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חשיפות סביבתיות וגדילת עוברים: מחקר עוקבת הריון חיפה

כותרת המחקר באנגלית

Environmental Exposures and Fetal Growth: The Haifa Pregnancy Cohort Study

סוג הדו"ח

מסכם

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תקציר

רקע: מתרבות העדויות לקשרים בין חשיפה במהלך הריון לחלקיקים נשימים עדינים עם קוטר פחות מ2.5 מיקרון ($PM_{2.5}$) לבין תוצאי לידה. למרות זאת, יש חוסר עקביות בממצאים בין מחקרים שונים, הנבדלים בשיטות ובאוכלוסיות, ויש חוסר יחסי של מידע מאיזור המזרח התיכון. סיבוך נוסף בהבנת הקשרים נובע מחשיפות סביבתיות מקבילות כדוגמת טמפרטורת הסביבה וחשיפה לכימיקלים כדוגמת מתכות כבדות. מטרת המחקר היתה הערכת החשיפות הסביבתיות במפרץ חיפה ובשאר הארץ והערכת השפעתם על נשים בהריון, גדילת העובר ותוצאי לידה בעזרת שני מחקרים: מחקר אוכלוסיה (עוקבה) ומחקר שדה.

שיטות:

ערכנו מחקר גיאוגרפי מקדים כדי לתמוך במחקר העוקבה. מחקר העוקבה כלל שלושה תתי-מחקרים שבחנו את הקשר בין חשיפה ל $PM_{2.5}$ ושלוש קבוצות תוצאי בריאות: א) מדדי גדילת העובר(משקל לידה נמוך, משקל נמוך בלידה במועד, קטן לגיל ההריון ; ב) שבוע הלידה; ג) מומים מולדים במערכת הנשימה, הלב, הדם, העיכול, הכסות (**integument**), השתן ואיברי המין, . לצורך מחקר האוכלוסייה נעזרנו בנתוני מכבי שירותי בריאות על מנת ליצור עוקבה בת כ-400,000 יילודים בין השנים 2004-2015 בישראל. קישרנו נתוני סוציו-דמוגרפיים ובריאותיים ממכבי, כולל מומים מולדים בגילאי ילדות, עם נתוני משקל לידה ומשך הריון ממשרד הבריאות. חשיפות לחלקיקים נשימים עדינים וגסים (PM_{10}) וטמפרטורת סביבה התבססו על מודל חדשני מבוסס-לווינים. כתובת בזמן הלידה קודדה וקושרה לנתוני החשיפה. על מנת לסייע למחקר העוקבה, נעזרנו במחקר גיאוגרפי מקדים שכלל ניתוח מרחבי למיפוי וזיהוי צבירי משקל לידה נמוך על פי מערכת מידע גיאוגרפית. הקשרים בין חשיפות לתוצאי הלידה נבחנו בעזרת מודל רגרסיה לוגיסטית. לצורך בחינת הקשר ללידה מוקדמת נעשה שימוש במודלים מעורבים תלויי זמן מסוג Cox regression תוך תקנון למשתנים נוספים, בכדי להתגבר על בעיית מיצוע נתוני החשיפה למשכי הריון שונים.

למחקר השדה גויסו נשים בתחילת ההריון המתגוררות באיזור מפרץ חיפה. הערכת החשיפה נעשתה בשנים 2018-19 בעזרת ניטור אישי ותוך-מבני (בבית) למשך 48 שעות בעזרת Duke real team air sensor**.** לכל אישה חושבו ממוצעי חשיפה שעתיים ויומיים. ריכוזי מתכות כבדות וקוטינין (מטבוליט של ניקוטין) בשתן נמדדו בקרב 48 משתתפות המחקר באמצעות ICP-MS במעבדה המרכזית לבריאות הציבור. חושבו הבדלים בריכוזי המתכות לפי משתנים סוציו-דמוגרפיים ואישיים בעזרת מבחנים א-פרמטריים. חושבו מקדמי ספירמן לבחינת הקורלציות בין החשיפות השונות.

תוצאות:

בהשוואה לאומית לא נמצאו הבדלים משמעותיים בהימצאות משקל לידה נמוך באיזור מפרץ חיפה לעומת שאר ישראל. במודל מתוקנן, עלייה בחשיפה ל-$PM_{2.5}$ היתה קשורה במשקל לידה נמוך במועד **(OR=1.25, 95% CI: 1.09-1.43)** וב-SGA **(1.15, 1.06-1.26).** הקשרים השתנו עם תקופת החשיפה, מין היילוד, סדר הלידה ומסת הגוף של האם לפני הלידה. משתני כתובת המגורים הסבירו פחות מ 0.4% מהשונות לעומת משתני האם שהסבירו כ-50% מהשונות. חשיפה לחלקיקים עדינים היתה קשורה ללידה מוקדמת ברמת חשיפה נמוכות מהממוצע (חמישון תחתון) וגבוהות מהממוצע (חמישון עליון), בהשוואה לחמישונים 2-4 (HR=1.18, 1.13-1.24 ו- 1.07, 1.02-1.12**,** בהתאמה). הקשר תווך באמצעות טמפרטורה. עבור אימהות שנחשפו לטמפרטורה נמוכה (מתחת לחציון) במהלך ההריון, הסיכון ללידה מוקדמת גדל עם העליה בחשיפה. כך למשל לגבי $PM_{2.5}$, הסיכון עלה מ--0.87) 0.93 1.00) **ל-**(1.14-1.29) 1.21 בין החשיפה לחמישון התחתון לבין החשיפה לחמישון העליון. מגמה זו לא נצפתה כאשר החשיפה הייתה לטמפרטורות גבוהות, כך שבמקרה זה החשיפה לחמישון התחתון של PM קשורה לסיכון מוגבר עוד יותר ללידה מוקדמת מאשר חשיפה לחמישונים 2-4 (1.39-1.58) 1.48. אחד ההסברים האפשריים לממצא זה הנו שחשיפה גם לטמפרטורות גבוהות וגם ל-PM גבוה קשורה לאובדן הריונות וללידות מת (livebirth bias) – ומידע זה לא היה זמין לעורכי המחקר. התוצאות היו דומות במודל מוגבל לאיזור מפרץ חיפה.

סך הכל נמצאו 73,237 מומים מולדים בעוקבה. עבור 57,638 לידות (14.5% מהלידות) הופיע מום אחד (מום מבודד) שאינו מום כרומוזומלי וב 7,644 לידות הופיע מום כרומוזומלי או מספר מומים. בחינת הקשר ל-$PM_{2.5}$ הדגימה עליה גבוהה יותר בסיכון למומים עבור הטווח של $PM_{2.5} < 20\ \mu g/m^3$ (בקירוב אחוזון 35 של התפלגות ממוצע המזהם על פני ההריון) ועליה מתונה יותר בסיכון למומים בטווח ערכים גבוהים יותר של המזהם. כלומר קשר סופרה-לינארי עם מומים במערכות הדם (**circulatory**) , נשימתית, עיכול, אברי המין (**genital**) וכסות הגוף (עור, שיער וכד' **integument**).

במחקר השדה, נמצאו קורלציות חזקות בין החשיפה האישית לחשיפה תוך-מבנית (r=0.79), במיוחד בקרב נשים ששהו זמן רב בבית (r=0.83). ב-100% או קרוב ל-100% מהדגימות של הנשים נמצאו רוב המתכות הכבדות שנמדדו.

<u>מסקנות</u>:

במחקר האוכלוסיה מצאנו שחשיפה לחלקיקים נשימים עדינים במהלך הריון קשור לתוצאי לידה שליליים הקשורים בגדילת העובר. הקשרים התחזקו כאשר נלקחה בחשבון ההיסטוריה האימהית. התחשבות בנתוני טמפרטורה סיפקה תובנות חדשות לגבי הקשר בין חשיפה לחלקיקים עדינים לבין לידות מוקדמות. ממצאים אלו יוכלו לכוון חוקרים ומקבלי החלטות ולתמוך במדיניות להפחתת חשיפה לחלקיקים עדינים. התוצאות היו דומות במודלים מוגבלים למפרץ חיפה.

במחקר השדה נמצאו רמות של מתכות כבדות בקרב נשים במפרץ חיפה, בריכוזים דומים לאלו שנמצאו באוכלוסיות אחרות.

סיכום והמלצות:

המחקר מספק ראיות מקומיות בישראל ובחיפה כי חשיפה לזיהום אוויר מסוג $PM_{2.5}$ קשורה משמעותית לתוצאי לידה שליליים כולל משקל לידה נמוך, לידה מוקדמת ומומים מולדים.

יש צורך במחקרים נוספים לבדיקת חשיפות שונות לזיהום אוויר (חלקיקים נשימים, אוזון, פחמימנים ארומטיים, תחמוצות גופרית ועוד) ומזהמי סביבה נוספים (מתכות כבדות, חומרי הדברה, עישון) והשפעתם על בריאות אוכלוסיות, במיוחד אוכלוסיות רגישות, במפרץ חיפה וביתר הארץ.

נדרש מסד נתונים לאומי מתעדכן אודות חשיפות סביבתיות ותוצאי בריאות לצורך ניטור וסיוע במדיניות מושכלת לגבי השפעת זיהום אוויר ושינוי האקלים על בריאות הציבור בישראל. ממצאי המחקר מדגישים את הצורך להגביר את המאמצים להפחית את זיהום האוויר בישראל, תוך התייחסות גם להשפעות השליליות על העובר המתפתח.

ניטור ביולוגי משולב עם הערכת חשיפה אישית ותוך-מבנית לזיהום אוויר הוא בר יישום בישראל, וניתן להשתמש בו באופן שיטתי לצורך קביעת מדיניות מושכלת.

Abstract:

Background: A growing body of literature reports associations between exposure to particulate matter with diameter ≤2.5 µm ($PM_{2.5}$) during pregnancy and birth outcomes. However, findings are inconsistent across studies, with different methodologies and populations, and with scarce data from the Middle East. These associations are further complicated by concomitant environmental exposures such as ambient temperature and heavy metals. We aimed to assess, in the Haifa Bay Area and the rest of Israel, the extent and impact of maternal exposures to $PM_{2.5}$ and other environmental exposures on fetal growth and birth outcomes in Israel by two studies: population (cohort) and field studies.

Methods: We conducted a preliminary geographic study to inform the cohort study. The cohort study included three sub-studies examining the association between $PM_{2.5}$ and three different categories of health outcomes: a) Fetal growth; b) Preterm birth; c) Congenital anomalies.

For the population study we used Maccabi health services data to establish a population-based cohort of ~400,000 singleton births between the years 2004-2015 in Israel. We linked socio-demographic and health data from Maccabi, including congenital anomalies (up to childhood), with data on birth weight and length of pregnancy, that were received from the Ministry of Health. Exposures to $PM_{2.5}$, PM_{10} and ambient temperature were based on innovative satellite-based models. Address at birth was coded and linked to exposure data. In order to inform the cohort study, we used spatial analysis for mapping and identification of increase and reduced relative risk (RR) clusters of low birth weight (LBW) by geographic information systems (ArcGIS, version 10.3) and SaTScan software with a Bernoulli mode. The associations between exposure and birth outcomes were modeled using multilevel logistic regression model with random effects for maternal locality of residence, administrative census area and mother. Mixed effects Cox regression models, adjusted for covariates, with a random intercept at the mother level were used to assess associations between mean exposure during pregnancy and pre term birth (PTB).

For the field study, pregnant women residing in the Haifa Bay Area were enrolled at early pregnancy. The exposure assessment was performed between 2018-2019 by personal and indoor (at home residence) monitoring for 48 hours using a Duke real time air sensor. For each woman a periodic average of personal and indoor exposure by hour and day was calculated. The concentrations of arsenic (As), chromium (Cr), cadmium (Cd), nickel (Ni), lead (Pb), selenium (Se), thallium (Tl), mercury (Hg) and cotinine in the urine were measured in 48 urine samples using an inductively coupled plasma mass spectrometry (ICP-MS) instrument at the National Laboratory for Public Health, Tel Aviv. Differences in metal concentrations according to demographic variables were calculated using the Mann-Whitney or Kruskal Wallis tests. Examination of the relationship between the metals, cotinine and $PM_{2.5}$ concentrations was performed using a Spearman correlation coefficient.

Results: National-level comparison suggests no significant differences between LBW prevalence in the Haifa Bay Area compared to the rest of Israel.

In a fully adjusted model, with a mother-level random intercept only, 10-$\mu g/m^3$ increase in $PM_{2.5}$ over the entire pregnancy was associated with term low birth weight (TLBW) (1.25, 1.09-1.43) and small for gestational age (SGA) (1.15, 1.06-1.26). Associations varied by exposure period, infants' sex, birth order, and maternal pre-pregnancy BMI. Locality-and ACA (administrative census area) -level effects accounted for <0.4% of the variance while mother-level effects explained ~50% of the variability.

We found that exposure to $PM_{2.5}$ was positively associated with PTB when the average exposure during pregnancy was either low (first quintile) or high (fifth quintile), compared to exposure in the 2nd-4th quintiles, with hazard ratios (HRs) 1.18 (1.13-1.24) and 1.07 (1.02-1.12), respectively. The results revealed effect modification of temperature. For mothers exposed to low (below median) average temperature during pregnancy, HRs of PTB were 0.93 (0.87-1.00) and 1.21 (1.14-1.29) for the first and fifth $PM_{2.5}$ quintiles, respectively, when compared to the 2nd-4th quintiles. The findings were similar in a model restricted to Haifa Bay area.

A total of 73,237 anomalies were diagnosed in our cohort, of which 57,638 (14.5 % of the births) were isolated anomalies. Analysis of continuous $PM_{2.5}$ indicated higher increased risk for anomalies in the range of $PM_{2.5} < 20\ \mu g/m^3$ (~35^{th} percentile), and a more moderate increased risk for higher concentrations. Thus, reflecting a supra-linear relation with anomalies in the circulatory, respiratory, digestive, genital and integument systems (79 % of CAs).

In the field study, strong correlation was found between personal and indoor exposure (r = 0.79), especially in women who reported a greater home stay during the day (r= 0.83). Strong correlation was also found between the first and second monitoring day of the indoor exposure (r= 0.7).

Most of the metals were detected in 100% or nearly 100% of the urine samples.

Conclusions: In the population-based study we found that exposure to $PM_{2.5}$ during pregnancy is associated with adverse birth outcomes: TLBW and SGA. These associations were stronger when mother-level clustering in the data was accounted for. Consideration of climatic factors provided new insights into the risk of PTB as a result of exposure to $PM_{2.5}$ during pregnancy. Results were comparabal in models restricted to the Haifa Bay Area.

In the field study, strong correlations were found between personal and indoor exposure, especially in women who reported a greater home stay during the day. The concentrations of heavy metals obtained among pregnant women in Haifa Bay area were overall similar to those found in other countries. However, further research is needed to assess other environmental exposures, such as to PAHs and VOCs.

Summary and recommendations:

We provided local evidence in Israel and in Haifa that exposure to $PM_{2.5}$ is significantly associated with poorer pregnancy outcomes, including low birth weight, preterm birth and congenital anomalies.
Further research is warranted for assessing various exposures to air pollution (PM, Ozone, VOCs, etc.) and other pollutants (Heavy metals, Pesticides, Environmental Tobacco Smoking) and their impact on population health in Haifa Bay Area and the rest of Israel.
A national on-going database of environmental exposures and health outcomes should be established for surveillance, aiming to inform policy-makers regarding the impact of air pollution and climate change on public health in Israel. These findings underscore the need to intensify efforts in reducing air pollution in Israel, taking into account the adverse impact on the developing fetus.
Bio-monitoring combined with assessment of personal and indoor exposure to air pollutants is feasible in Israel and should be used systematically to inform policy-makers regarding exposure.

Keywords: Exposure assessment, Cohort, Indoor air pollution, Air pollution, Personal exposure, Fetal growth, Low birth weight, congenital anomalies.

Publications (attached):

1: Golan R, Kloog I, Almog R, Gesser-Edelsburg A, Negev M, Jolles M, Shalev V, Eisenberg VH, Koren G, Abu Ahmad W, Levine H. Environmental exposures and fetal growth: the Haifa pregnancy cohort study. BMC Public Health. 2018 Jan12;18(1):132. doi: 10.1186/s12889-018-5030-8. PMID: 29329571; PMCID: PMC5767054.
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Temperature: A Population-Based Pregnancy Cohort Study. Available at SSRN: https://ssrn.com/abstract=4419825 or http://dx.doi.org/10.2139/ssrn.4419825.
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LIST OF ABBREVIATIONS

Birth Outcomes		**Definitions**
ABO	Adverse birth outcome	
BW	Birth weight	
EPTB	Extreme preterm birth	Delivery with less than 28 weeks completed gestational weeks
LBW	Low birth weight	Birth weight less than 2500 g
PTB	Preterm birth	Delivery before 37 completed gestational weeks
SGA	Small for gestational age	<10th percentile of birth weight for gestational age
TBW	Term birth weight	Birth weight for gestational age ≥ 37 weeks
TLBW	Term low birth weight	Birth weight less than 2500 g and gestational age ≥ 37 weeks
VPTB	Very preterm birth	Delivery between 28 to 32 gestational weeks
Exposure		
AOD	Aerosol Optical Depth	
PM	Particulate matter	

$PM_{2.5}$	Particulate matter with diameter ≤2.5 μm
PM_{10}	Particulate matter with diameter ≤10 μm
$PM_{10-2.5}$	particulate matter with aerodynamic diameter between 2.5-10 μm
Covariates	
ACA	Administrative census area
BMI	Body mass index
SES	Socio-economic status
Statistical abbreviations	
AIC	Akaike information criterion
CI	Confidence interval
HR	Hazard ratio
ICC	Intra-class correlation
IQR	Interquartile range
M	Mean
MD	Median
p	P-value
Q_1 to Q_5	First quintile to fifth quintile
OR	Odds ratio
SD	Standard deviation

Introduction and scientific background:

Air pollution is a well-known environmental risk factor to human health (Kloog, Melly, Ridgway, Coull & Schwartz, 2012 ; Perez et al., 2013; Yishak-Sade, Novack, Ifergane, Horev, & Kloog, 2015). Fetal development is a global public health concern since *in utero* growth is suggested as a crucial predictor of perinatal and postnatal health and mortality (Gluckman, Hanson, Cooper, & Thornburg, 2008; Kramer, 2003).

Since the developing fetus is particularly susceptible to environmental insults (Stillerman, Mattison, Giudice, & Woodruff, 2008) studying the effects of air pollution on fetal growth may outline the first step on the causal pathway between prenatal air pollution exposure and poorer pregnancy outcomes such as gestational duration, fetal growth, pregnancy loss and congenital anomalies (Estarlich et al., 2011; Srám, Mattison, Giudice, & Woodruff, 2005; Stieb, Chen, Eshoul, & Judek, 2012) as well as adverse health effects later in life such as childhood obesity (Rundle et al., 2012), cardiovascular disease (Kelishadi & Poursafa, 2014) and respiratory morbidity (Patel, 2011). However, there is scarcity of data regarding the most relevant exposure in terms of type and chemical nature, dose and timing. There are several known determinants of fetal growth that could confound, modify or mediate the association between air pollution and fetal growth such as maternal smoking, socio-demographic position, pregnancy complications and parental characteristics. Other environmental factors could also play an important role. Recent evidence shows that air temperature during pregnancy is also associated with lower birth weight and shorter gestational age (Kloog et al., 2015).

