controlling for confounders[21]. Therefore, our findings for PR may reflect chance and require replication in at least another Israeli study.

Mechanisms underlying the observed associations

While the pathophysiology of smoking related adverse outcomes of pregnancy is not completely understood, several possible mechanisms have been proposed. The best-studied cause of adverse outcome in pregnant women who smoke is impaired fetal oxygen delivery. Pathologic evaluations of placentas of smokers have shown structural changes, including a reduction in the fraction of capillary volume and increased thickness of the villous membrane when compared to nonsmokers[43,44]. Both of these factors may contribute to abnormal gas exchange within the placenta that in turn may have long-term cardiovascular

consequences. Parental smoking may result in fetal growth retardation, which was shown to be associated with a more rapid postnatal weight gain[45], with abnormal glucose tolerance and with insulin resistance in adults[46]. Other possible mechanisms responsible for adverse fetal outcomes in mothers who smoke include direct toxicity of numerous substances found in cigarettes[47]. Animal studies have suggested an association between maternal nicotine exposure and changes in adipose tissue and glucose metabolism[48]; nicotine may also affect neurotransmitter levels and in-utero hypothalamic development and function including longer term effects on appetite control[49].

Whether these intrauterine mechanisms can explain solely long-term outcomes is a matter of debate. Some suggest that the observed long term effects are mainly related to familial and lifestyle factors[23,24]. Horta el al. failed to show any significant associations between maternal smoking and offspring cardiovascular risk factors after controlling for lifestyle factors and BMI and thus concluded that previously reported associations are likely due to lack of adjustment for postnatal exposure to lifestyle patterns[20]. Our findings, however, may suggest that the role of the intrauterine environment may change over time. First, our data show that the effect of maternal smoking on outcomes measured at age 17 is stronger than that of paternal smoking. A similar differential effect of parental smoking is seen for birth weight (data not shown), potentially pointing to an intrauterine mechanism. Second, the strengthening with age (from age 17 to 32) of the associations with anthropometric measurements, as was also demonstrated in the 1958 British cohort[16], propose that the long term effect of early life tobacco exposure may be influenced by accumulating exposures to the post natal environment. The “mismatch concept” supports this line of reasoning by suggesting that it is the gap between the environment experienced by the offspring in utero and the one experienced later in life that exerts the observed effects on adult disease, regardless of size at birth[50]. It is thus reasonable to assume that the gaps between the early and later environments grow over time leading to a larger effect on outcomes measured at age 32, independent of birth weight. Alternatively, differences between the associations observed at the two time points may also be attributed to differences in sample sizes, sampling differences or the presence of different determinants of CMR in adolescence and adulthood.

Previous studies have shown that genetic variation in genes encoding enzymes that detoxify the products of cigarette smoking modify the associations between maternal cigarette smoking and infant birth weight and preterm delivery[51,52]. We, however, used a limited set of candidate genes related specifically to CMR outcomes. This set of genes was used to add to precision of our estimates rather than to explore a genetic mechanism underlying the examined associations. It is noteworthy that the contribution of epigenetic mechanisms, rather than genetic, may potentially underlie the long-term effects of maternal smoking[53].

Strengths and limitations

The major strength of our study is the combination of high-quality detailed records of pre- and peri-natal maternal and offspring characteristics with comprehensive long-term follow-up data on offspring at ages 17 and 32 years. Availability of information collected in early life, including both pregnancy-related factors and socio-demographic characteristics,

together with characteristics of offspring at early adulthood, improved the characterization of the environment during pregnancy, birth, and adulthood, permitting control for these important factors. We also added precision to our estimates by taking into account offspring common genetic variation.

There are several limitations to this study. Confounding by socioeconomic status remains a concern in studies of the relationship of parental smoking and adult offspring cardio-metabolic risk factors. Unlike many studies, we had information that allowed us to characterize and control for the socioeconomic environment at birth and young adulthood.

To assess the reliability of smoking information provided by the mother at time of delivery, we recently interviewed 784 fathers of offspring who completed the 32 year follow-up study, regarding their own and their wife's (i.e. offspring's mother) smoking status during the time of the pregnancy. For maternal smoking status, the agreement percentage between data reported by fathers in the interview and data reported by the wives at time of birth was 85% and the κ estimate was 0.66. The agreement percentage between reports of paternal smoking status from fathers and their wives was 93% and the κ estimates was 0.68. Smoking information ascertained by self-report or through a spouse has been shown by others to have a relatively strong concordance[54].

In addition, in the original cohort of offspring born during 1974–76, we have examined the relation between maternal and paternal smoking during pregnancy and birth weight of their offspring. Offspring born to either mothers or fathers that smoked during pregnancy had a significantly lower mean birth weight, compared to offspring born to non-smoking parents[55]. These associations lend support to the predictive validity of the reported parental smoking during pregnancy.