Evidence of exposure effects during specific prenatal periods is still inconclusive (Stieb et al., 2012). Most studies rely on assessment at birth, yet these do not fully capture the timing of the in utero growth over the course of the pregnancy. Therefore, the ability to determine the age at which fetal growth failure begins is compromised. Exposures during early pregnancy may affect fetal growth differently (van den Hooven et al., 2012) than exposures in later pregnancy (Slama, Khoshnood, & Kaminski, 2008). Identifying exposure windows within pregnancy may allow the investigation of the mechanisms leading to these adverse outcomes (Slama et al., 2009).

In addition, individuals are exposed to multiple environmental exposures at once and the combined exposure and its effects on growing fetus, as well as correlations between the different components of exposure, is largely unknown as most studies focused on one type of exposure assessment.

Although intrauterine growth has been associated with exposure to air pollution, it is still unclear which sources and components are most likely responsible. Current research on the effects of air pollution has been limited by lack of a comprehensive assessment of environmental exposure assessment, as most studies focus on limited assessment of exposure or lack of assessment of personal exposure. Traffic-related air pollution has increasingly been identified as an important contributor to adverse health effects (Brook et al., 2010). Traffic-related air pollution has been related to adverse pregnancy outcomes. In a study of 2.5 million Canadian births (Stieb et al., 2016), nitric dioxide (NO2) was associated with small gestational age and term birth weight. In California (Laurent et al., 2016), a positive significant association was observed between TLBW and secondary organic aerosols, elemental carbon (EC), nitrates and ammonium as well as primary PM emitted by on-road gasoline and diesel or by commercial meat cooking sources. A recent study with pooled data from 14 population-based mother-child cohort studies in 12 European countries confirmed previous findings that exposure to traffic during pregnancy is associated with restricted fetal growth (Dadvand et al., 2013). In Taiwan, the prevalence of delivery of preterm birth infants was significantly higher in mothers living near oil refinery plants than among control mothers (Yang et al., 2003). Similarly, delivery of preterm birth infants was significantly higher in mothers living within 0-2 km of a Portland cement plant compared to mothers living within 2-4 km from the plant (Yang et al., 2004). In one of the only studies which assessed maternal personal exposure to airborne benzene among women in France, maternal benzene exposure was associated with decreases in birth weight and head circumference during pregnancy and at birth (Slama et al., 2009).

Several studies have shown associations between environmental exposures based on human bio-monitoring and reduced fetal growth. Human bio-monitoring integrates the actual exposure of the individual from various sources (air, water, food, etc.). Among 1027 participants in North Carolina, high maternal cadmium levels during pregnancy were inversely associated with birth weight percentile by gestational age and associated with increased odds of infants being small for gestational age (Johnston, Valentiner, Maxson, Miranda, Fry, 2014). These findings were independent of cotinine-defined smoking status, which is an important confounder as smoking is strongly associated with both cadmium exposure and fetal growth. Studies have shown that fetal exposure to polycyclic aromatic hydrocarbons (PAHs) is associated with poor fetal growth in different populations. A study using personal air monitoring found an association with reduced birth weight in both Krakow Caucasians and in NYC African Americans (Choi et al., 2016). However, evidence from human biomonitoring studies is scarce Exposure of the Israeli population, and specifically exposure in Haifa area, to VOCs, PAHs, and heavy metals, using human bio-monitoring, is largely unknown. We previously found in the Ministry of Health human biomonitoring study wide exposure of the Israeli population to PAHs (Levine et al., 2015), as well as to environmental tobacco smoke (Levine et al., 2013), with significant disparities between population groups.

Central monitoring sites are limited in their ability to assess personal exposure, which is also greatly influenced by indoor environments and are related to daily activities (Klepeis et al., 2001). Moreover, central monitoring is usually limited to criteria pollutants, and generally don't provide an assessment of exposure to volatile organic compounds (VOCs) and heavy metals. Given that people from industrialized countries spend most of their time indoors (Gauvin et al., 2002; Nethery, Brauer, & Janssen, 2008) for many, major part of exposure to fine particulate matter ($PM_{2.5}$) occurs while indoors (Meng et al., 2005). Indoor air pollution can thus contribute substantially to total exposure, even when outdoor levels are considered low (Lanki et al., 2002). In a study of pregnant women conducted in Spain, personal NO2 levels were more influenced by indoor than by outdoor NO2 levels (Valero et al., 2009). In Tanzania, personal exposures to carbon monoxide (CO) and $PM_{2.5}$ was measured in 239 pregnant women. $PM_{2.5}$ and CO were not associated with birth length or head circumference but were associated with adverse birth weight (Wylie et al., 2016). In a cohort study in Poland, personal air monitoring was measured in 362 pregnant women. Increased exposure to $PM_{2.5}$ (between 10 to 50 μg/m3) was associated with a reduction of 140gr at birth (Jedrychowski et al., 2004). In a Meta-analysis by Pope et al. (Pope et al., 2010) indoor air pollution from solid fuel combustion processes was associated with an increased risk of LBW (OR 1.38, 95% CI 1.25 to 1.52). Similarly, in a review by (Misra, Srivastava, Krishnan, Sreenivaas, & Pandac, 2012) the risk of LBW increased 1.45-fold due to indoor air pollution exposure. In a recent review, Patelarou et al. (Patelarou & Kelly, 2014) examined indoor exposures and adverse birth outcomes in "westernized" countries. They highlighted the limited number of studies to date that attempt to quantify indoor exposure and/or all-day personal exposure to specific pollutants during pregnancy (Perez et al., 2013).

Measurements of personal exposure might be more accurate metrics of biologically relevant exposure. Given the ability to accurately measure both exposure to air pollution and health parameters on an individual level, cohort and panel design studies have proven to be effective approaches of investigating adverse health effects of air pollution (Delfino et al., 2008; McCreanor et al., 2007; Mirabelli et al., 2015;

Sarnat et al., 2012). For small cohort and panel studies, in particular characterizing indoor pollutant concentrations and personal exposures may lead to more accurate exposure assessments, depending on the particular pollutant and target cohort.

Ambient exposure assessment provides useful information at the population level. The broad spatial coverage enabled by satellites and reliable repeated measurements allows us to expand exposure data far beyond the range of conventional ground monitoring, particularly for areas and exposure scenarios where surface PM monitors are not available. This greatly enhances our ability to estimate subject-specific ambient exposures. Most studies rely on a limited number of PM monitors in their study regions, which introduces exposure error, and likely biases the effect estimates downward (Zeger et al., 2000), and are unable to produce estimates in locations without monitoring stations. As previously done by our group, by using satellite-based hybrid PM estimation models (Kloog et al., 2014; Kloog et al., 2015) we can significantly reduce exposure bias and reliably assess short term and long-term human ambient exposures in order to investigate both the acute and effects of ambient particles, respectively.

Studies involving monitoring often mention both the complexity and the importance of communication between researchers and subjects about the need, risk and importance of participating in biomonitoring research (Brody et al., 2014; Exley et al., 2015; Keune, Morrens, & Loots., 2008). Studies indicate that the communication aspect is often neglected, which hinders, delays and damages the research and affects participants' responsiveness. This study suggests putting an emphasis on communication in the course of biomonitoring, as many health organizations already do, including the CDC, and the California Department of Public Health (CDC, 2015; State of California, 2016).

The working hypothesis for this study is that exposure of pregnant mothers to environmental pollutants through air pollution may harm the growth of the fetus. This hypothesis is somewhat supported by results of study by Farhi et al which found a possible association between exposure to air pollution and the risk for congenital anomalies in an Israeli population (Farhi et al., 2014). Effects differ by the specific pollutant, dose and timing of exposure and the possibility of interactions ("mixture" effect). There is a serious concern regarding the possible adverse health effects of exposure to the industrial activity in the Haifa Bay area (HBA), with specific concern regarding the effects of the exposure on the developing fetus. However, there is a lack of comprehensive evaluation that can provide scientific evidence regarding actual exposure of Haifa residents to environmental pollutants that includes human bio-monitoring and assessment of the associations between environmental exposures and fetal growth.

Against this background, we proposed to conduct a prospective cohort study of pregnant women in Israel, establishing a comprehensive assessment of exposure to air pollution and assessment of multiple growth outcomes in the fetus, through prenatal and postnatal life. We have the unique opportunity of a **population-based study** of Maccabi health services members, which reduces the possibility of a selection bias, which is a common problem in such studies. Furthermore, we were able to model individual exposure in a large sample, overcoming the common problem of insufficient power in such studies. This unique setting allowed assessment of further growth and development through the offspring life course. The additional field study provides evidence regarding the personal exposure to air pollution and multiple chemicals of residents in Haifa.

Objectives:

1. **Examine whether differences in environmental exposures on the individual level during different stages of pregnancy, are independently associated with fetal growth and congenital anomalies** among ~~10000 pregnant women residing in Haifa Bay Area and ~400000 residing in Israel, controlling for a plethora of personal, obstetrical, medical, environmental and sociodemographic characteristics.

2. **Evaluate and compare multiple environmental exposures on the individual level**, by Human bio-monitoring, personal and indoor exposure to air pollution among 50 pregnant women residing in the Haifa Bay Area.

Innovation:

Detailed in the research protocol published in the scientific literature: Golan R, et al.

BMC Public Health, (2018) 18: 132. (19) [Article 1 Attached].

Scientific innovation of this work:
This research represents a comprehensive analysis, with reliable data that allowed us to evaluate environmental exposures of pregnant women and in utero growth over the course of the pregnancy during different exposure windows in the national level (population study) and in Haifa Bay area. There is currently a gap in our knowledge regarding the actual environmental exposures of residents of the Haifa Bay area, especially from air pollution, and the potential impact on health, and especially the possible effects on the growing fetuses. The study provides evidence regarding the actual environmental exposures of residents in Haifa, in comparison to another area in Israel, and the possible impact on fetal growth.

These assessments were performed using advanced methods for assessing time and space, addressing a variety of variables and an overall assessment of air pollution and additional environmental exposures in the field research. Findings not only inform policy in Israel but will also greatly advance our scientific understanding of the complex associations between environmental exposure and fetal growth. Findings and established methodology will inform public policy and prioritization regarding protection of the public from environmental pollution, especially air pollution, in Haifa and other areas in Israel and will inform policy regarding air quality standards.

The ambient exposure model and fetal outcomes were extended well and beyond the original proposal to cover all geographic regions in Israel and much larger population which allow further research on environmental exposures and fetal outcomes in Israel. We also extended the study to include anomalies identified during childhood. The exposure assessment data from this study will be a basis for future studies on the effects of ambient, indoor and personal environmental exposure and adverse birth outcomes in Israel. Our data and methodology will be available for researchers in the field of public health and Environmental epidemiology and would be a valuable resource for surveillance and for environmental epidemiology studies and a vast improvement over currently available exposure assessment methods. The results of the proposed study in this grant adds important knowledge to the current literature.

Study description:

Methods:

Data for population including geographic studies: The studies include potentially information on 443,427 newborns. However, the actual sample size for each study and analysis may differ due to missing data on exposure or outcome. Data on birth weight and week of birth were obtained from the Ministry of Health. In addition, the Data on socio-demographic and health were obtained from Maccabi. After data cleansing for the socio-demographic data, $PM_{2.5}$ exposure data were developed and transferred from the laboratory of Prof. Itai Kloog. The home address at birth was coded and crossed against the exposure data. Further details are available in the published papers attached.

We conducted a preliminary geographic study to inform the cohort study. The cohort study included three sub-studies examining the association between $PM_{2.5}$ and three different health outcomes: a) Fetal growth; b) Preterm birth; c) Congenital anomalies. In addition, we conducted a field study.

Geographic preliminary study methods:

Statistical analysis**:**

We used SaTScan software to identify and evaluate clusters of LBW in Israel and in HBA in particular. The software calculates the Likelihood function for each window (according to the distribution of the event), as well as the number of observed and expected cases in each window. For the Bernoulli model, we defined the address as the latitude and longitude of all the "cohort group". Then the "cohort group" was split into 'cases group' which was defined by LBW (<2500g), and the 'control group' with the rest of the neonates. Both of them were analyzed by the Bernoulli method (Kulldorff, 1997). The Bernoulli method, in general, uses a case and control to identify and determine if there are significant clusters. This means that in those areas there is higher number of cases than would have been expected by chance and there may be a higher risk of low birth weight. Therefore, for the Bernoulli model, the likelihood function is:

$$\left(\frac{c}{n}\right)^{c} \left(\frac{n-c}{n}\right)^{n-c} \left(\frac{C-c}{N-n}\right)^{C-c} \left(\frac{(N-n)\,(C-c)}{N-n}\right)^{(N-n)(C-c)} I\,()$$

where C is the total number of cases, c is the observed number of cases within the window, n is the total number of cases and controls within the window, N is the combined total number of cases and controls in the dataset, and I() is an indicator function. When SaTScan is set to scan only for clusters with high rates, I() is equal to

1 when the window has more cases than expected under the null hypothesis, and 0 otherwise. When the program scans for clusters with either high or low rates, then I()=1 for all windows (Kulldorff, Huang, & Konty, 2009).

In the first analysis for all of Israel, we used the default options for defining clusters: 50% of the population at risk within a 1-km-radius circle, but in the second analysis for HBA, we reduced the proportion of the population at risk to only 25%, due to the small area.

Population- based study methods: This was a population-based retrospective cohort of singleton live births in Israel from 2004 to 2015 (N= 443,427). This cohort was built from data provided by Maccabi health services, which provide universal health care for ~25% of all Israelis, and by the Ministry of Health (State of Israel) registries. These data included information on maternal-infant health status and outcomes, reproductive history, maternal risk factors and attributes, and residential addresses. We included births with gestational age of 23–42 weeks and birth weight of 500–5,000 g born to mothers who were members in Maccabi health services. We excluded births with implausible (<500 g or >5000 g) birth weight (n=123, 0.03%), births with gestational age less than 23 or greater than 42 weeks (n=1312, 0.3%), multiple pregnancy (n=22,740, 5.1%) and missing birth weight or gestational age (n=7052, 1.6%). We further excluded 69 births (0.02%) with missing data for exposure to $PM_{2.5}$, 13,013 births (3.2%) with imputed exposure data by center of locality of residence, in large localities and 17,853 births (4.3%) from localities in which the exposure model could not provide predictions, due to lack of monitors. Our final analytical data set included 381,265 births.

Exposure assessment**:** Residence-specific exposures to $PM_{2.5}$ were estimated using a novel spatiotemporal model incorporating high resolution imaging spectroradiometer satellite-derived aerosol optical depth (AOD) measurements at a *1 × 1 km* spatial resolution. The model was fitted with a smooth function of latitude and longitude and a random intercept for each cell. Calibrations of AOD-$PM_{2.5}$ relationship were performed using ground $PM_{2.5}$ measurements from monitoring stations covering Israel, land use regression and meteorological variables using mixed models with random slopes for day, nested within region (Kloog, Melly, Coull, Nordio, &

Schwartz, 2015). Estimates from areas without monitoring stations couldn't be calibrated. Hence this model didn't supplied data for these areas.

Definitions of birth outcomes are presented in Table 1.

Statistical analysis:

Fetal growth: Associations between $PM_{2.5}$ and birth outcomes (TLBW and SGA) were assessed by multiple logistic regression models. At the first step, our core models included exposure to $PM_{2.5}$ during entire pregnancy, then covariates were added sequentially as follows: (1) gestational age for TLBW models, (2) mother age at birth and birth order, (3) SES, (4) maternal height and maternal smoking status, and (5) year of birth, birth season and temperature during whole pregnancy (the variable with the highest percentage of missing data). We used Akaike information criterion (AIC) model selection to distinguish among the aforementioned models, and a complete case analysis was used in the fully adjusted models. $PM_{2.5}$ exposures were analyzed as continuous measures, rescaled to an increment of 10 μg/m3. For preterm birth, $PM_{2.5}$ exposures were analyzed as categorical variable, as the results suggested non-linear association. Our first paper focus on the associations with SGA and TLBW and we compared between models with different levels of nested groups (clusters): 4-level, 3-level and 2-level, by sequentially eliminating random intercepts at locality of residence, administrative census area (ACA) and mother. The overall variation explained by different levels of clustering was assessed by the intra-class correlation coefficient (ICC) of the core models. ICC values <10% were interpreted as null intra-cluster correlations implying that births within clusters are no more similar than births from different clusters.

For sensitivity analysis, we carried out a negative control exposure analysis , by including average $PM_{2.5}$ during 180 days postnatal in the model (Sanderson, Macdonald-Wallis, and Smith 2018) to test for residual confounding. Second, we included maternal active smoking during pregnancy (yes/no), rather than smoking status before conception. While smoking during pregnancy is more relevant it is also prone to self-reporting bias (Shipton et al. 2009). Third, we included exposures during all trimesters in the same model instead of single-trimester models to evaluate possible independent or joint associations. Fourth, we examined whether the associations between entire pregnancy $PM_{2.5}$ and birth outcomes were sensitive to differential omission of missing covariate data. Using this approach, we dropped for all sequential models ~13.5% of the births with incomplete data in *any* of the covariates, compared to our main analysis in which a different set of missing values were omitted for each model (depending on the specific covariates in the model). Lastly, we included pre-pregnancy BMI in our final models, and included interaction terms between BMI category and $PM_{2.5}$, as the inclusion of the BMI had changed the associations by more than 50%. BMI was categorized as suggested by the CDC (CDC 2022): Underweight; ≤18.5 kg/m^2, normal; 18.5-24.9, overweight; 25.0-29.9 and obese; ≥30).

Preterm birth: The associations between PM and PTB were assessed by a mixed effects Cox model with birth censored at 37 gestational weeks as the outcome and a random intercept for mother. We used this model rather than a logistic regression model in order to account for averaging exposures over different durations for preterm and term births, thus decreasing the risk of differential misclassification bias (O'Neill et al., 2003; Slama et al., 2014). The proportional hazards assumption was tested using the Schoenfeld residuals. At the first step, our core models included exposure to PM during entire pregnancy, then covariates were added sequentially as follows: (1) mother age at birth and birth order, (2) SES, (3) season and year of birth, (4) maternal height and maternal smoking status, and (5) temperature during whole pregnancy. Data for temperature had the highest percentage of missing values (2.3%), in particular, data were not available for October-December 2015 and this variable was therefore added last to the model. We also used AIC model to distinguish among the aforementioned models. PM exposures were analyzed, first, as continuous measures, rescaled to an increment of a 10 μg/m3 for $PM_{2.5}$ and 20 μg/m3 for $PM_{10-2.5}$, then analyzed by quintiles of exposure: 1st and 5th quintiles, compared to 2nd-4th quintiles, to assess the effect of extreme PM levels and enable assessing non-linear associations. Another association that we focus on was between PM and temperature. To study effect modification by temperature we stratified births to those with mean temperature during pregnancy below or above the median (20.6 °C).

For sensitivity analysis, we also used a negative control exposure approach to test for residual confounding by including average $PM_{2.5}$ during 180 days postnatal in the model (Sanderson et al., 2018) to test for residual confounding. Second, our final fully-adjusted model was stratified by season of birth rather than level of temperature, to test whether the results are sensitive for alternative definition of heat conditions exposure. Season of birth was categorized as a warm season, which included spring and summer (March to August) and a cold season (autumn and winter, September to February). Third, we tested for fixed cohort bias (Neophytou et al., 2021; Strand et al., 2011) by excluding births that conceived more than 22 weeks before the study start date (January 01, 2004) and less than 41 weeks before the study end date (31 December, 2015) because pregnancy duration in our study population were between 23 and 42 weeks. That is, we excluded births conceived before May 25, 2004 and after March 13, 2015. Lastly, we rerun our final models to assess the association between PM and extremely preterm birth (EPTB, less than 28 weeks of gestation), very preterm birth (VPTB, 28 to 31 weeks) and moderate to late preterm birth (MLPTB, > 32 to 37 weeks) (WHO 2022), to test sensitivity of the association for different sub-categories of the outcome. This last analysis was tested by Cox-regression models with fixed-effects only as there were very few siblings born below 37 weeks of pregnancy.

To assess the possible confounding biasing the crude PM-PTB association we constructed a directed acyclic graph (DAG), thereby exploring backdoor paths from PTB to PM. We added common ancestors of exposure and outcome as observed factors.

Analyses were conducted in Stata/SE version 15.0 (StataCorp) and R statistical software version 3.5.0 (R Project for Statistical Computing). Two-sided P-values less than 0.05 were considered statistically significant for all models.

<u>Congenital anomalies:</u> As part of this population based study, we specifically examined associations between maternal exposure to fine and coarse particulate matter and congenital anomalies in offspring. The data included an anomaly group for those born from 2004 to 2015 and were followed until October 2018 (n=396,334). Anomalies were classified into 9 anomaly groups according to the International Classification of Disease Ninth Revision (ICD-9). These groups included CAs in the nervous system (codes 740-742), eye, ear, face and neck (EEFN, 743-744), circulatory (745-747), respiratory (748) and digestive (749-751) systems, genital organs (752), urinary system (753), integument (757) and other (759). In our primary analysis we considered cases with isolated anomalies in the organ system groups, that is, cases that had birth defects in one of the above nine organ systems.

This study required data processing and other statistical analyzes and in particular separate conditional logistic regression models to evaluate associations of air pollutants ($PM_{2.5}$, $PM_{10-2.5}$) during the first trimester of pregnancy with any isolated anomalies and with each anomaly group. We used the generalized estimating equations (GEE) approach to account for mothers who had more than one child in the cohort.

To examine the possibly non-linear relationship between PM averages and the OR of a congenital anomaly, we used exposure levels as categorical variables.

We performed sensitivity analysis to assess the possible effect of outcome misclassification on the PM-Congenital anomalies association and possible uncontrolled confounding.

Field study:

In November 2018, recruitment began in two clinics of Dr. Nina Gordon (20 Margalit St., Haifa, 8 Dor St, Haifa), The participants came from a wide geographical distribution in Haifa. Every potential candidate (non-smoking, residing in Haifa Bay area), on a first trimester visit, were assessed for eligibility and offered to join the study. After signing an informed consent form, each participant filled out a basic questionnaire. When the woman arrives to Maccabi clinic for laboratory tests, blood and urine tests are sent for further treatment and storage by Dr. Ronit Almog at Rambam Medical Center. Each participant has a home visit that includes the installation of personal and indoor exposure monitoring devices for 48 hours, as well as the collection of questionnaires.

The $PM_{2.5}$ count monitoring device is called the Duke real time air sensor. This device was placed centrally in the pregnant woman's home and on her backpack that she carried with her during the day. The kit will be inside a ventilated glasses box. At each minute of measurement, a line of values will be added to the memory card with an average of $PM_{2.5}$ at the same minute. The sensor is widely used in scientific research (see appendix bibliography). For the purpose of the study we examine reliability by comparing two sensors over 48 hours. The correlation was 0.97, similar to 0.96 in other study (Zheng et al.). The field study was informed by a communication study, aimed to facilitate good communication with the participants.

Lab analysis:

Cotinine and Heavy metals concentrations were evaluated using validated lab protocols. Based on the method "Cotinine: determination in urine to ascertain passive exposure to smoking. Capillary gas chromatography/mass spectrometric detection

(MS)", Author: Müller M. , Deutsche Forschungsgemeinschaft. "Analyses of Hazardous Substances in Biological Materials", Biomonitoring methods,Vol 8. Weinheim: Wiley-VCH; 2003 (71)

Gas Chromatography-Mass Spectrometry was used to measure the quantity of urinary cotinine concentration. In brief, cotinine was extracted by dichloromethane from urine samples, spiked with isotope labeled analogue used as internal standard. Final extract after drying, evaporation and solvent change was injected to Agilent 7000GC/MS Triple Quad Instrument and analyzed in MRM Mode. The Method followed standard quality assurance and quality control procedures. Urinary cotinine concentrations were quantified using internal standard calibration procedure and certified analytical standards. Limit of quantification (LOQ) was 0.5µg. Heavy metals: Metals analysis was performed by inductively coupled plasma mass spectrometry (ICP-MS), using Agilent 7800x ICP-MS Instrument, equipped with Integrated Sample Introducing System (ISIS) and High Matrix Introducing mode (HMI). The procedure involved acid dilution of urine and direct injection to ICPMS, followed by "helium dilution" in instrument HMI. The method followed standard quality assurance and quality control procedures. Urinary metals concentrations were quantified using internal standard calibration procedure and certified analytical standards. Quality control was performed by analyzing aliquots of control material in each series (each ten samples) and accuracy was validated by the annual successful participation in international proficiency test (G-EQUAS) for all parameters. Limits of quantification (LOQ) for metals in urine as followed: 0.02µg/L (excluding selenium with LOQ 0.2 µg/L.

Statistical analysis:

The relationship between continuous variables, between the metals and cotinine was examined using a Spearman correlation coefficient. The relationship between $PM_{2.5}$ exposure levels within a indoor, personal and general context and the metal concentrations was examined using the Spearman correlation coefficient. According to the kurtosis, skewness and Shapiro-Wilk tests, the metal concentrations are not normally distributed. Moreover, the sample size is small, less than 50. In addition, differences in metal concentrations by demographic variables, such as age, years of schooling, religion, etc., were performed by corresponding tests - Mann – Whitney or Kruskal Wallis.

Religion/ethnicity is of particular interest due to the percentage of Arabs in the Haifa district (12%). Due to the differences in life style and behaviors, especially in the food consumption, it was interesting to examine whether this is associated with different exposures. For example, Arabs consume on average more red meat, pond and canned fish than Jews (Ministry of Health, 2019). Arabs and secular Jews eat a wide variety of fish and seafood, compared to religious Jews who are forbidden by Jewish kosher laws to eat certain types of fish and seafood in general (Abu-Saad et al., 2012).

The women's participation time is divided into 4 seasons, in order to see if there is a difference in the metal concentrations according to the seasons. At a more advanced stage, participation time is also divided into two categories: hot or cold weather. To see if there is an association between exposure to cotinine and the concentrations of the various metals. The cotinine concentration is divided into two categories. Women with a lower cotinine concentration than LOQ and women above LOQ (LOQ cotinine = 0.5 µg \ L). All statistical tests were calculated at an alpha significance level of 0.05 for bilateral testing.

In the second stage of data processing, multivariate regression models with used to predict the set of factors that may be associated with the metals in the urine, with respect to limited statistical power. These models included the univariable analyzes at the earlier stage, at a significance level of 0.2 (P-value <0.2). The guidelines of the regression model were examined by examining the normal distribution of the dependent variable and the distribution of the residues. Because the distribution is not normal then an LN transformation was made to metals with which there were significant relationships, at a significance level of 0.2, with the $PM_{2.5}$ concentrations. The categorical demographic variables were given a demy variable to compare the reference group.

In the final stage, a spatial mapping for the concentration of the metals is done based on the address of the women's residence (by Geocoding and the use of ArcGIS Pro software. In addition, the description of the biological monitoring results was done with the help of box-plot diagrams and appropriate descriptive statistics indices: mean (standard deviation), geometric mean, median (bottom quarter - top quarter) and the percentage of samples that were above the quantification threshold (LOQ). For samples with a concentration lower than LOQ, the original concentration was replaced by the concentration threshold quantification of root parts 2 (LOQ / √2) (69). Also, to ensure the accuracy and flatness of the method of analysis of the metals, duplicate duplicates were made for 10% of the samples (re-examination). Accuracy was tested using the Pearson correlation index. Then, an average is made for its sample and duplicate.

Ethics approval and consent to participate: The Helsinki committee of Assuta Medical Center approved the study protocol. For the population study, the committee granted exemption from informed consent since it includes de-identified electronic medical records. For the field study, informed consent was obtained from all women upon recruitment.

Results:

Geographic sub-study:

The prevalence of LBW was significantly higher in males compared to females, both in HBA and rest of Israel (ROI) (51.2% males and 48.8% females; 54.4% males and 48.5% females respectively, p<0.001). LBW prevalence was similar in HBA and ROI for both males (4.7% vs. 4.7%) and females (6.0% and 6.1%) There was no significant difference in either sex in the prevalence of LBW between the two examined regions. There was no significant difference in gestational age between the two examined regions. Mothers with preeclampsia had significant higher LBW in both HBA (13.0%) and ROI (16.9%) compared to mothers without preeclampsia (5.1%) (p<0.001). Moreover, a significant difference was found between the examined regions for women with preeclampsia (p<0.001).

The highest prevalence of LBW was found in the youngest (≤ 20) and oldest (≥ 39) mothers in both HBA (7.0% and 6.3% respectively) and ROI (6.9% and 6.7% respectively). No significant differences were found among the different SES groups in each region. However, in HBA it was found that those with the lowest SES have the highest prevalence of LBW (7.3%), although they constitute a very small percentage of all newborns (0.2%).

The LBW prevalence rate in HBA as well as in the Northern and Haifa Districts, has remained similar over the years. In the Center and Tel-Aviv districts there was no consistent trend, while in the Jerusalem and Southern districts the LBW rate declined over the years (Figure. 1).

The map of Israel presents the spatial analysis clusters We found 3 low clusters in HBA, one of which was significant (RR=0.31, P<0.01). A separate analysis for HBA only found 20 clusters: 13 high clusters, none of which were significant, and 7 low clusters, of which 2 were significant. Using the cluster analysis method, 14 out of 57 clusters all over Israel were significant Among them, 5 clusters were found in the Tel- Aviv District; 3 with low relative risk (RR) and 2 with high RR (RR=4.38, p<0.05; RR=2.58, p<0.05). Also, 2 out of 20 clusters in HBA were found to be significant, both were of lower risk for LBW (RR=0.31, p<0.01; RR=0.30, p<0.01). However, all the other 18 non-significant clusters in HBA were with excess risk, with the largest cluster at RR=14.96, p=0.79 (Figure.2).

Population-based study (further detailed in articles 2,3,4):

<u>Characteristics of the study population:</u>

Overall, our data included 381,265 eligible births of insured infants in Maccabi Healthcare Services from 2004 to 2015. The cohort included 223,780 mothers (M(SD)=2.3(1.3) births per mother). Of these, 108,489 (48.4%) had one delivery in the cohort, 68,926 (30.8%) had two deliveries and 38,872 (16.6%) had three deliveries or more.

For the fetal growth study population: the mean of term birth weight was 3315 g (SD=432), the overall prevalence of TLBW was 2.6%, and the prevalence of SGA was 7.1% (Table 2). The proportion of TLBW births were higher among female births (3.5% vs. 2.0%) and mothers who were smokers (3.7% for smokers vs. 2.8% for non-smokers). The prevalence of TLBW decreased by birth order (4.0% for first child vs. 1.9% for third child or higher order), maternal age at birth (3.1% and 2.7% for mothers aged ≤24 and 35-39 years, respectively), gestational age, SES (except for the 1-2 SES level) and maternal anthropometric measures. SGA exhibited similar trends, and for TBW we observed comparable but inverse trends except for maternal smoking and SES.

For the preterm birth study population: overall PTB prevalence was 5.3% (20,259 of 381,265 total births) (Table 3). The proportion of PTB was higher among male births (5.7% vs. 4.9%) and mothers who were smokers (6.5% for smokers vs. 5.1% for non-smokers). The prevalence of PTB decreased by birth order and maternal anthropometric measures. PTB increased by maternal age at birth (4.8% and 7.4% for mothers aged ≤24 and 40+ years, respectively) and SES (4.6% and 5.5% for SES of 1-2 and 9-10, respectively).

$PM_{2.5}$ exposures during pregnancy:

Table 4 present daily $PM_{2.5}$ and $PM_{10\text{-}2.5}$ exposure during pregnancy in Haifa and other district of the mother's place of residence (μg/m3).

The mean $PM_{2.5}$ level over the entire pregnancy was 21.8 μg/m^3 (interquartile range, IQR = 2.8 μg/m3). Average $PM_{2.5}$ values were highest among births that occurred during summer and lowest in areas with low socioeconomic levels (1-2) and late birth years (2013-2015) (Table5).

Multilevel models: In 2-level models with a random intercept at the mother-level only, the intra-class correlation coefficients (ICCs) ranged between 45% and 50% for all birth outcomes, suggesting that in adjusted models about half of the total variance was accounted for by the between-mother variability (Table 6). In 3- and 4-level models, mother-level ICCs were similar to those observed for the 2-level models while the ICCs for the ACA-level and locality of residence grouping were negligible (0.2-0.9%). In 2-level model, the ORs for TLBW and SGA associated with a 10 $\mu g/m^3$ increase in entire-pregnancy average $PM_{2.5}$

were 1.19)95%CI: 1.09-1.31(and 1.14)95%CI: 1.06, 1.21(, respectively, and in 4-level model 1.12 (95%CI: 0.99, 1.27) and 1.08 (95%CI: 1.00, 1.17), respectively. Estimated coefficients for TBW were -29.4 (95%CI: -34.4, -24.4) and -23.8 (95%CI: -29.5, -16.9) in the 2- and 4-level models, respectively.

Associations between $PM_{2.5}$ and birth outcomes:

Fetal growth: In view of the low explanatory power of the geographic clustering in the 3- and 4-level models, we further analyzed models with a random intercept at the mother-level only. The associations between $PM_{2.5}$ and birth outcomes by level of adjustment for covariates are shown in Table 8. In all levels of adjustment, a 10 $\mu g/m^3$ increase in average $PM_{2.5}$ over the entire pregnancy exhibited positive associations with TLBW and SGA and negative associations with TBW. Associations of $PM_{2.5}$ with all birth outcomes were not sensitive to adjustment for neighbourhood SES (added at model 3) but changed substantially when year and season of birth were added to the models in the fourth step. For example, the OR for TLBW from 1.13 (95%CI: 1.02,1.25) to 1.23 (95%CI: 1.09,1.41). In the fully adjusted models ORs/B for TLBW, SGA and TBW were equal to 1.26 (95%CI: 1.09,1.45), 1.15 (95%CI: 1.06,1.26) and -10.2 (95%CI: -16.9,-3.5), respectively.

Preterm birth: We found that exposure to $PM_{2.5}$ was positively associated with PTB when the average exposure during pregnancy was either low (first quintile) or high (fifth quintile), compared to exposure in the 2nd-4th quintiles, with hazard ratios (HRs) 1.18 (95% confidence interval [CI], 1.13-1.24) and 1.07 (95% CI, 1.02-1.12), respectively. The results revealed effect modification of temperature. For mothers exposed to low (below median) average temperature during pregnancy, HRs of PTB were 0.93 (95% CI, 0.87-1.00) and 1.21 (95% CI, 1.14-1.29) for the first and fifth $PM_{2.5}$ quintiles, respectively, when compared to the 2nd-4th quintiles. However, a reverse trend was indicated for high-temperature pregnancies, where the corresponding HRs were 1.48 (95% CI, 1.39-1.58) and 0.92, (95% CI, 0.96-0.98). The PM-PTB associations in Haifa Bay area were consistent with the main analysis conducted for the entire study area. We found that the risk of PTB increased with PM level, when exposed to low temperature levels during pregnancy (below the median) (Table 9). Moreover, the risk of PTB was highest when exposed to high temperature levels (above the median). However, associations with $PM_{2.5}$ tended to be stronger in Haifa Bay area, compared to other areas, when exposed to low temperature levels, but weaker when exposed to high temperature levels. Associations with $PM_{10-2.5}$ were stronger in Haifa Bay area when exposed to high $PM_{10-2.5}$ level (5th quintile), in both temperature levels, but weaker when exposed to low $PM_{10-2.5}$ level (1st quintile).

PM-PTB associations by level of adjustment for covariates are shown in Table 9. In all levels of adjustment, a 10 μg/m^3 and a 20 μg/m^3 increase in average PM2.5 and PM10-2.5 over the entire pregnancy, respectively, exhibited nonsignificant associations with PTB, except for PM10-2.5 in model 5 that indicated a significant inverse association. Associations with PM2.5 were sensitive to adjustment for season and year of birth (added at model 3) and to temperature (added at model 5), as the hazard ratios (HRs) decreased from 1.006 (95% CI (0.999-1.012)) (model with PM only) to 0.996 (0.989-1.003) in model 3 and to 0.993 (0.985-1.001) in model 5, the model with lowest AIC.

Estimated associations by quintiles of exposure are shown in Table 10 and Figure 10. In fully-adjusted models, estimates were U-shaped with positive associations for maternal exposure at the 1st and 5th PM2.5 quintiles compared to the 2nd-4th quintiles (HRs 1.18 (1.13-1.24) and 1.07 (1.02-1.12), respectively). A similar pattern was observed for PM10-2.5 (1.52 (1.46-1.60) and 1.29 (1.23-1.35), respectively).

Associations Between Temperature and PTB: In a fully-adjusted model, a 10°C increase in mean temperature during pregnancy was positively associated with PTB (1.17, 95% CI (1.05-1.30)) (data not shown). However, assessing the association by temperature quintiles revealed that estimates were U-shaped with highest positive associations for maternal exposure at the 1st and 5th temperature quintiles compared to the 2nd-4th quintiles (HRs 1.80 (1.73-1.88) and 2.06 (1.98-2.15), respectively) (Table 10).

Critical exposure window: Analysis by exposure period revealed similar patterns for TLBW and SGA. For example, significant positive associations were indicated between TLBW and $PM_{2.5}$ exposures during the second and third trimesters (ORs 1.13 (95%CI: 1.02, 1.24) and 1.21 (95%CI: 1.10, 1.33), respectively) and lower estimate for exposure during the first trimester (OR 1.05 (95%CI: 0.95, 1.16)). Associations with TBW were not statistically significant for all trimesters (Figure 3).