Conclusions

Our study adds importantly to the limited evidence for long-term relationships of parental smoking during pregnancy with offspring cardio-metabolic health in adolescence and adulthood. Our results emphasize the potential adverse impact of exposure to active and passive smoking in-utero on various cardio-metabolic risk factors that are associated with sub-clinical and clinical disease, such as diabetes, myocardial infarction and stroke. The findings highlight the importance of health care interventions to reduce smoking of mothers and fathers before pregnancy, not only for the prevention of known immediate complications, but also of long term outcomes related to cardio-metabolic risk in their adolescent and adult children.

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Highlights

- We examine offspring cardio-metabolic risk in relation to parental smoking during pregnancy.
- Parental smoking was positively associated with offspring adiposity at ages 17 and 32.
- Associations with offspring insulin and lipid levels at age 32 were nonsignificant.
- Results highlight potential long-term health impact of exposure to parental smoking.
- Efforts to promote smoking cessation of parents before pregnancy may be warranted.

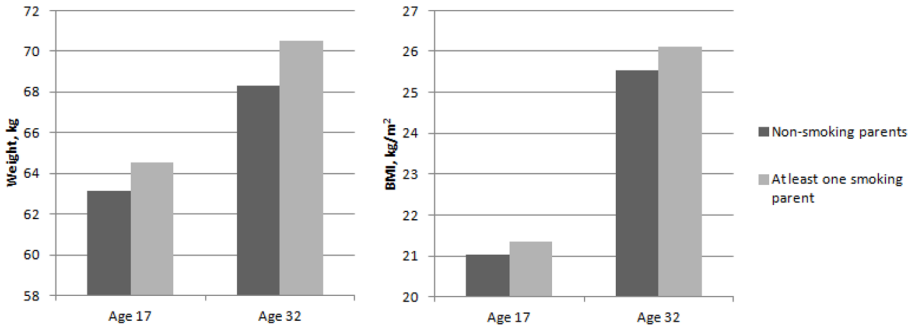

Figure 1.

Adjusted means of offspring weight and BMI by parental smoking. Estimates from linear regressions adjusted for all confounders (presented in model 2, tables 2 and 3) were used to determine adjusted means for offspring weight and BMI at ages 17 and 32 by parents' smoking status.

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Table 1a

Age 17 analyses - Sample characteristics by gender

	Women (N=4387)		Men (N=7143)		Total (N=11 530)	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Characteristics obtained at birth*						
Smoking any parent %	59.5		49.3		53.2	
Smoking mothers %	26.2		18.0		21.1	
Smoking fathers %	51.9		44.5		47.4	
Maternal pre-pregnancy BMI, kg/m^2	21.84	(2.91)	21.92	(2.91)	21.89	(2.91)
Maternal ethnic origin %						
Israel	12.7		14.7		14.1	
Middle East	31.0		29.4		28.8	
North Africa	24.2		22.4		23.1	
Ashkenazi	32.1		35.3		34.1	
Parents' years of education, avg yrs	11.85	(3.37)	12.09	(3.41)	12.0	(3.39)
Parents' age, avg yrs	29.12	(5.40)	29.15	(5.54)	29.14	(5.49)
Socioeconomic status %						
Low	24.9		42.4		23.1	
Medium	44.8		35.6		39.1	
High	30.3		22.0		37.8	
Birth weight, grams	3188.54	(472.99)	3312.66	(497.78)	3265.43	(492.1)
Mothers with any background disease† %	4.9		4.8		4.8	

Cardio-metabolic outcomes at age 17*	Women		Men		Total	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Systolic BP, mmHg	111.34	(11.39)	118.42	(11.84)	115.72	(12.17)
Diastolic BP, mmHg	70.32	(8.01)	72.78	(8.10)	71.84	(8.15)
Weight, kg	57.24	(9.46)	64.76	(11.33)	61.90	(11.26)
Height, cm	162.68	(6.22)	174.22	(6.98)	169.83	(8.74)

Cardio-metabolic outcomes at age 17*

	Women		Men		Total	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
BMI, kg/m^2	21.62	(3.30)	21.30	(3.33)	21.43	(3.32)
Pulse, BPM	78.31	(9.74)	75.36	(9.86)	76.49	(9.92)

*Values are expressed as mean (SD) or percent.

†Diabetes, hypertension, heart disease or toxemia.