Effect modification: Figure 4 summarizes modification analyses by SES and birth order. Positive significant associations between $PM_{2.5}$ and both TLBW and SGA were estimated for all SES levels, and ORs decreased monotonically with an increase in the SES index. For TBW, associations were negative and strongest for infants living in areas with higher SES and null for the lower SES levels. Associations between $PM_{2.5}$ and all outcomes were strongest for the first child.

Additional results as well as all the sensitivity analyses are detailed in the attached articles.

Congenital anomalies:

We captured 57,638 isolated CAs with estimated prevalence of 96 and 136 anomalies per 1000 births in the first year of life and by age 6 years, respectively.

The most common anomalies were ascertained in the genital (2.9 %), Integument (2.7 %), digestive (2.5%) and circulatory (2.5 %) systems. Rise in the prevalence between age 1 and 10 y varied between organ systems: prevalence increased by 13–19 % for the circulatory, respiratory and digestive systems; 33–50 % for genital and urinary anomalies; 100–125 % for the nervous, EEFN and Other systems and 288 % for CAs in the integument system.

Births with CAs were more common in mothers who smoked (10.8%), mothers who lived in areas with lower SES (20.3%) and those who were diabetic. Anomalies were more frequent among male infants, pre-term (<37 weeks) births and multiple births (Table 11).

The median of PM2.5 concentrations during the first trimester was 21.5 µg/m3 (IQR = 4.1) and for PM10–2.5 it was 28.1 µg/m3 (IQR =14.6). Exposure levels were similar for births with any isolated CA when compared to normal births (Table 12), and varied very slightly among CA groups. The Pearson correlation between 1st trimester PM2.5 and PM10–2.5 concentrations was 0.56.

Analysis of continuous PM with diameter < 2.5 µm (PM2.5) indicated a supra-linear relation with anomalies in the circulatory, respiratory, digestive, genital and integument systems (79 % of CAs). The slope of the concentration response function was positive and steepest for PM2.5 lower than the median concentration (21.5 µg/m3) and had a less steep or negative slope at higher levels. Similar trends were observed for PM2.5 quartiles. For example, for cardiac anomalies, the ORs were 1.09 (95% confidence interval: 1.02, 1.15), 1.04 (0.98, 1.10) and 1.00 (0.94, 1.07) for births in the second, third and fourth quartiles, respectively, when compared to the first quartile. See article 4 for further details.

Field study:

As detailed in the flow chart (Figure 5), 131 women were assessed for eligibility, 53 enrolled, 78 were excluded. The compliance rate was 39%. Two of the enrolled participants had an abortion and three withdrew consent, three women's didn't. In total, 48 participants were enrolled, signed a consent form, filled out a questionnaire and were sampled for $PM_{2.5}$ exposures. 48 blood and urine samples were accepted at Rambam hospital. 20 face to face interviews (communication) were conducted. Table 13 describes the socio-demographic and exposure characteristics of the population study.

Personal and indoor exposure to $PM_{2.5}$ was - 13.21 µg/m^3 (SD 7.10), 13.12 µg/m3 (SD 7.55), respectively. The maximum mean personal and indoor exposure values (35.83, 31.39, respectively). Hourly $PM_{2.5}$ exposure levels showed that pregnant women had two exposure peaks, around 9am and 6:30pm, with peak level of 17.85 µg/m^3 and 15.11 µg/m^3 respectively. The $PM_{2.5}$ exposure level was not significantly higher in daytime (7am-9pm) than nighttime (10pm-6am). Stronger correlation (r=.83) between personal and indoor exposure was found in women who reported spending more time (12 hours and more) at their residence compared to the correlation among women who spent less than 12 hours at home (r=.70). Between the two consecutive days of sampling, a stronger correlation was found in the indoor exposure (r=.74) than the personal exposure (r=.49).

Overall the average age of the mothers is 324 years and all 48 women who participated in the study are married. About 54.2% of women are above the socioeconomic average of 7.06. In addition, the majority of participants were natives of the country, 60%, and Jews, 91.5%. The study population does not smoke and is not exposed to forced smoking, but 37.5% of women have smoked in the past. 77% of the respondents use a gas stove and about 75% do not use a steam collector during cooking. About 66.7% of the women have a normal BMI, 12.5% of them are vegetarians and about 60.4% of the respondents use microwave-safe plastic containers (Table 13)

Concentration of heavy metals and Cotinine are presented in Table 14. Most of the metals were detected in 100% or nearly 100% of the urine samples. Selenium metal (Se) had the highest concentration with a geometric average of 31.84 micrograms per liter followed by the arsenic (As) concentration with 6.11 micrograms per liter. The geometric mean of cotinine was 0.44 micrograms per liter and lower than the LOQ value. The geometric average for nickel is 0.94 micrograms per liter and in the other metals the average did not exceed 0.2 micrograms per liter.

The participants home address was geocoded and mapped. Spatial dispersion of heavy metal concentrations is detailed in Appendices Figures 6-7.

Christian women has a significantly (P-value = 0.005) higher arsenic concentration (GM = 18.40 µg / L) than Jewish women (GM = 5.53 µg / L) [Table 14]. For secular women, the concentration of arsenic (GM = 7.00 µg / L) was twice as high as for religious women (P-value = 0.034, GM = 3.50 µg / L). High arsenic concentration is found in women with high BMI compared to women with normal weight (20.82 µg / L 5.25 µg / L respectively).

About 41.8% of the variance in arsenic concentration is explained by sociodemographic variables (socio-economic index, BMI, religion, level of religiosity, recruitment season, heating in plastic containers in the microwave) ($r = 0.676$) (P value = 0.013). Increase in one unit per bar BMI lead to an increase of 0.538 micrograms per liter in the arsenic concentration, on average (Beta = 0.538, P value <0.001).

Women with high SES had a high concentration of cadmium (GM = 0.21 μg / L) compared to women with lower than average SES (GM = 0.10 μg / L). There was a difference in the cadmium concentration depending on the mother's education level (P-value = 0.034 and by employment (P-value = 0.043).

Housewives and office workers had a higher thallium concentration (GM = 0.22 μg / L, P-value = 0.023) compared to the other participants.

Participants who studied less than 12 years had a higher selenium concentration (GM = 43.68μg / L) than women with a bachelor's degree (GM = 23.64μg / L). Women with a normal BMI had a higher selenium concentration (GM = 33.08 μg / L) than women underweight (GM = 26.97 μg / L). Participants who defined themselves as vegetarian were found to have a lower selenium concentration (GM = 29.21 μg / L) than non-vegetarian women (GM = 32.57 μg / L).

Heavy metals concentration were not well correlated with personal or indoor $PM_{2.5}$ exposure (Table 15). There were strong correlations between exposure to different heavy metals, but not with cotinine (Table 16).

The average personal exposure to $PM_{2.5}$ is 13.21 $\mu g/m^3$ (SD 7.10, median 12.10) and the average indoor exposure ($PM_{2.5}$) is 13.12 $\mu g/m^3$. (standard deviation 7.55, median 12.59). The average "general" exposure - personal and indoor - is 13.13) $\mu g/m^3$ (standard deviation 6.77, median 12.17).

Furthermore, a strong correlation was found in indoor exposure between the first day of monitoring and the second day (in the same woman) ($r = 0.74$) but less in the personal exposure ($r = 0.49$) (Table 17).

Figures 8&9 show the indoor and personal mean exposure to $PM_{2.5}$ throughout the day (by hours).

Communication study (led by Prof. Gesser- Edelsburg)

The team, informed by researchers and participants (pilot) developed study communication tools including a flyer. Based on the interviews, difficulties were identified such as requests for more detailed explanation of the research, some concern and technical issues with monitoring devices and blood collection. Insights served to improve recruitment and explanation process, clarifying the questionnaires, informing communication materials, informing the study team communication, solving technical issues, and addressing concerns. Risk perceptions regarding residing in Haifa (from 17 participants): 10 perceived that residing in Haifa is more dangerous than other areas in Israel, 3 perceived as similarly dangerous to other areas and 4 did not see Haifa region as dangerous. The women indicated they expected a solution to air pollution in the Haifa area from a number of sources: 13 from the government (including from the health services and the Ministry of Environmental Protection), 2 from industry, 8 from the municipality. Example of quotes: " Of course it is dangerous. There are factories here." "People say there's pollution. I pray that it's not true or that it's not serious… it's scary." "I expect government bodies to supervise or the industries themselves."

Discussion:

<u>Geographic sub-study</u>:

We conducted a geographical cluster analysis of birth weights in Israel, with a focus on the Haifa Bay area. While this is an ecological study, our main national-level comparison suggests no significant differences between LBW rate in HBA and rest of Israel and no changes in LBW rate in HBA during the years of the study. This may indicate that HBA is not an exceptional area in terms of birth weight distribution.

The attempt to reveal clusters with the highest risk for LBW in Israel and in HBA is a common and accepted method in Israel and in other countries to study various health outcomes, such as cancer (Eitan et al., 2010; Fazzo et al., 2016; Mohebbi et al., 2008; Ortega-garcía et al., 2017), tuberculosis (Oeltmann et al., 2008) and cholera (Osei & Duker, 2008). In contrast to these outcomes (particularly cancer), which have a long latency period, LBW has no latency period, giving it an advantage for identifying and treating environmental hazards more rapidly. It is common practice to examine the impact of air pollution on LBW using methods such as time series analysis and adverse models (Arroyo et al., 2016; Pirani et al., 2015), but few studies have used a spatial approach (Coker et al., 2016; Gong, Lin, Bell, & Zhan, 2018). In addition, there is scarce literature about birth weight clusters and there is a serious need to monitor birth-related parameters (Golan et al., 2018).

In our study there were no significant clusters of excess risk of LBW in HBA. These outcomes were received repeatedly even when changes were made in the maximum proportion of the population at risk and the distance chosen for defining the clusters. It worth mentioning that LBW is only one parameter of several adverse pregnancy outcomes. Focusing on one outcome may miss clusters which manifest due to other outcomes, such as head circumference, pre-term birth or congenital anomalies.

During the geographic analysis, inaccuracies with residential addresses were identified. This finding informed regarding needed corrections that were employed in the population-based cohort study. We consider the geographic analysis as ecologic and preliminary that only served as a basis for the cohort study.

Fetal growth**:**

To the best of our knowledge, this study uniquely explored the association between exposure to $PM_{2.5}$ during pregnancy and birth outcomes via a multilevel framework with random effects accounting for two nested geographic levels (maternal locality of residence and ACA) as well as a mother-level term. We found that the ICC estimates for maternal locality of residence and ACA were ignorable (<1%) while the ICC estimate for the mother effect was high (>45%). In addition, the conditional probability of LBW of non-first child given that the first delivery was non-LBW was 4.5%, but the probability of LBW given that the first child was LBW was 22.5% (Article 2, Supplemental Material, Table S5). These findings are consistent with previous studies that related birth outcomes and maternal characteristics (Bacci et al. 2014; Warrington et al. 2019). Most studies accounted for dependencies between births within the same geographical areas (Abdo et al. 2019; Choe et al. 2019; Guo et al. 2020). However, dependencies in combination between siblings was less explored. These births share some, unmeasured or unknown, common characteristics which maybe relevant to the associations between exposure to $PM_{2.5}$ during pregnancy and birth outcomes, and result in large biases in the standard errors. Taking into account the grouping structure of the data by enabling random variability across the mothers, lead to higher standard errors, allowed us to better model the sources of variability in the data rather than enabling random variability across geographical areas because some mothers may have a greater probability of having TLBW, and others may have a lower probability – even after adjusting for individual covariates. This adjustment may yield more precise confidence intervals for the effect estimates of $PM_{2.5}$ and enable to explain some of the heterogeneity between results from different studies. Precise estimates could be crucial for promoting and maintaining health, as a primary prevention.

Our mixed-effect models indicated positive associations between $PM_{2.5}$ and both TLBW and SGA and negative associations with TBW. Estimates in the multilevel models were sensitive to the level of clustering in the models. When we sequentially added higher levels of clustering (the geographic groupings: ACA and locality of residence) to the 2-level models, with random intercepts at the mother level only, the standard errors of the point estimates, as expected, decreased monotonically for all outcomes. Interestingly, the magnitude of point estimates decreased. Additional analysis revealed that this could be partially explained by the differences in total number of births between models (as there were missing data in locality of residence). The estimates for TLBW and SGA in births with missing data (ORs 1.25, (95%CI: 0.99,1.55) and 1.20, (95%CI: 1.03,1.38), respectively) were greater than the estimates in births without missing data (ORs 1.15, (95%CI: 1.03,1.30); 1.09, (95%CI: 1.02,1.19), respectively). For TBW we observed comparable but inverse trend (B=-19.4, (95% CI: -30.7,-8) and B=-29.0, (95% CI: -34.7,-23.3), for births with and without missing data, respectively). Our generalized linear models (multiple logistic regression models for TLBW and SGA, and multiple linear regression models for TBW, without random effects, Table 5), drew similar conclusions to some studies that applied similar models (Savitz et al. 2019; Schembari et al. 2015; Xiao et al. 2018), but different from others, some found weaker associations (Morello-Frosch et al. 2010; Ng et al. 2017), some found stronger associations (Pedersen et al. 2013; Strickland et al. 2019; Wu et al. 2018) and others reported non-significant associations (Madsen et al. 2010; Starling et al. 2020; Tu, Tu, and Tedders 2016; Yuan et al. 2020), suggesting that there are other factors underlying these variations in results, rather than the statistical model applied to the data. First, there are differences in the constituents and the sources of $PM_{2.5}$ in different regions (Bell et al. 2010), and some specific $PM_{2.5}$ chemical constituents may have larger toxic effects on birth outcomes (Basu et al. 2014; Ebisu and Bell 2012; Fong, Di, et al. 2019; Sun et al. 2016). Second, in cohorts with short coverage time period and in countries with low fertility rates it is not frequent to find two births for the same mother, so in such cases we can assume that the independence assumption holds, then generalized linear models (GLMs) are expected to yield similar results as controlling for the mother-level (Harris et al. 2014; Hyder et al. 2014; Kumar 2016; Li et al. 2019; Lin et al. 2020; Y. Liu et al. 2019). This might also be attributable in part to the greater exposure misclassification due to using concentrations of $PM_{2.5}$ from monitoring data or from low spatial resolution, in most of previous studies, such as each 10x10km grid cell, rather than 1x1km grid cell we used in our study. Additionally, some studies suggested factors which may explain differences in associations across studies. Guo et al. (2019)

suggested some limitations: monitoring effects with significant heterogeneity, small sample sizes, different adjustments for confounders, missing a tool for evaluating the risk of bias in systematic reviews. Sun et al. (2016) found different summary OR of $PM_{2.5}$ exposure on TLBW in studies with different estimation methods of exposure, study designs and study settings. Although the direction of our estimates from fully-adjusted 2-level models with random intercepts at the mother-level (Model 5, Table 4) were consistent with studies that did not account for clustering in the data (Gray et al. 2014; Harris et al. 2014; Kloog et al. 2012; Kloog, Melly, et al. 2015; Laurent et al. 2016; Pedersen et al. 2013) and meta-analyses (Dadvand et al. 2013; Sun et al. 2016; Zhu et al. 2015), our ORs for TLBW and SGA were generally stronger than most of other studies applied the same models and accounted for geographical areas as a random intercepts, rather than for mothers, (Coker et al. 2015; Hao et al. 2016; Kumar 2016; Laurent et al. 2016; Stieb, Chen, Hystad, et al. 2016). For example, in meta-analyses for TLBW, Sun et al. (2016) and Dadvand et al. (2013) reported summary ORs of 1.09 (95%CI: 1.03,1.15) and 1.16 (95%CI: 1.07,1.26) in association with a 10-μg/m3 increase in $PM_{2.5}$ during the entire pregnancy, respectively, while Guo et al. (2019), Li et al. (2017) and (Stieb et al. 2012) reported insignificant summary ORs (1.00, (95%CI: 0.98,1.03); 1.05, (95%CI: 0.98,1.12); and 1.05, (95%CI: 0.99,1.12), respectively). Our associations for TBW were generally weaker (Erickson et al. 2016; David M Stieb, Chen, Beckerman, et al. 2016). Such inconsistency may partly result from accounting for geographic area in previous studies, which yielded misspecification in the models, since the analysis assumes spatial independence among neighboring areas, but as suggested by Erickson et al. (2016) environmental processes can extend beyond neighbor geographical areas, as the authors reported an existence of significant clustering in the residuals.
Analysis by trimester-specific exposure indicated that for TLBW and SGA associations with second- and third-trimester exposures were significantly positive and were stronger than associations with the first-trimester exposure. However, for TBW the risk was highest during the first trimester. These trends persisted in multi-trimester models, with attenuated ORs for TLBW and SGA but stronger negative and significant association for TBW in the first trimester. Results in previous studies have been mixed, with some studies identifying the second or third trimester as critical exposure windows for TLBW or SGA (Ha et al. 2014; Ng et al. 2017), other finding consistently positive associations across all individual trimesters (Liang et al. 2019; Stieb et al. 2012), and additional studies reporting null associations across all individual trimesters (Brown et al. 2015; David M. Stieb, Chen, Beckerman, et al. 2016). Our results regarding TBW were in contrast to other studies which found that the critical

windows were second or third trimester (Bell et al. 2010; Sun et al. 2016), or across all individual trimesters (Basu et al. 2014; Xiao et al. 2018), or null associations across all trimesters (Lavigne et al. 2018; Parker et al. 2005). This inconsistency between our results for TBW and previous studies could partly be attributable to the adjustment for correlation among exposure in different trimesters, which was not done in all studies.

Strengths of our study include the availability of daily $PM_{2.5}$ exposure estimates with high spatiotemporal resolution assigned at address level. The markedly larger associations between exposure and birth outcomes than the associations between negative control and birth outcomes strengthens inference that the exposure has a causal effect on the birth outcomes. Our sample of newborns contains siblings and was very large, with precise data of gestational age and birthdate for 12 years across Israel. These enabled us to incorporate the mothers in the analysis to account for variability at the mother level that may be associated with both exposure and birth outcomes.

In addition, most published studies were conducted in Europe and the USA where the air pollution levels are generally low compared to Asian countries (Kumar et al. 2018) especially in China (Lu et al. 2015). In Israel, sources of ambient $PM_{2.5}$ are diverse and include anthropogenic activity such as emissions from industry and transportation, transport of anthropogenic particles from Europe across seas, natural phenomena such as atmospheric mineral dust from Sahara desert (Kloog, Sorek-Hamer, et al. 2015; Sorek-Hamer et al. 2013), which leading to high $PM_{2.5}$ concentrations which exceed the WHO standard. Therefore, this study is relevant to wide populations around the world.