Table 1b

Age 32 analyses - Sample characteristics, by gender

	Women (N=718)		Men (N=722)		Total (N=1440)	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Characteristics obtained at birth *						
Smoking any parent %	50.07		46.70		48.39	
Smoking mothers %	17.41		17.87		17.64	
Smoking fathers %	45.89		41.37		43.64	
Maternal pre-pregnancy BMI, kg/m^2	24.40	(3.89)	23.76	(3.60)	24.08	(3.76)
Maternal ethnic origin %						
Israel	13.09		13.85		13.47	
Middle East	28.13		25.90		27.01	
North Africa	23.26		23.13		23.19	
Ashkenazi	35.52		37.12		36.32	
Parents' years of education, avg yrs	11.89	(3.31)	12.10	(3.39)	11.99	(3.35)
Parents' age, avg yrs	30.31	(6.04)	30.10	(5.77)	30.20	(5.90)
Socioeconomic status %						
Low	21.59		23.82		22.71	
Medium	42.06		32.41		37.22	
High	36.35		43.76		40.07	
Birth weight, grams	3.27	(0.61)	3.53	(0.62)	3.40	(0.63)
Mothers with any background disease† %	10.45		10.11		10.28	
Characteristics obtained at age 32 *						
Education years	14.91	(2.57)	15.30	(3.64)	15.11	(3.16)
Smokers %	18.53		35.28		26.88	
Physically active %	48.36		53.57		50.96	

Cardio-metabolic outcomes at age 32‡

	Total		Women		Men	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Systolic BP, mmHg	106.32	(12.42)	98.92	(9.50)	113.80	(10.38)
Diastolic BP, mmHg	71.61	(8.52)	68.52	(7.92)	74.73	(7.95)
Weight, kg	75.42	(16.90)	68.11	(15.06)	82.76	(15.41)
Height, cm	168.60	(9.50)	161.93	(6.34)	175.32	(7.13)
BMI, kg/m^2	26.44	(5.16)	25.98	(5.57)	26.91	(4.67)
Waist circumference, cm	86.64	(13.35)	81.75	(12.60)	91.54	(12.25)
Pulse, BPM	69.54	(10.14)	71.66	(9.53)	67.43	(10.29)
Glucose§, mg/dL	79.39	(11.77)	77.29	(11.82)	81.45	(11.35)
Insulin§, μU/mL	12.65	(8.79)	11.98	(8.24)	13.30	(9.24)
LDL-C§, mg/dL	112.74	(28.84)	107.95	(28.49)	117.51	(28.41)

Cardio-metabolic outcomes at age 32[‡]

	Total		Women		Men	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
HDL-C[§], mg/dL	49.73	(14.58)	56.45	(14.79)	43.12	(10.90)
Cholesterol[§], mg/dL	183.79	(33.28)	182.82	(33.18)	184.74	(33.37)
Triglycerides[§], mg/dL	107.70	(73.84)	92.94	(57.35)	122.11	(84.56)

[*] Values are expressed as mean (SD) or percent.

[†] Diabetes, hypertension, heart disease or toxemia.

[‡] N=1438 for BP and adiposity (717 women, 721 men) and N=1371 for blood assays (677 women, 694 men).

[§] Based on blood plasma assays at fasting (at least 8 hours).

Table 2

Associations* of maternal and paternal smoking with offspring cardio-metabolic outcomes at age 17

	Maternal smoking†				Paternal smoking†				Any parent smoking‡			
	Model 1§		Model 2§		Model 1§		Model 2§		Model 1§		Model 2§	
	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value
SYSTOLIC BP, mmHg	−0.37 (0.28)	0.18	−0.27 (0.28)	0.33	−0.47 (0.23)	0.04	−0.31 (0.23)	0.18	−0.50 (0.22)	0.02	−0.31 (0.22)	0.17
DIASTOLIC BP, mmHg	−0.15 (0.19)	0.43	−0.09 (0.19)	0.63	0.03 (0.16)	0.83	−0.05 (0.16)	0.77	0.01 (0.15)	0.94	0.05 (0.16)	0.75
PULSE RATE, BPM	−0.80 (0.23)	0.001	−0.73 (0.23)	0.002	−0.49 (0.19)	0.01	−0.53 (0.20)	0.007	−0.78 (0.19)	<0.001	−0.78 (0.19)	<0.001
HEIGHT, cm	0.48 (0.16)	0.002	0.71 (0.15)	<0.001	0.23 (0.13)	0.08	0.37 (0.13)	0.004	0.39 (0.13)	0.002	0.59 (0.13)	<0.001
WEIGHT, kg	1.36 (0.25)	<0.001	1.71 (0.24)	<0.001	0.73 (0.21)	<0.001	0.80 (0.20)	<0.001	1.23 (0.20)	<0.001	1.39 (0.20)	<0.001
BMI, kg/m^2	0.36 (0.08)	<0.001	0.43 (0.08)	<0.001	0.18 (0.07)	0.005	0.17 (0.06)	0.009	0.31 (0.06)	<0.001	0.32 (0.06)	<0.001

*Linear regression models; coefficient indicates the mean difference in cardio-metabolic outcome between offspring of smoking and non-smoking parents.