Limitations: Foremost is the lack of data on maternal pre-pregnancy weight and BMI, which was available only for 67.3% of the total births eligible in our final fully-adjusted model. Low maternal pre-pregnancy BMI increases the risk of low birth weight (L. Liu et al. 2019) and reducing maternal obesity before conception decreased the risk of adverse birth outcomes (Ma et al. 2016). Similarly, our data did not include information on maternal education and alcohol consumption during pregnancy which are known risk factors for adverse birth outcomes. Maternal education was found to be negatively associated with adverse birth outcomes (Correia and Barros 2015; Pillas et al. 2014). However, smoking during pregnancy was strongly associated with maternal secondary or lower education, maternal age less than 20 years, maternal alcohol consumption during pregnancy (Gilbert et al. 2014; Širvinskiene et al. 2016) and neighborhood low SES (Wood et al. 2014); thus, including smoking status, maternal age and SES variables in our models may partially compensate for dearth of these data. Furthermore, we utilized complete case analysis by excluding births with imputed exposure data, such as births in some of the localities within Israeli bounders at year 1967 (Golan Heights and West Bank) or births with missing exposure data but live in large cities – in such cases we preferred to exclude these births from analysis in order to avoid misclassification in exposure data. In addition to reducing statistical power, this approach will often result in biased estimates of the associations between covariates and outcomes. Finally, like other studies, we were unable to control for maternal nonresidential exposures and residential mobility during pregnancy. Previous studies estimated that 11%–25% of mothers moved residence while pregnant (Bell, Banerjee, and Pereira 2018; Hodgson et al. 2015; Pennington et al. 2017) and in USA is especially common among young (Benetsky, Burd, and Rapino 2015). Hence, further research is needed to assess the effect of moving residence in the association between $PM_{2.5}$ and birth outcomes.

Preterm birth:

The results of our population-based cohort study in Israel indicated U-shaped relationships between exposure to PM during pregnancy and PTB, rather than a linear association. When the exposures in the first and fifth quintiles of PM were compared to quintiles 2-4, we found positive and significant associations with PTB for both high and low PM levels. A population-based cohort study in Nova Scotia, Canada, found similar trends in quartile analyses, with lowest OR for the third $PM_{2.5}$ quartile, although none of the estimates reached statistical significance, possibly due to smaller sample size (Poirier et al., 2015). Another study conducted in Lima, Peru, reported inverse ("protective") and significant association for exposure to 2nd and 4th $PM_{2.5}$ quartiles, compared to the 1st quartile (Tapia et al., 2020). When we used linear PM-PTB links in our models, like most previous studies, associations in our fully adjusted models were null with small inverse point estimates. These inverse results were consistent with the linear analysis of Poirier et al. (2015) and Tapia et al. (2020) as well as with a population-based cohort study in 24 Canadian cities (Stieb et al., 2019), in the central five counties of metropolitan Atlanta, US (Darrow et al., 2009) and in California, USA (Wilhelm and Ritz, 2005). However, our results were inconsistent with other studies that reported positive associations (Qian et al., 2016; Wu et al., 2011), or studies that reported null or mixed associations (Padula et al., 2014; Zhao et al., 2015). As for PM-VPTB associations, these were generally stronger and had comparable trends to PM-PTB associations, consistent with results from a cohort study in China (Guo et al., 2018). The comparison between the non-linear and linear analyses may help to better understand previous null or mixed associations.

Stratification analysis by temperature revealed a significant modification effect that suggested a decomposition of the associations into two exposure-response parts: decreasing and increasing, thus offering a possible explanation for the above “U-shape” finding. Women with pregnancies under lower temperature conditions (below the median) were at lowest risk when PM levels were low, with estimates increasing monotonically with PM concentrations. In contrast, women who were exposed to higher average temperature levels during pregnancy (above the median of the average temperature) were at highest risk of PTB when exposed to low PM, with HRs decreasing with PM levels. This inverse association could be explained by a potential selection bias that may be particularly high under heat conditions. Our findings suggested that the association between PM and EPTB (<28 weeks) was highest, and the risk of preterm birth decreased as the outcome reflected births of greater gestational weeks (28-31 and 32-37 weeks). Stillbirths and births with gestational age <24 weeks may be the most vulnerable to PM (Padula et al., 2014; Xue et al., 2022) and high temperature exposure (Sun et al., 2019). As these pregnancies and births were not included in our cohort, this could result in selecting a group less likely to have co-exposure to both high PM levels and other causes of PTB, including high temperature levels.

Stratification by season of birth revealed similar trends. This is expected as pregnancies with average low temperatures are typically those ending during the warmer seasons while warm-weather pregnancies typically end during the colder seasons. Our findings for season of birth were consistent with results from a cohort study in Finland that found that for babies born in the warm season the risk of PTB increased with $PM_{2.5}$ while for those born during the cold seasons PM-PTB association was inverse but with wider CIs (Siddika et al., 2019). Findings were also consistent with a cross-sectional study conducted in Wuhan, China, that reported inverse and null association for births conceived at a warm season (mostly born at a cold season), but positive and significant association for births conceived at a cold season (Zhang et al., 2020). However, a large 10-year cohort conducted in Rome, Italy, found that exposure to PM_{10} indicated a significant effect in the warm season of birth, but not in the cold season (Schifano et al., 2013).

Many previous studies reported associations of meteorological factors, such as ambient temperature and relative humidity, with PTB (Beltran et al., 2013; Olsson et al., 2012; Strand et al., 2011; Yitshak-Sade et al., 2021; Yuan et al., 2020). However, few studies considered the possible modification role of these factors on the PM-PTB association (Basu et al., 2010; Giorgis-Allemand et al., 2017; Strand et al., 2012). In a review of the epidemiological evidence on the association between season or ambient temperature and birth outcomes, authors reported that failing to include confounders and possible effect modifiers may lead to invalid results (Strand et al., 2011). A recent study suggested that temperature may modify the linear $PM_{2.5}$-PTB association, but reported mixed results across pregnancy months of exposure (Alman et al., 2019).

Israel is situated in a region with complex geo-climatic conditions with different geographic and weather patterns within a relatively small area - ranging from desert conditions in the south to snow-capped mountains in the north (Kloog et al., 2015b). Further, sources of PM are both natural and anthropogenic (Shtein et al., 2018) and the level, sources and constitutes of PM are diverse across seasons (Kloog et al., 2015a). The reverse association that we found may also be attributed to the diverse sources of PM in Israel. In summer, a dry season, PM levels are relatively low but carry mostly anthropogenic and potentially toxic aerosols (Dayan and Levy, 2005), mostly transported from Europe (Kalderon-Asael et al., 2009). It has been reported that a substantial percentage of PTB was associated with anthropogenic $PM_{2.5}$ (18% (95% CI, 13% to 24%) of total preterm births globally (Malley et al., 2017). Nevertheless, this explanation should be treated with caution since our ambient PM measurements may be a poor proxy of the average level of pollution to which the woman is exposed. For example, in heavily polluted hot days pregnant women may stay indoors and are therefore less exposed to heat and pollution. Additionally, different women may have different heating, air-conditioning and window-opening habits.

Limitations: owing to missing data on body mass index, mother's height was used instead, which may an imperfect indicator of maternal size and body composition. We also utilized a complete case analysis to avoid making assumptions on missing data. In addition to reducing statistical power, this approach can result in biased estimates of the associations between covariates and outcomes. Like other studies, we were unable to control for maternal exposure to indoor air pollution or nonresidential exposures or residential mobility during pregnancy. This can result in non-differential exposure measurement error that can bias our results towards the null hypothesis, as worker mothers are exposed to higher exposures from industry, transportation, workplaces, and busy roads. The model didn't consider the contribution of other air pollutants. Finally, as discussed above, we cannot rule out selection bias due to exclusion of stillbirths and live births with < 24 gestational weeks that could attenuate the estimates, particularly for warmer-weather pregnancies that were exposed to high levels of PM.

Congenital anomalies:

In this large (~400,000 births) population-based cohort study we observed a nonlinear concentration-response relation between exposure to PM2.5 during the first trimester of pregnancy and occurrence of any isolated congenital anomaly(CA). The pattern of the associations between $PM_{2.5}$ and different CA subtypes was mixed. For anomalies in the circulatory, respiratory, digestive, genital and integument systems (79 % of CAs in the study) the slope of the concentration-response (C-R) function was positive and steepest for $PM_{2.5}$ lower than the median concentration (21.5 μg/m3) and had a less steep or negative slope at higher levels. We observed positive linear association with urinary anomalies and inverse associations with CAs in
the nervous, EEFN and Other groups. This study adds new evidence for adverse impact of PM air pollution on neonatal health even with low-level air pollution. To our knowledge, this is the first study that examined the associations between PM and CAs by age at which an anomaly was first ascertained. We found that the estimated cumulative prevalence of FFU-isolated CAs increase by 42 % between age 1 and 6 and that the increment varied from 13% to 175 % depending on the type of anomaly. Compared to our data, a study based on the Western Australian Birth Defects Registry reported a lower overall increment in diagnosis rates between age 1 and 6 y (about 14%) with 3 % to 32 % increments for different organ systems over the 1 to 6 y period (Bower et al., 2010a). Our findings suggest that first-year CA ascertainment potentially underestimates the health burden of congenital anomalies. Study limitations are elaborated in the article 4.

Congenital anomalies are a public health concern and their causes are largely unknown. Our study may help to improve the understanding of the scope of CAs and the role of PM air pollution, one of the suspected environmental causes. Maccabi follows children from birth throughout childhood, which is important because some anomalies are not diagnosed until the child is older. Our analysis indicated that of the isolated CAs ascertained by 10 years of age, only 63 % were diagnosed in the first year of life. Information on late diagnosis of anomalies is important in evaluating the burden of disease and for planning screening tests at early age. This study adds new evidence for adverse effects of air pollution on neonatal health even with low-level air pollution. Further research is required to better understand the possible effect of live-birth selection on the estimated association between air pollution and congenital malformations; a case in which the outcome is also one of the main causes of selection due to fetal loss.

Summary and recommendations:

Population-based study: We found that associations between exposure to $PM_{2.5}$ during pregnancy and TLBW and SGA were positive and significant, in a region with high fertility rates and elevated air pollution. Our findings indicated that inference about these associations was more accurate when mother-level clustering in the data was accounted for and that, in contrast, clustering due to geographic grouping did not contribute much to our understanding of these relations. Similarly, exposure to $PM_{2.5}$ was positively associated with PTB when the average exposure during pregnancy was either low (first quintile) or high (fifth quintile), compared to exposure in the 2^{nd}-4^{th} quintiles. The results revealed effect modification of temperature. Women who had lower average temperature during pregnancy were at a higher risk of PTB when exposed to high PM levels (5^{th} quintile) compared to the 2^{nd}-4^{th} quintiles, but those who had higher average temperature during pregnancy were at a higher risk of PTB when exposed to low PM level (1^{st} quintile), which could be explained by livebirth bias.
We provided local evidence in Israel and in Haifa that exposure to $PM_{2.5}$ is significantly associated with poorer pregnancy outcomes, including low birth weight, preterm birth and congenital anomalies.
These findings underscore the need to intensify efforts in reducing air pollution in Israel, taking into account the adverse impact on the developing fetus.
On a more general note, for the purpose of this study we invested a huge amount of effort in linking a combined dataset of environmental exposure based on geocoded addresses, together with health outcomes from the Ministry of Health and Maccabi data. **In light of environmental challenges such as air pollution and climate change, national ongoing infrastructure providing data and insights for decision-makers regarding the impact of the environment on health (surveillance), is strongly needed in Israel.**
Field study: Personal and indoor exposure levels to $PM_{2.5}$ and to heavy metals were not very high compared to data in Israel and around the world. This is a small sample and further monitoring is recommended. Bio-monitoring combined with assessment of personal and indoor exposure to air pollutants is feasible in Israel and should be used to inform policy-makers regarding exposure and its impacts. A national biomonitoring program, similar to other countries, would allow ongoing monitoring of the exposure of the Israeli population in different areas and populations.

Following the findings from the field study and the congenital anomalies study that present evidence for adverse effects of air pollution on neonatal health even with low-level air pollution, we see a high necessity and importance for additional field studies that will examine the effect of exposure to air pollution along with the concentration of heavy metals in mothers in order to examine birth outcomes and congenital anomalies.

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Note: the format of citations in this report vary according to the articles and papers included in it, as appropriate for a consolidated and summary report.

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Tables and figures:

Population study:

Table 1. Birth outcome variables and their definitions.

Variable	Definition
Low birth weight (LBW)	≤2500 g
Term low birth weight (TLBW)	≤2500 g + week of pregnancy ≥37
Small for gestational age (SGA)	The lower decile of birth weight, by gestational age (weeks)
Birth weight (BW)	Continuous variable in grams
Preterm birth (PTB)	Gestational age less than 37 weeks.

Table 2. Characteristics of the study population and distribution of pregnancy outcomes, Israel 2004-2015.

Characteristic	Full population, n (% of total)	TLBW, n (% of category)[a]	SGA, n (% of category)
Full population	381,265 (100.0)	9950 (2.6)	26,875 (7.1)
Newborn sex			
Male	196,279 (51.5)	3783 (2.0)	13,490 (6.9)
Female	184,986 (48.5)	6167 (3.5)	13,385 (7.2)
Gestational age, weeks			
≤36	20,259 (5.3)	–	1709 (8.4)
37–38	87,985 (23.1)	6795 (7.7)	6380 (7.3)
39	97,117 (25.5)	1991 (2.1)	6922 (7.1)
40	109,198 (28.6)	894 (0.8)	7497 (6.9)
41–42	66,706 (17.5)	270 (0.4)	4367 (6.6)
Birth season[b]			
Autumn	99,412 (26.1)	2652 (2.8)	7191 (7.2)
Winter	94,777 (24.9)	2541 (2.8)	6860 (7.2)
Spring	91,167 (23.9)	2371 (2.7)	6313 (6.9)
Summer	95,909 (25.2)	2386 (2.6)	6511 (6.8)
Birth order[c]			
First child	131,296 (34.4)	4840 (4.0)	12,996 (9.9)
Second child	128,084 (33.6)	2860 (2.4)	7545 (5.9)
Third or higher child	121,885 (32.0)	2250 (1.9)	6334 (5.2)
Maternal age at birth, years			
≤24	43,560 (11.4)	1300 (3.1)	4028 (9.3)
25–29	92,871 (24.4)	2433 (2.8)	6858 (7.4)
30–34	130,015 (34.1)	3257 (2.6)	8749 (6.7)
35–39	88,817 (23.3)	2228 (2.7)	5530 (6.2)
40+	25,999 (6.8)	732 (3.0)	1710 (6.6)
Maternal smoking before conception			
Smoker	36,584 (9.6)	1281 (3.7)	3123 (8.5)
Past smoker	6079 (1.6)	1419 (2.8)	3592 (6.7)
Non-smoker	308,078 (80.8)	6417 (2.6)	17,797 (6.8)
Unknown	30,524 (8.0)	833 (2.9)	2363 (7.7)

Socioeconomic status			
1–2	17,606 (4.6)	410 (2.4)	1253 (7.1)
3–4	62,926 (16.5)	1681 (2.8)	4697 (7.5)
5–6	145,048 (38.0)	3869 (2.8)	10,594 (7.3)
7–8	112,688 (29.6)	2941 (2.8)	7572 (6.7)
9–10	42,908 (11.3)	1047 (2.6)	2755 (6.4)
Unknown	89 (0.0)	2 (2.3)	4 (4.5)
Last pre-pregnancy weight, kg, M(SD)	66.2 (15.2)		
≤64 (=Median)	100,881 (26.5)	3450 (3.6)	9152 (9.1)
>64	94,286 (24.7)	1654 (1.8)	4455 (4.7)
U nknown	186,098 (48.8)	4846 (2.8)	13,268 (7.1)
Maternal height, cm, M (SD)	163.1 (6.8)		
≤163 (=Median)	190,687 (50.0)	6383 (3.6)	17,028 (8.9)
>163	174,898 (45.9)	3201 (1.9)	8720 (5.0)
Unknown	15,680 (4.1)	366 (2.4)	1127 (7.2)
Last pre-pregnancy BMI, kg, M(SD)	24.3 (5.1)		
≤23.24 (=Median)	90,265 (23.7)	2829 (3.3)	7631 (8.5)
>23.24	88,435 (23.2)	1924 (2.3)	4956 (5.6)
Unknown	202,565 (53.1)	5197 (2.7)	14,288 (7.1)

Abbreviations: M, mean; SD, standard deviation; MD, median; IQR, interquartile range. n, number of cases; % percentage of cases; TLBW, term low birth weight; SGA, small for gestational age.

Note: Number in subgroups do not sum to the overall number rounding and missing data.

[a] The percentage of term LBW was obtained by dividing the number of term LBW by the number of term births in the corresponding category.

[b] Birth season: Autumn (September–November), winter (December–February), spring (March–May), summer (June–August).

[c] Available only for births from 1999 onward.

Table 3. Characteristics of study population and distribution of PTB, Israel 2004-2015

Characteristic	Full population, n (% of total)	Term birth, n(%)	PTB, n(%)
Full population	381,265 (100.0)	361,006 (94.7)	20,259 (5.3)
Characteristic of births			
Newborn sex			
Male	196,279 (51.5)	185,164 (94.3)	11,115 (5.7)
Female	184,986 (48.5)	175,842 (95.1)	9,144 (4.9)
Gestational age, weeks			
≤36	20,259 (5.3)	0 (0.0)	20,259 (100.0)
37-38	87,985 (23.1)	87,985 (100.0)	0 (0.0)
39	97,117 (25.5)	97,117 (100.0)	0 (0.0)
40	109,198 (28.6)	109,198 (100.0)	0 (0.0)
41-42	66,706 (17.5)	66,706 (100.0)	0 (0.0)
Birth season[a]			
Autumn	99,412 (26.1)	94,218(94.8)	5,194 (5.2)
Winter	94,777 (24.9)	89,664 (94.6)	5,113 (5.4)
Spring	91,167 (23.9)	86,422 (94.8)	4,745 (5.2)
Summer	95,909 (25.2)	90,702 (94.6)	5,207 (5.4)
Birth order[b]			
First child	131,296 (34.4)	122,604 (93.4)	8,692 (6.6)
Second child	128,084 (33.6)	121,637 (95.0)	6,447 (5.0)
Third or higher child	121,885 (32.0)	116,765 (95.8)	5,120 (4.2)
Characteristic of mothers			
Maternal age at birth, years			
≤24	43,560 (11.4)	41,473 (95.2)	2,087 (4.8)
25-29	92,871 (24.4)	88,328 (95.1)	4,543 (4.9)
30-34	130,015 (34.1)	123,278 (94.8)	6,737 (5.2)
35-39	88,817 (23.3)	83,850 (94.4)	4,967 (5.6)
40+	25,999 (6.8)	24,076 (92.6)	1,923 (7.4)
Maternal smoking before conception			
Smoker	35,684 (9.4)	34,211 (93.5)	2,373 (6.5)
Past smoker	53,386 (14.0)	50,381 (94.4)	3,005 (5.6)
Non-smoker	260,771 (68.4)	247,410 (94.9)	13,361 (5.1)
Unknown	31,424 (8.2)	29,004 (95.0)	1,520 (5.0)
SES			
1-2[c]	17,606 (4.6)	16,795 (95.4)	811 (4.6)
3-4	62,926 (16.5)	59,723 (94.9)	3,203 (5.1)
5-6	145,048 (38.0)	137,306 (94.7)	7,742 (5.3)
7-8	112,688 (29.6)	106,529 (94.5)	6,159 (5.5)
9-10	42,908 (11.3)	40,566 (94.5)	2,342 (5.5)
Unknown	89 (0.0)	87 (97.8)	2 (2.3)
Last pre-pregnancy weight, kg, M(SD)	66.2 (15.2)		
<64 (=Median)	100,881 (26.5)	95,176 (94.3)	5,705 (5.7)
>64	94,286 (24.7)	89,693 (95.1)	4,593 (4.9)
Unknown	186,098 (48.8)	176,137 (94.7)	9,961 (5.4)

Maternal height, cm, M(SD)	163.1 (6.8)		
<163 (=Median)	190,687 (50.0)	179,661 (94.2)	11,026 (5.8)
>163	174,898 (45.9)	166,356 (95.1)	8,542 (4.9)
Unknown	15,680 (4.1)	14,989 (95.6)	691 (4.4)
Last pre-pregnancy BMI, kg, M(SD)	24.3 (5.1)		
<23.24 (=Median)	90,265 (23.7)	85,313 (94.5)	4,952 (5.5)
>23.24	88,435 (23.2)	83,700 (94.7)	4,735 (5.4)
Unknown	202,565 (53.1)	191,993 (94.8)	10,572 (5.2)

Table 4. Summary of daily $PM_{2.5}$ and $PM_{10-2.5}$ exposure during pregnancy by district of the mother's place of residence (µg/m3).