†Maternal and paternal smoking are included together in each model.

‡Al least one parent smokes.

§**Model 1:** Adjusted for gender and ethnicity. **Model 2:** Model 1 plus age of parents, socioeconomic status, parent's years of education, birth weight, maternal pre-pregnancy BMI and maternal health conditions

Table 3

Associations* of maternal and paternal smoking with offspring cardio-metabolic outcomes at age 32

	Maternal smoking†				Paternal smoking†				Any parent smoking‡			
	Model 1§		Model 2§		Model 1§		Model 2§		Model 1§		Model 2§	
	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value	B (SE)	P-value
SYSTOLIC BP, mmHg	−1.55 (1.05)	0.14	−0.94 (0.72)	0.24	0.24 (0.87)	0.78	0.56 (0.68)	0.41	−0.29 (0.79)	0.72	0.04 (0.65)	0.96
DIASTOLIC BP, mmHg	−0.82 (0.85)	0.33	−0.56 (0.62)	0.37	−0.15 (0.72)	0.83	0.46 (0.52)	0.38	−0.28 (0.65)	0.67	0.27 (0.49)	0.59
WEIGHT, kg	−0.64 (1.39)	0.65	0.84 (0.96)	0.38	2.29 (1.12)	0.04	2.12 (0.80)	0.008	2.34 (1.06)	0.03	2.22 (0.78)	0.004
HEIGHT, cm	−0.25 (0.67)	0.70	0.27 (0.51)	0.60	0.57 (0.51)	0.27	0.81 (0.39)	0.04	0.60 (0.50)	0.23	0.95 (0.39)	0.01
BMI, kg/m^2	−0.16 (0.45)	0.71	0.30 (0.29)	0.30	0.76 (0.37)	0.04	0.56 (0.25)	0.03	0.75 (0.34)	0.03	0.57 (0.24)	0.02
WAIST CIRCUMFERENCE, cm	0.07 (1.12)	0.95	0.78 (0.80)	0.33	1.60 (0.91)	0.08	1.34 (0.65)	0.04	1.94 (0.86)	0.02	1.46 (0.62)	0.02
PULSE RATE, BPM	0.23 (0.99)	0.82	0.17 (0.67)	0.80	−1.64 (0.76)	0.03	−0.98 (0.52)	0.06	−1.44 (0.77)	0.06	−0.74 (0.51)	0.15
GLUCOSE, mg/dL	1.54 (1.16)	0.18	1.70 (0.77)	0.03	0.74 (1.00)	0.46	0.16 (0.70)	0.82	1.89 (0.92)	0.04	0.71 (0.65)	0.27
INSULIN, μU/mL‖	0.00 (0.03)	0.91	0.01 (0.02)	0.55	0.01 (0.02)	0.63	0.01 (0.01)	0.62	0.03 (0.02)	0.10	0.02 (0.01)	0.13
LDL-C, mg/dL	−1.89 (2.84)	0.50	0.29 (2.06)	0.89	3.37 (2.37)	0.16	2.02 (1.68)	0.23	2.86 (2.26)	0.21	1.99 (1.61)	0.22
CHOLESTEROL, mg/dL	1.48 (3.17)	0.64	1.80 (2.40)	0.45	2.42 (2.68)	0.37	1.12 (1.98)	0.57	2.73 (2.60)	0.29	1.46 (1.90)	0.44
HDL-C, mg/dL	1.33 (1.44)	0.36	0.27 (0.97)	0.78	−1.20 (1.03)	0.24	−1.09 (0.83)	0.19	−1.10 (1.04)	0.29	−1.12 (0.80)	0.16
TRIGLYCERIDES, mg/dL‖	0.03 (0.02)	0.29	0.01 (0.02)	0.41	0.01 (0.02)	0.57	0.01 (0.01)	0.53	0.02 (0.02)	0.20	0.01 (0.01)	0.34

*Linear regression models; coefficient indicates the mean difference in cardio-metabolic outcome between offspring of smoking and non-smoking parents.

†Maternal and paternal smoking are included together in each model.

‡Al least one parent smokes.

§**Model 1:** Adjusted for gender and ethnicity. **Model 2:** Model 1 plus socioeconomic status, age of parents, parent's years of education, birth weight, maternal pre-pregnancy BMI, maternal health conditions, offspring smoking status, physical activity at age 32, education at age 32 and genetic propensity score

‖Log-transformed values (base 10) due to asymmetrical distribution