		$PM_{2.5}$		$PM_{10-2.5}$	
District	**n**	**M(SD)**	**Range**	**M(SD)**	**Range**
Whole region	320,987	21.7 (2.4)	10.4-40.7	30.1 (5.3)	8.7-55.1
Jerusalem	17,200	20.4 (1.8)	11.8-26.7	**31.3 (5.6)**	16.7-55.1
North	20,177	**19.3 (2.5)**	10.4-27.3	**26.1 (4.0)**	13.3-43.3
Haifa	29,929	20.2 (2.5)	13.2-32.7	26.3 (5.2)	8.7-48.7
Center	96,711	**22.3 (2.3)**	14.5-38.5	30.2 (5.0)	11.7-51.1
Tel-Aviv	106,538	**22.5 (2.0)**	14.9-32.9	**31.9 (4.8)**	16.4-53.6
South	41,556	21.4 (2.2)	12.4-40.7	29.4 (5.1)	12.5-50.6
West Bank	9,423	20.1 (2.2)	11.5-28.8	28.5 (4.8)	15.7-45.9
Haifa-Bay area	10,112	20.7 (2.2)	13.6-27.5	26.1 (4.6)	11.8-42.1

Table 5. Associations[a] between $PM_{2.5}$ over the entire pregnancy and birth outcomes by type of regression model applied.

Model	TLBW			SGA		
	N	OR (95% CI)	p	N	OR (95% CI)	p
random intercept at the mother level	312,015	1.25 (1.09,1.43)	0.001	329,634	1.15 (1.06,1.26)	0.001
Multiple logistic regression model without random effect	312,015	1.20 (1.07,1.35)	0.001	329,634	1.14 (1.06,1.22)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; TLBW, term low birth weight; SGA, small for gestational age; p, p-value.
All models were adjusted for mother age at birth, birth order, socioeconomic status, maternal height, maternal smoking status, year and season of birth, and temperature. TLBW models were additionally adjusted for gestational age.
[a] Effect estimates (95% CIs) are reported per a 10-μg/m^3 increase in mean $PM_{2.5}$ over the entire pregnancy (Mean (SD) = 21.8 (2.4)).

Table 6. Associations[a] between $PM_{2.5}$ and birth outcomes and ICCs by level of adjustment for clustering.

Outcome	N	Model	OR (95% CI)	ICC		
				Locality of residence	**Administrative census area**	**Mother**
TLBW	361,006	$PM_{2.5}$ only[b]	1.06 (0.98,1.15)			
	361,006	1-Level[c]	1.13 (1.03,1.22)			
	332,001	2-Level[d]	1.16 (1.04,1.29)			44.6%
	332,001	3-Level	1.15 (1.03,1.28)		0.4%	44.6%
	268,134	4-Level	1.06 (0.93,1.21)	0.2%	0.4%	44.6%
SGA	381,265	$PM_{2.5}$ only[b]	1.06 (1.01,1.12)			
	350,738	2-Level[d]	1.12 (1.05,1.20)			48.0%
	350,738	3-Level	1.13 (1.05,1.21)		0.2%	47.9%
	283,266	4-Level	1.05 (0.97,1.15)	0.2%	0.4%	44.8%

Abbreviations: OR, odds ratio; CI, confidence interval; TLBW, term low birth weight; SGA, small for gestational age; ICC, intra-class correlation coefficient.
[a] Effect estimates (95% CIs) are reported per a 10-μg/m^3 increase in mean $PM_{2.5}$ over the entire pregnancy.
[b] Simple logistic regression model (without covariates).
[c] Adjusted for gestational age,.
[d] 2-Level model to 4-Level stand for models with random intercepts of mother, administrative census area and locality of residence, entered sequentially. All models were adjusted for mother age at birth, SES, maternal height and maternal smoking status. TLBW models were additionally adjusted for gestational age.

Table 7. Associations between quintiles of mean $PM_{2.5}$ and $PM_{10-2.5}$ over the entire pregnancy and preterm birth in fully adjusted models by district of the mother's place of residence (n=320,987).

District	Quintiles - $PM_{2.5}$	OR	CI 95%	Quintiles –$PM_{10-2.5}$	OR	I95%
Jerusalem	<19.0	1.75	1.33-2.32	<26.8	1.24	0.94-1.65
n=17,200	19.0-20.1	1.12	0.85-1.48	26.8-29.4	1.13	0.86-1.49
	20.1-20.9	Ref=1.00		29.4-31.7	Ref=1.00	
	20.9-21.9	1.02	0.76-1.23	31.7-35.4	1.22	0.93-1.60
	>21.9	1.31	0.97-1.77	>35.4	1.00	0.75-1.33
North	<17.3	1.12	0.89-1.42	<22.6	2.03	1.58-2.59
n=20,177	17.3-18.8	1.00	0.80-1.26	22.6-25.0	1.27	1.00-1.61
	18.8-20.0	Ref=1.00		25.0-27.1	Ref=1.00	
	20.0-21.5	1.02	0.81-1.29	27.1-29.4	1.22	0.96-1.55
	>21.5	1.11	0.89-1.40	>29.4	1.75	1.37-2.22
Haifa	<18.2	1.14	0.93-1.40	<22.1	1.52	1.24-1.87
n=29,292	18.2-19.4	0.98	0.80-1.19	22.1-25.1	0.96	0.79-1.16
	19.4-20.5	Ref=1.00		25.1-27.6	Ref=1.00	
	20.5-22.2	0.95	0.79-1.15	27.6-30.4	0.95	0.77-1.16
	>22.2	1.08	0.89-1.31	>30.4	1.33	1.10-1.62
Center	<20.4	1.20	1.08-1.34	<25.9	1.70	1.52-1.90
n=96,711	20.4-21.5	1.02	0.92-1.14	25.9-28.8	0.94	0.84-1.05
	21.5-22.5	Ref=1.00		28.8-31.6	Ref=1.00	
	22.5-24.1	1.14	1.02-1.26	31.6-34.6	1.17	1.05-1.31
	>24.1	1.11	1.00-1.23	>34.6	1.30	1.17-1.45
Tel-Aviv	<20.9	1.28	1.14-1.42	<27.8	1.98	1.76-2.23
n=106,538	20.9-21.9	1.02	0.91-1.13	27.8-30.7	1.14	1.02-1.28
	21.9-22.8	Ref=1.00		30.7-32.9	Ref=1.00	
	22.8-24.0	1.02	0.91-1.13	32.9-35.8	1.25	1.12-1.40
	>24.0	1.17	1.05-1.30	>35.8	1.76	1.57-1.97
South	<20.0	1.32	1.11-1.56	<25.5	1.51	1.28-1.78
n=41,556	20.0-21.1	1.20	1.02-1.41	25.5-27.9	0.98	0.83-1.16
	21.1-21.8	Ref=1.00		27.9-30.1	Ref=1.00	
	21.8-22.7	0.99	0.84-1.17	30.1-33.2	0.97	0.82-1.15
	>22.7	1.15	0.98-1.35	>33.2	1.16	0.98-1.37
West Bank	<18.6	1.39	0.92-2.09	<24.3	0.97	0.65-1.44
n=9,423	18.6-19.7	1.09	0.72-1.64	24.3-26.7	0.78	0.53-1.14
	19.7-20.4	Ref=1.00		26.7-29.3	Ref=1.00	
	20.4-21.8	2.07	1.42-3.04	29.3-32.5	1.14	0.79-1.66
	>21.8	1.64	1.09-2.46	>32.5	1.09	0.75-1.59

Abbreviations: OR, odds ratios; CI, confidence interval. [a] Effect estimates (95% CI) were derived from logistic regression mixed-effect models, and are reported for quintiles of mean PM over the entire pregnancy compared to the third quintile.
The models were adjusted for: mother age at birth, birth order, SES, maternal height, maternal smoking status, year and season of birth, and temperature.

Table 8. Associations[a] between $PM_{2.5}$ and birth outcomes and ICCs by level of adjustment for clustering.

	TLBW			SGA		
Model	N	OR (95% CI)	p	N	OR (95% CI)	p
random intercept at the mother level	312,015	1.25 (1.09,1.43)	0.001	329,634	1.15 (1.06,1.26)	0.001
Multiple logistic regression model without random effect	312,015	1.20 (1.07,1.35)	0.001	329,634	1.14 (1.06,1.22)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; TLBW, term low birth weight; SGA, small for gestational age; p, p-value.
All models were adjusted for mother age at birth, birth order, socioeconomic status, maternal height, maternal smoking status, year and season of birth, and temperature. TLBW models were additionally adjusted for gestational age.
[a] Effect estimates (95% CIs) are reported per a 10-μg/m^3 increase in mean $PM_{2.5}$ over the entire pregnancy (Mean (SD) = 21.8 (2.4)).

Table 9. Associations between quintiles of mean $PM_{2.5}$ and $PM_{10-2.5}$ over the entire pregnancy and preterm birth by temperature[¥] and study area.

	Exposure to low temperature (8.5-20.6 °C)		Exposure to high temperature (20.6-38.9 °C)	
	Haifa-Bay area (n=4,443)	Other areas (n=149,161)	Haifa-Bay area (n=5,669)	Other areas (n=161,624)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
$PM_{2.5}$ Quintiles (μg/m^3)				
Q_1 (10.4-19.9)	0.98 (0.73-1.32)	0.94 (0.88-0.99)	1.21 (0.95-1.55)	1.36 (1.29-1.44)
Q_{2-4} (19.9-23.5) (Ref.)	1.00	1.00	1.00	1.00
Q_5 (23.5-40.7)	1.29 (0.88-1.89)	1.16 (1.10-1.23)	0.90 (0.59-1.37)	0.93 (0.88-0.99)
$PM_{10-2.5}$ Quintiles (μg/m^3)				
Q_1 (8.7-25.7)	0.84 (0.63-1.12)	0.96 (0.89-1.04)	1.48 (1.16-1.88)	1.60 (1.53-1.68)
Q_{2-4} (25.7-34.5) (Ref.)	1.00	1.00	1.00	1.00
Q_5 (34.5-55.1)	1.42 (0.92-2.19)	1.40 (1.34-1.47)	1.22 (0.57-2.65)	0.90 (0.83-0.97)

[¥] Temperature was divided into two categories: below the median of mean temperature during whole pregnancy (8.5-20.6 °C) and above the median (20.6-38.9 °C).
Abbreviations: HR, hazard ratios; CI, confidence interval.
[a] Effect estimates (95% CI) are reported for quintiles of mean PM over the entire pregnancy compared to quintiles 2-4.
The models were adjusted for: mother age at birth, birth order, SES, maternal height, maternal smoking status, year and season of birth, and temperature.

Table 10. Associations between quintiles of mean $PM_{2.5}$ and $PM_{10-2.5}$ over the entire pregnancy and preterm birth in fully adjusted model (n=329,634).

$PM_{2.5}$ Quintiles (μg/m³)	HR (95% CI)	$PM_{10-2.5}$ Quintiles (μg/m³)	HR (95% CI)	Temperature Quintiles (°C)	HR (95% CI)
Q_1 (10.4-19.9)	1.18 (1.13, 1.24)	Q_1 (8.7-25.7)	1.52 (1.46, 1.60)	Q_1 (8.5-18.7)	1.80 (1.73, 1.88)
Q_{2-4} (19.9-23.5) (Ref.)	1.00	Q_{2-4} (25.7-34.5) (Ref.)	1.00	Q_{2-4} (18.7-22.4) (Ref.)	1.00
Q_5 (23.5-40.7)	1.07 (1.02, 1.12)	Q_5 (34.5-55.1)	1.29 (1.23, 1.35)	Q_5 (22.4-38.9)	2.06 (1.98, 2.15)

Abbreviations: HR, hazard ratios; CI, confidence interval.
[a] Effect estimates (95% CI) are reported for quintiles of mean PM over the entire pregnancy compared to quintiles 2-4.
The models were adjusted for: mother age at birth, birth order, SES, maternal height, maternal smoking status, year and season of birth, and temperature.

Table 11. Associations between quintiles of mean $PM_{2.5}$ and $PM_{10-2.5}$ over the entire pregnancy and preterm birth in fully adjusted model (n=329,634).

Characteristic	Follow-up throughout childhood			First year follow-up
	Isolated anomaly[a], n (%) or Mean ± SD (N = 57,654)	No anomaly[b], n (%) or Mean ± SD (N = 331,036)	% CA[c]	Isolated anomalies[a] n (%) or Mean ± SD (N = 40,571)
Maternal age (years)				
Mean ± SD	31. 6 ± 5.3	31.5 ± 5.4		31.6 ± 5.4
16–25	7850 (13.6 %)	49,170 (14.8 %)	13.5 %	5689 (14.0 %)
26–30	16,559 (28.7 %)	90,646 (27.4 %)	15.1 %	11,546 (28.5 %)
31–35	19,656 (34.1 %)	110,726 (33.4 %)	14.8 %	13,564 (33.4 %)
36–40	11,060 (19.2 %)	65,411 (19.8 %)	14.2 %	7904 (19.5 %)
>40	2529 (4.4 %)	15,083 (4.6 %)	14.0 %	1868 (4.6 %)
Smoking				
Current smoker	6125 (10.6 %)	33,247 (10.1 %)	15.3 %	4278 (10.5 %)
Past smoker	1027 (1.8 %)	5759 (1.7 %)	14.8 %	734 (1.8 %)
Never smoked	49,862 (86.5 %)	287,247 (86.8 %)	14.5 %	35,173 (86.7 %)
Unknown	640 (1.1 %)	4783 (1.4 %)	11.7 %	386 (1.0 %)
Infant sex				
Male	33,384 (50.1 %)	165,760 (57.9 %)	16.4 %	24,260 (59.8 %)
Female	24,270 (49.9 %)	165,276 (42.1 %)	12.6 %	16,311 (40.2 %)
Birth weight (g)				
Mean ± SD	3180.2 ± 586.7	3229.8 ± 518.2		3165.6 ± 605.6
<2500	5891 (10.2 %)	24,484 (7.4 %)	18.6 %	4475 (11.0 %)
≤2500	51,536 (89.4 %)	304,279 (91.9 %)	14.2 %	35,975 (88.7 %)
Unknown	227 (0.4 %)	2273 (0.7 %)	9.0 %	121 (0.3 %)
Gestational age (weeks)				
Mean ± SD	38.7 ± 2.2	39.0 ± 1.8		38.7 ± 2.3
<3	5878 (10.2 %)	23,814 (7.2 %)	19.0 %	4435 (10.9 %)
≥37	51,776 (89.8 %)	307,222 (92.8 %)	14.2 %	36,136 (89.1 %)
Plurality				
1	54,164 (94.0 %)	314,249 (94.9 %)	14.4 %	37,992 (93.6 %)
2	3401 (5.9 %)	16,366 (5.0 %)	16.8 %	2507 (6.4 %)
>2	89 (0.1 %)	421 (0.1 %)	17.0 %	72 (0.2 %)

Socioeconomic status[d]				
Low 1–4	10,519 (18.2 %)	68,682 (20.8 %)	13.3 %	7818 (19.3 %)
Medium 5–7	33,371 (57.9 %)	185,663 (56.1 %)	15.2 %	23,333 (57.5 %)
High 8–10	13,750 (23.9 %)	76,613 (23.1 %)	15.2 %	9420 (23.2 %)
Unknown	14 (0.03 %)	78 (0.03 %)	15.2 %	11 (0.03 %)
Year of conception				
2003–2007	22,981 (40.6 %)	123,756 (38.3 %)	15.3 %	13,805 (34.0 %)
2008–2011	19,543 (34.6 %)	112,740 (34.9 %)	14.5 %	14,072 (34.7 %)
2012–2015	14,003 (24.8 %)	86,691 (26.8 %)	13.7 %	12,964 (31.3 %)
Season of conception				
Winter[e]	14,720 (25.5 %)	85,771 (25.9 %)	14.4 %	10,609 (26.1 %)
Spring	14,180 (24.6 %)	84,405 (25.5 %)	14.1 %	9927(24.5 %)
Summer	14,082 (24.4 %)	78,948 (23.9 %)	14.8 %	9740 (24.0 %)
Autumn	14,672 (25.5 %)	81,912 (24.7 %)	14.9 %	10,295 (25.4 %)
Urbanicity				
<5000 residents	3979 (6.9 %)	23,763 (7.2 %)	14.1 %	2823 (7.0 %)
5000–19,999	2307 (4.0 %)	12,238 (3.7 %)	15.5 %	1647 (4.1 %)
20,000–99,999	18,423 (32.0 %)	103,893 (31.4 %)	14.8 %	12,799 (31.6 %)
100,000–199,999	12,056 (20.9 %)	72,380 (21.8 %)	14.0 %	8904 (22.0 %)
≥200,000	19,483 (33.8 %)	110,235 (33.3 %)	14.7 %	13,507 (33.3 %)
Unknown	1406 (2.4 %)	8527 (2.6 %)	13.9 %	891 (2.2 %)

CA, congenital anomaly; SD, standard deviation.

[a] Anomalies in one organ system only or combined with a musculoskeletal malformation; chromosomal and multiple anomalies were not included.

[b] Infants with no anomaly or infants with an isolated musculoskeletal anomaly.

[c] Percentages were calculated out of all births in group.

[d] We used a 10-level socioeconomic (SES) index. Low: 1–4, Medium: 5–7, High: 8–10.

[e] Winter: December–February, Spring: March–May, Summer: June–August, Autumn: September–November.

Table 12. Distribution of air pollutants and temperature by exposure period, 2003–2015[b].

Exposure period and pollutant	Isolated anomaly[c] N	Mean (SD)	q2 (q1, q3)	(Min, Max)	Pearson correlation With 1st trimester	No anomaly[d] N	Mean (SD)	q2 (q1, q3)	(Min, Max)	Pearson correlation With 1st trimester
First trimester										
$PM_{2.5}$ (μg/m^3)	57,654	21.9 (3.4)	21.5 (19.7, 23.7)	(8.0, 53.1)	–	331,036	21.9 (3.5)	21.5 (19.7, 23.8)	(8.0, 56.0)	–
$PM_{10-2.5}$ (μg/m^3)	57,654	30.3 (10.4)	28.0 (22.4, 36.7)	(6.6, 88.9)	–	331,036	30.4 (10.4)	28.1 (22.5, 37.1)	(6.2, 91.1)	–
Temperature (°C)	54,155	20.2 (4.8)	20.1 (15.9, 24.8)	(8.3, 44.8)	–	310,410	20.2 (4.8)	20.2 (16.0, 24.7)	(7.8, 46.3)	–
Weeks 3–8										
$PM_{2.5}$ (μg/m^3)	57,654	21.9 (4.3)	21.3 (19.2, 23.7)	(7.8, 62.3)	0.81	331,036	21.9 (4.3)	21.3 (19.2, 23.7)	(7.8, 61.1)	0.82
$PM_{10-2.5}$ (μg/m^3)	57,654	30.3 (13.4)	26.8 (20.8, 36.1)	(2.3, 130)	0.47	331,036	30.5 (13.3)	27.0 (20.9, 36.3)	(4.2, 128.5)	0.46
Temperature (°C)	54,155	20.3 (5.2)	20.3 (15.6, 25.2)	(7.2, 46.5)	−0.34	310,410	20.3 (5.2)	20.3 (15.6, 25.1)	(6.2, 48.9)	−0.34
Weeks 9–13										
$PM_{2.5}$ (μg/m^3)	57,654	21.8 (4.5)	21.1 (19.1, 23.6)	(7.8, 61.3)	0.75	331,036	21.8 (4.6)	21.1 (19, 23.6)	(7.7, 67.4)	0.76
$PM_{10-2.5}$ (μg/m^3)	57,654	30.2 (14)	26.2 (20.5, 35.8)	(4.8, 141.1)	0.39	331,036	30.3 (14.1)	26.2 (20.6, 35.9)	(−0.2, 140.9)	0.40
Temperature (°C)	53,444	20.3 (5.3)	20.4 (15.6, 25.3)	(6.8, 47.7)	−0.18	306,639	20.4 (5.3)	20.5 (15.7, 25.3)	(6.1, 49.2)	−0.18

SD, standard deviations; q1, 25th percentile; q2, median; q3, 75th percentile.

[a] Individual exposures were the mean of daily measurements in the respective exposure period. Exposure is assigned by the level at the 1 km^2 pixel corresponding to maternal place of residence at the time of birth.

[b] Because the study population includes births in 2004, the corresponding exposure data for these pregnancies include 2003.

[c] Anomalies in one organ system only or combined with a musculoskeletal malformation that were diagnosed throughout childhood; chromosomal and multiple anomalies were not included.

[d] Infants with no anomaly or infants with an isolated musculoskeletal anomaly only.

Tables of field study:

Table 13. Characteristics of the study population.

Characteristics	Mean(range)	n	%
Maternal age	32.4 (20-39)		
<25 years		2	4.2
25-29 years		7	14.6
30-34 years		28	58.3
>35 years		11	22.9
Country of birth			
Israel		29	60.4
Former Soviet Union		15	31.3
Other		4	8.3
Marital status			
In a relationship		48	100
Religion			
Jewish		43	91.5
Christian		4	8.5
Missing		1	2.1
Religious level			
Religious		9	18.8
Non-religious		38	79.2
Missing		1	2.1
Years of education			
<12 years		10	20.8
13-16 years		23	47.9
> 17 years		14	29.2
Missing		1	2.1
Occupation			
Student		2	4.2
Housewife		3	6.3
Management		5	10.4
Business		5	10.4
Education		5	10.4
Healthcare		6	12.5
Office		4	8.3
Missing		25.0	12
Transportation way to destination in the morning			
Walking		3	6.3
Car		37	77.1
Public transportation		4	8.3
Other		3	6.3
Missing		1	2.1

Standing in traffic		
Yes	33	68.8
No	14	29.2
Missing	1	2.1
Average of daily hours in the car		
> an hour	27	56.3
1-2 hours	19	39.6
<3 hours	2	4.2
Past smoker		
Yes	18	37.5
No	30	62.5
Smoking family member		
Yes	4	8.3
No	44	91.7
Exposure to secondhand smoke		
At home	1	2.1
Yes	46	97.9
No	1	2.1
Missing		
At work		
Yes	10	20.8
No	37	77.1
Missing	1	2.1
outside home and work		
Yes	24	50.0
No	23	47.9
Missing	1	2.1
Stove type at home		
Gas	37	77.1
Electrical	10	20.8
Not in use	1	2.1
Stove hood at home		
Yes, in use	7	14.6
Yes, not in use	5	10.4
Don’t have one	36	75.0
BMI		
Underweight	5	10.4
Healthy weight	32	66.7
Overweight	7	14.6
Obese	4	8.3
exercising weekly	31	64.6
Yes	16	33.3
No	1	2.1

Missing		
Pets at home		
Yes	18	37.5
No	30	62.5
Vegetarian or vegan		
Vegetarian	6	12.5
None	41	85.4
Missing	1	2.1
Frequency of eating grilled food		
More than once a week	2	4.2
Once a week	6	12.5
2-3 times a month	7	14.6
4 times a month	12	25.0
Less than once a month or not at all	20	41.7
Missing	1	2.1
Frequency of eating smoked food		
More than once a week	2	4.2
Once a week	8	16.7
2-3 times a month	8	16.7
4 times a month	6	12.5
Less than once a month or not at all	23	47.9
Missing	1	2.1
Drinking water from a container of 10 liters or more		
Yes	17	35.4
No	30	62.5
Missing	1	2.1
Drinking water from a hard plastic sports bottle		
Yes	25	52.1
No	21	43.8
Missing	2	4.2
Using microwave adjusted plastic food containers		
Yes	29	60.4
No	9	18.8
I don't know	4	8.3
Other (using glass containers)	1	2.1
Not heating in the microwave	2	4.2
Missing	3	6.3
Home / Garden pest control		
No	47	97.9
Yes	1	02.1

Table 14. Concentrations (µg/L) of metals and cotinine in urine specimens from 48 pregnant Women from Haifa.

	Mean ± Std. Deviation	GM*	Median	Min	25th Percentiles	50th Percentiles	75th Percentiles	95th Percentiles	Max	Proportion above LOQ**
Chromium Cr	0.31±0.2	0.25	0.27	0.01	0.17	0.27	0.38	0.68	1.22	97.9%
Nickel Ni	1.11±0.65	0.94	1.05	0.26	0.66	1.05	1.49	2.32	3.74	100%
Arsenic As	9.23±9.89	6.11	5.76	1.07	3.62	5.76	9.49	30.5	54.55	100%
Cadmium Cd	0.22±0.18	0.15	0.16	0.02	0.08	0.16	0.31	0.60	0.89	97.9%
Lead Pb	0.23±0.17	0.16	0.21	0.01	0.09	0.21	0.32	0.62	0.66	91.7%
Selenium Se	40.35±28.9	31.84	34.23	6.38	20.61	34.23	54.94	99.66	162.31	91.7%
Thallium Tl	0.14±0.08	0.12	0.13	0.02	0.07	0.13	0.20	0.29	0.36	97.9%
Mercury Hg***	0.37±0.36	0.24	0.26	0.02	0.12	0.26	0.51	1.05	2.06	95.7%
Cotinine	1.12±3.63	0.44	0.35	0.35	0.35	0.35	0.35	8.76	21	8.3%

Total number of samples is 48 for all metals and cotinine
*GM Geometric Mean, Max maximum, Min minimum
** Limit of Quantification (LOQ) for Metals is 0.02 µg/L, and for Cotinine is 0.5 µg/L. Values below LOQ were imputed by LOQ/sqrt (2).
*** Total number of samples is 46 for Mercury.

Table 15. Geometric mean of metals urinary concentrations (μg/L) for pregnant women in Haifa (n=48) by baseline study characteristics.

	Cr	Ni	As	Cd	Pb	Se	Tl	Hg
Maternal age								
<25	0.41	1.54	3.33	0.10	0.32	37.16	0.10	0.13
25-29	0.36	0.96	6.89	0.24	0.30	35.85	0.14	0.14
30-34	0.24	0.92	5.41	0.13	0.13	30.43	0.11	0.25
>35	0.21	0.92	8.61	0.18	0.15	32.19	0.12	0.31
Socio-economic								
Lower than mean socioeconomic index	0.20	0.81	4.78	**0.10***	0.13	25.67	0.10	0.19
Higher than mean socioeconomic index	0.28	1.06	7.60	**0.21***	0.18	36.88	0.13	0.23
Country of birth								
Israel	0.28	**1.13***	5.77	0.18	0.19	35.45	0.13	0.24
Former Soviet Union	0.18	**0.63***	7.02	0.10	0.10	27.25	0.10	0.22
other	0.36	**1.17***	5.53	0.18	0.17	26.15	0.11	0.32
Religion								
Jewish	0.25	0.93	**5.53***	0.14	0.15	30.21	0.11	0.23
Christian	0.27	1.04	**18.40***	0.22	0.24	46.44	0.17	0.52
Religious level								
Religious	0.21	1.06	**3.50***	0.13	0.15	22.50	0.10	0.18
Non-religious	0.26	0.90	**7.00***	0.15	0.15	33.89	0.12	0.26
BMI								
Underweight	0.26	1.09	5.77	0.14	0.07	26.97	0.11	0.23
Healthy weight	0.26	0.98	5.25	0.15	0.18	33.08	0.11	0.21
Overweight	0.23	0.82	6.32	0.19	0.15	30.42	0.16	0.36
Obese	0.21	0.71	20.82	0.10	0.14	31.19	0.14	0.44
Years of education								
12	0.29	1.17	7.72	**0.16***	0.17	43.68	0.15	0.25
13-16	0.19	0.85	4.93	**0.13***	0.15	23.64	0.10	0.21

more than 17	0.34	0.88	6.83	**0.18***	0.16	36.86	0.12	0.27
Occupation								
Student	0.40	0.68	3.66	**0.13**	0.17	24.84	**0.13**	0.17
Housewife	0.40	0.98	9.88	**0.19**	0.35	70.70	**0.22***	0.27
Management	0.15	0.60	4.36	**0.15**	0.17	29.89	**0.08**	0.17
Business	0.28	1.28	4.85	**0.15**	0.10	30.16	**0.09**	0.14
Education	0.23	0.95	4.30	**0.18**	0.27	30.30	**0.09**	0.30
Healthcare	0.19	0.59	5.44	**0.05**	0.13	16.01	**0.07**	0.15
Office	0.27	1.46	8.98	**0.44***	0.25	48.71	**0.22***	0.79
Smoking family member								
Yes	0.16	0.56	11.21	0.10	0.12	19.30	0.07	0.14
No	0.26	0.99	5.78	0.16	0.16	33.32	0.12	0.25
Past smoker								
Yes	0.20	0.78	6.40	0.14	0.12	25.91	0.09	0.22
No	0.29	1.06	5.94	0.16	0.18	36.03	0.13	0.25
Stove type at home								
Gas	0.27	0.98	6.15	0.15	0.16	31.34	0.12	0.24
Electrical	0.18	0.81	5.72	0.16	0.14	30.06	0.11	0.24
Stove hood at home								
Yes, in use	0.24	1.03	5.22	0.11	0.13	28.93	0.10	0.13
yes, not in use	0.32	1.14	6.26	0.19	0.18	31.34	0.09	0.13
Don’t have	0.24	0.90	6.28	0.16	0.16	32.51	0.13	0.30
Vegetarian or vegan								
Vegetarian	0.27	1.07	5.09	0.19	0.15	29.21	0.14	0.32
None	0.25	0.92	6.48	0.15	0.16	32.57	0.12	0.23
Grilled food								
more than once a week	0.41	1.12	11.44	0.20	0.31	73.70	0.17	0.41

2-4 times a month	0.25	1.01	6.11	0.16	0.17	34.36	0.13	0.21
Less than once a month or not at all	0.24	0.84	6.12	0.14	0.13	27.16	0.11	0.27
Smoked food								
more than once a week	0.38	0.80	13.43	0.13	0.28	72.38	0.23	0.26
2-4 times a month	0.27	1.00	7.34	0.16	0.14	34.74	0.13	0.23
Less than once a month or not at all	0.23	0.89	5.07	0.14	0.16	27.76	0.10	0.25
Drinking water from a container of 10 liters or more								
Yes	0.21	0.91	7.83	**0.10***	0.14	30.12	0.09	0.19
No	0.28	0.95	5.54	**0.19***	0.17	33.31	0.14	0.28
Drinking water from a hard plastic sports bottle								
Yes	0.27	0.92	5.49	0.16	0.15	28.63	0.12	0.30
No	0.24	0.97	7.17	0.14	0.16	37.62	0.13	0.19
Using plastic food containers in the microwave								
Couple of times a day	0.05	0.39	10.30	0.04	0.07	16.54	0.04	0.14
Everyday	0.27	1.10	7.19	0.19	0.23	36.75	0.12	0.17
Once a week	0.28	1.05	4.49	0.14	0.18	31.38	0.13	0.27
Once a month	0.29	0.87	3.98	0.15	0.12	32.47	0.10	0.34
Less than once a month or not at all	0.28	0.92	7.46	0.18	0.13	33.36	0.14	0.29
Using microwave adjusted plastic food containers								
Yes	0.26	0.94	5.41	0.16	0.16	33.11	0.12	0.27
No	0.36	1.16	8.19	0.16	0.21	38.38	0.14	0.23
I don’t know	0.13	0.50	5.55	0.10	0.16	21.57	0.07	0.13
Other (using glass containers)	0.09	0.26	24.11	0.02	0.04	15.91	0.05	0.18
Not heating in the microwave	0.26	1.83	14.07	0.20	0.06	29.11	0.17	0.29
Home pest control over the past week								
No	0.25	0.92	6.12	0.15	0.15	31.92	0.12	0.23
Yes	0.20	2.41	20.50	0.59	0.23	42.69	0.21	1.17
Season								

Cold	0.30	0.93	5.09	0.15	0.17	32.43	0.11	0.24
Warm	0.21	0.95	7.58	0.15	0.14	31.15	0.13	0.25

*significant values at the level of significance alpha=0.050 (two-tailed test).

Table 15. Correlation between $PM_{2.5}$ concentrations and metals concentrations:

Metals	Personal and indoor average exposure to $PM_{2.5}$		Indoor exposure to $PM_{2.5}$		Personal exposure to $PM_{2.5}$	
	Correlation Coefficient	Sig. (2-tailed)	Correlation Coefficient	Sig. (2-tailed)	Correlation Coefficient	Sig. (2-tailed)
Cr	-0.221	0.131	-0.278	0.062	-0.143	0.345
Ni	-0.069	0.641	-0.118	0.435	-0.44	0.776
As	0.102	0.492	0.178	0.236	0.215	0.166
Cd	0.118	0.445	-0.013	0.930	0.064	0.665
Pb	-0.126	0.394	-0.268	0.072	0.02	0.898
Se	-0.146	0.321	-0.153	0.309	-0.095	0.538
Tl	0.019	0.897	-0.006	0.971	-0.033	0.832
Hg	0.063	0.676	0.013	0.935	0.042	0.789

Table 16. Spearman correlation coefficients between metals and cotinine (unadjusted to creatinine) in urine specimens from 48 pregnant women from Haifa:

Spearman's rho		Cr	Ni	As	Cd	Pb	Se	Tl	Hg	Cotinine
Cr	Correlation Coefficient	1.000	.554**	.358*	.540**	0.244	**.748****	.572**	0.262	0.160
	Sig. (2-tailed)		0.000	0.012	0.000	0.095	0.000	0.000	0.079	0.277
Ni	Correlation Coefficient		1.000	.332*	**.596****	.303*	**.594****	**.597****	0.268	-0.125
	Sig. (2-tailed)			0.021	**0.000**	0.037	**0.000**	**0.000**	0.072	0.399
As	Correlation Coefficient			1.000	.373**	0.171	.396**	.399**	0.226	0.056
	Sig. (2-tailed)				0.009	0.245	0.005	0.005	0.131	0.704
Cd	Correlation Coefficient				1.000	0.279	**.675****	**.621****	**0.601****	0.101
	Sig. (2-tailed)					0.055	**0.000**	**0.000**	**0.000**	0.494
Pb	Correlation Coefficient					1.000	0.213	0.238	**0.426****	0.139
	Sig. (2-tailed)						0.147	0.104	**0.003**	0.345
Se	Correlation Coefficient						1.000	**.718****	**0.338***	0.035
	Sig. (2-tailed)							**0.000**	**0.022**	0.815
Tl	Correlation Coefficient							1.000	**0.439****	0.013
	Sig. (2-tailed)								**0.002**	0.933
Hg	Correlation Coefficient								1.000	
	Sig. (2-tailed									
Cotinine	Correlation Coefficient								-0.033	1.000
	Sig. (2-tailed)								0.829	

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 17. Spearman correlation between first and last day of the indoor and personal monitor.

N	*p* value	Correlation coefficient	
49	< 0.01	0.74	**Indoor exposure to**
39	< 0.01	0.49	**Personal exposure to**

Figure 1. LBW prevalence rate in HBA and in six Israel's districts, divided to three periods (2002-2006, 2007-2011, 2012-2016).

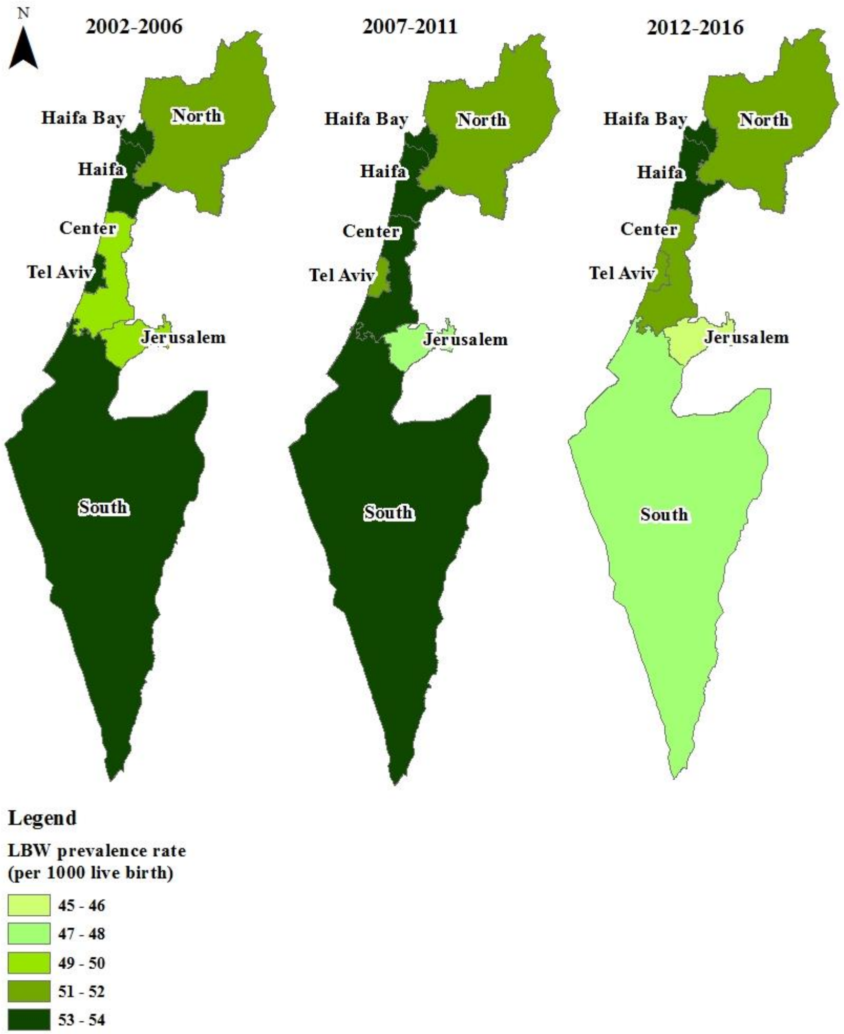


Figure 2. High and low rate clusters of LBW in Haifa Bay area (circle size represents cluster size)

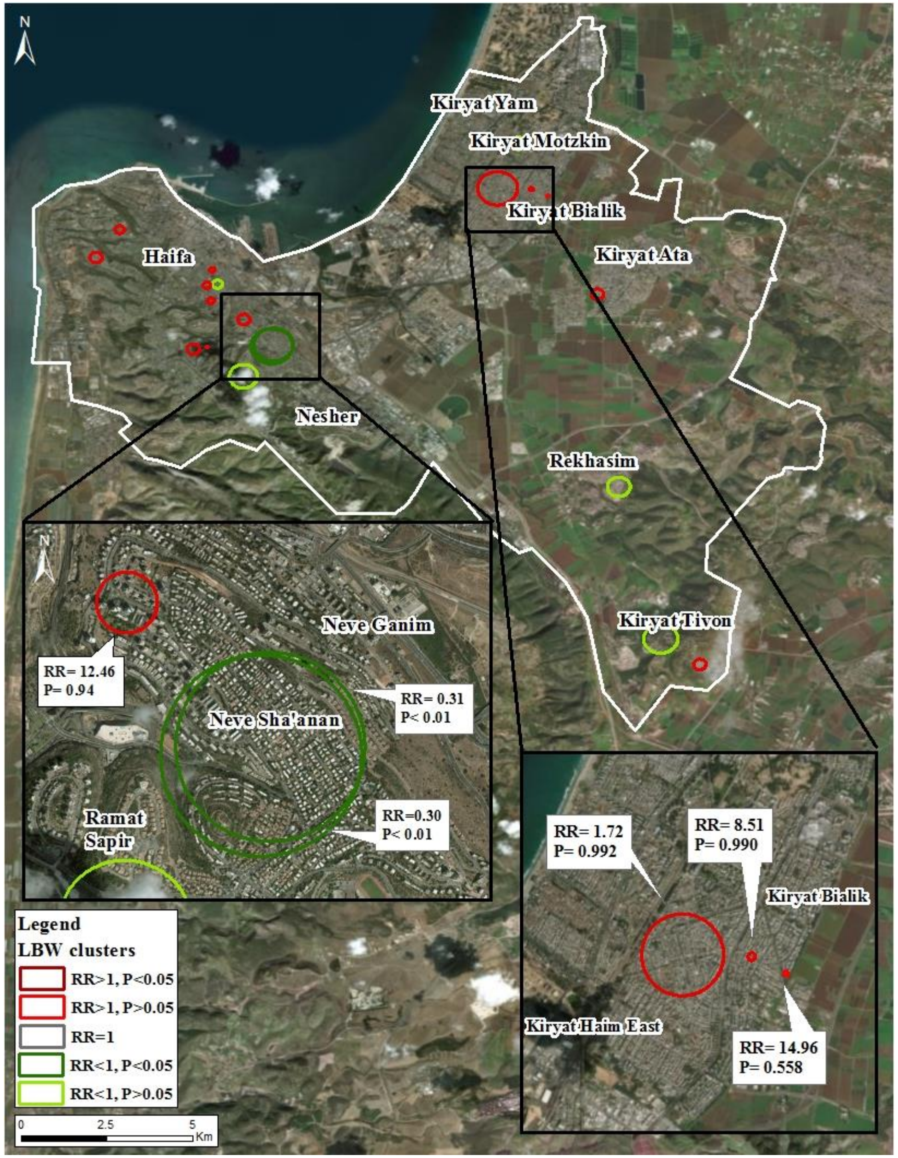
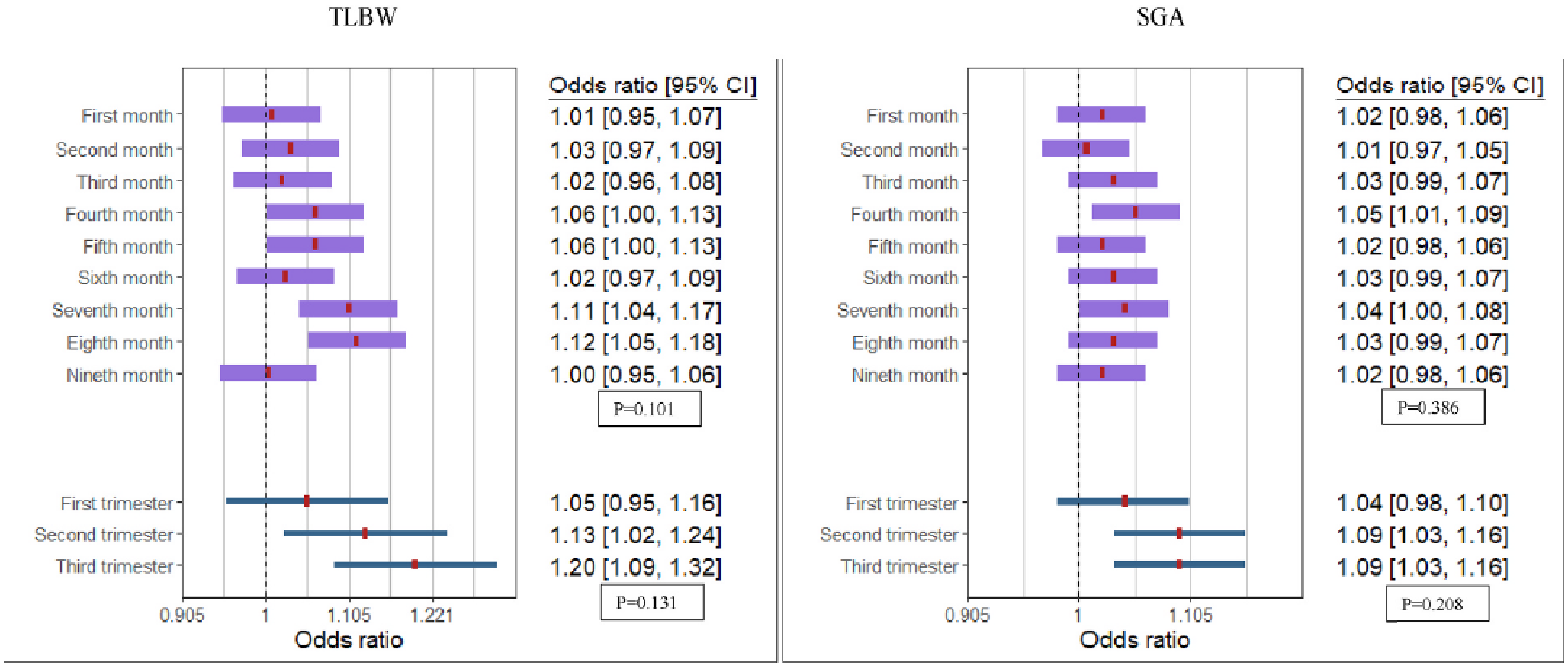


Figure 3. Associations between PM2.5 and birth outcomes by month and trimester of exposure in models with random intercepts at the mother level.



Effect estimates (95% CI) are reported per a 10-μg/m^3 increase in mean $PM_{2.5}$ over the entire pregnancy. All models were adjusted for sex, gestational age, mother age at birth, birth order, socioeconomic status, maternal height, maternal smoking status, year and season of birth, and temperature. Abbreviations: OR, odds ratio; B, regression coefficient; CI, confidence interval; TLBW, term low birth weight; SGA, small for gestational age; TBW, term birth weight.

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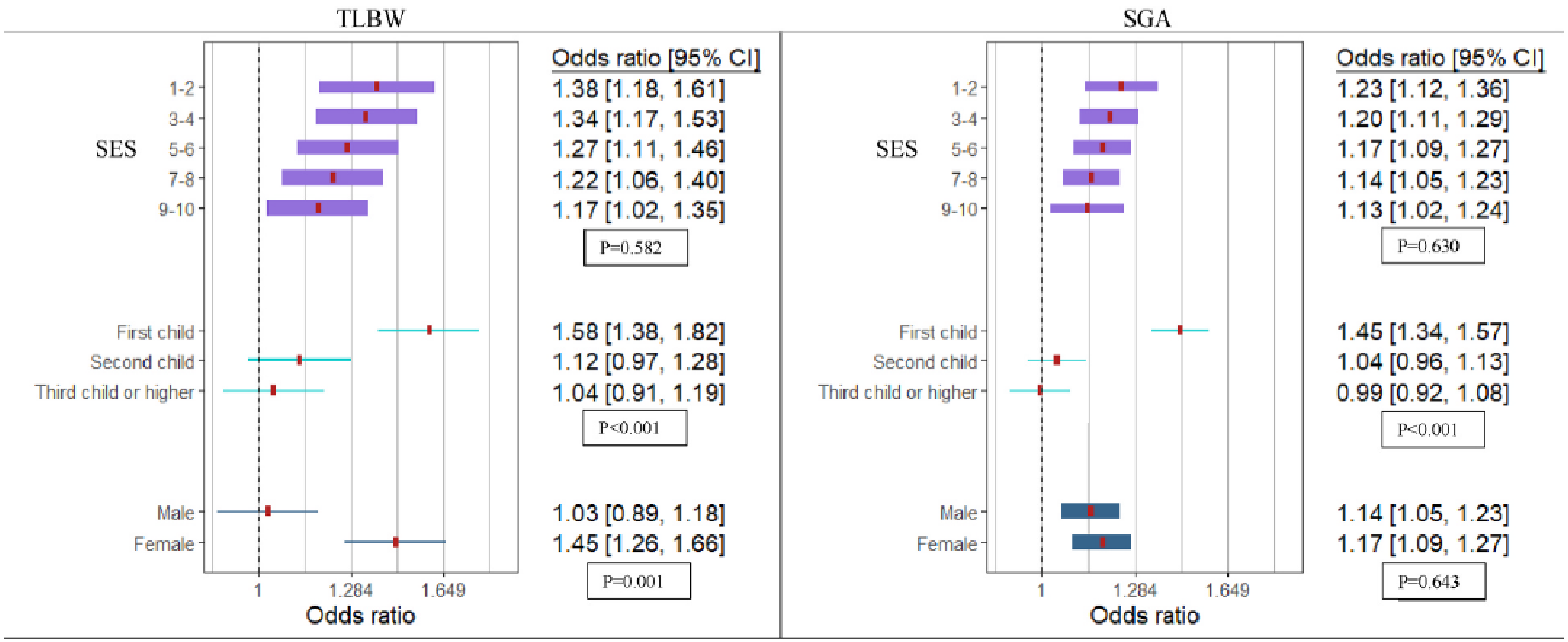
Figure 4. Associations between PM2.5 and birth outcomes by socioeconomic status and birth order in models with random intercepts at the mother level.



Effect estimates (95% CI) are reported per a 10-µg/m^3 increase in mean $PM_{2.5}$ over the entire pregnancy. All models were adjusted for sex, gestational age, mother age at birth, birth order, socioeconomic status, maternal height, maternal smoking status, year and season of birth, and temperature.
Abbreviations: OR, odds ratio; B, regression coefficient; CI, confidence interval; TLBW, term low birth weight; SGA, small for gestational age; TBW, term birth weight.

Figure 5. Flow chart of the field study.

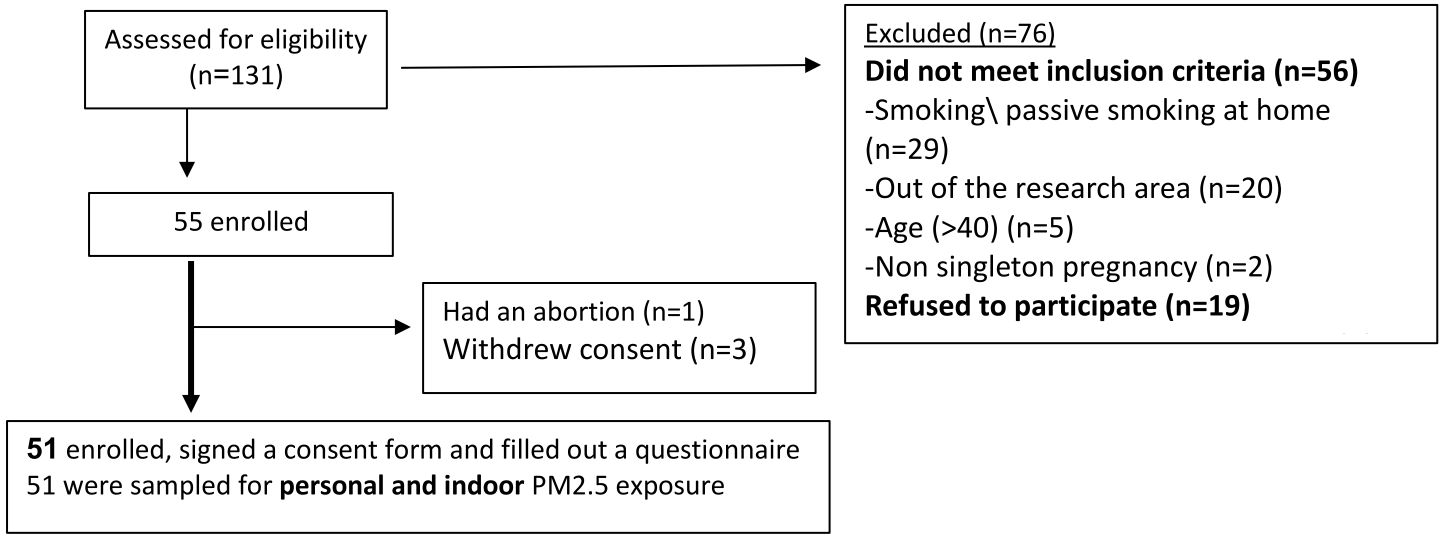


Figure 6. Spatial distribution of cadmium concentrations in the urine of 48 pregnant women from Haifa Bay

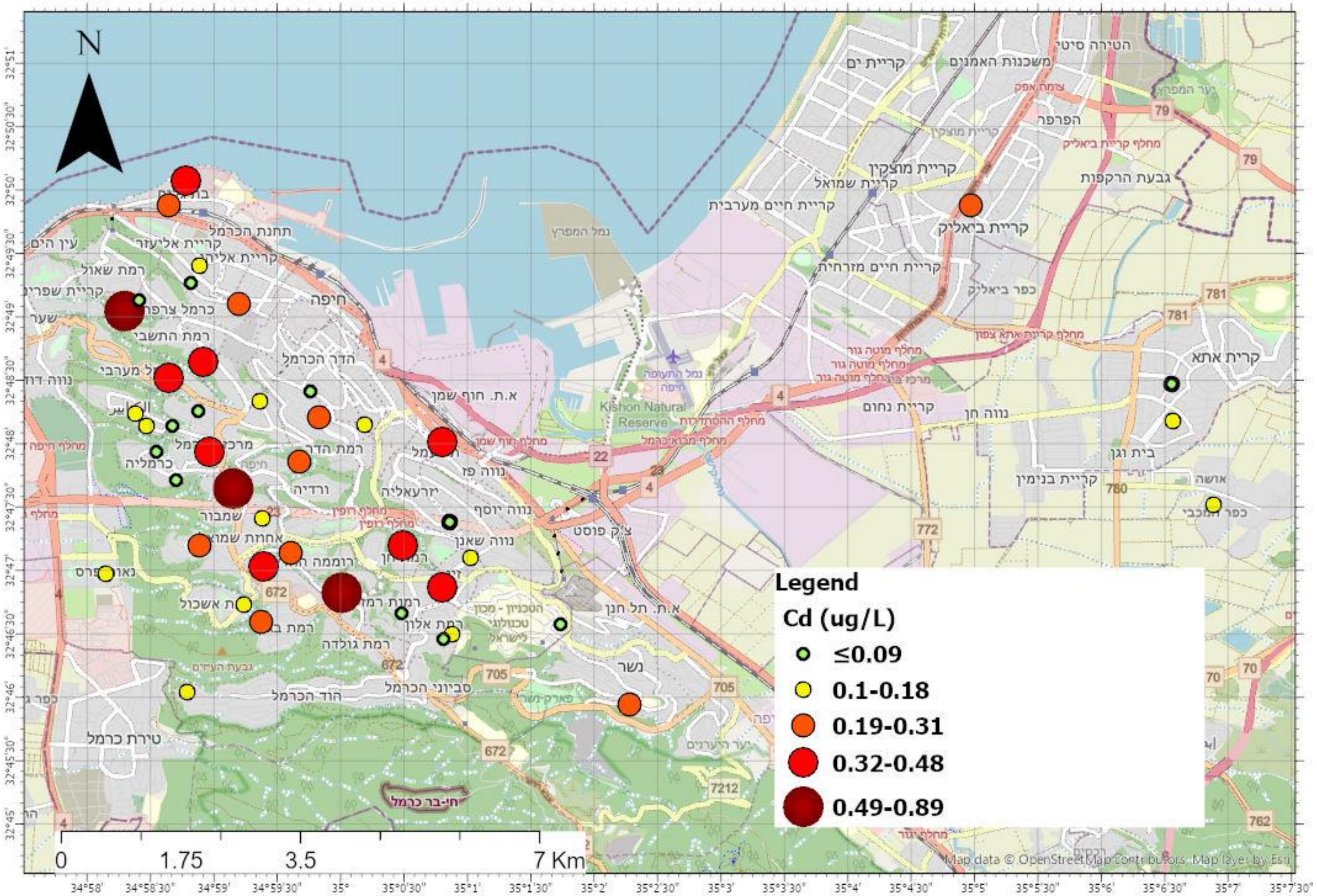


Figure 7. Spatial distribution of lead concentrations in the urine of 48 pregnant women from Haifa Bay.

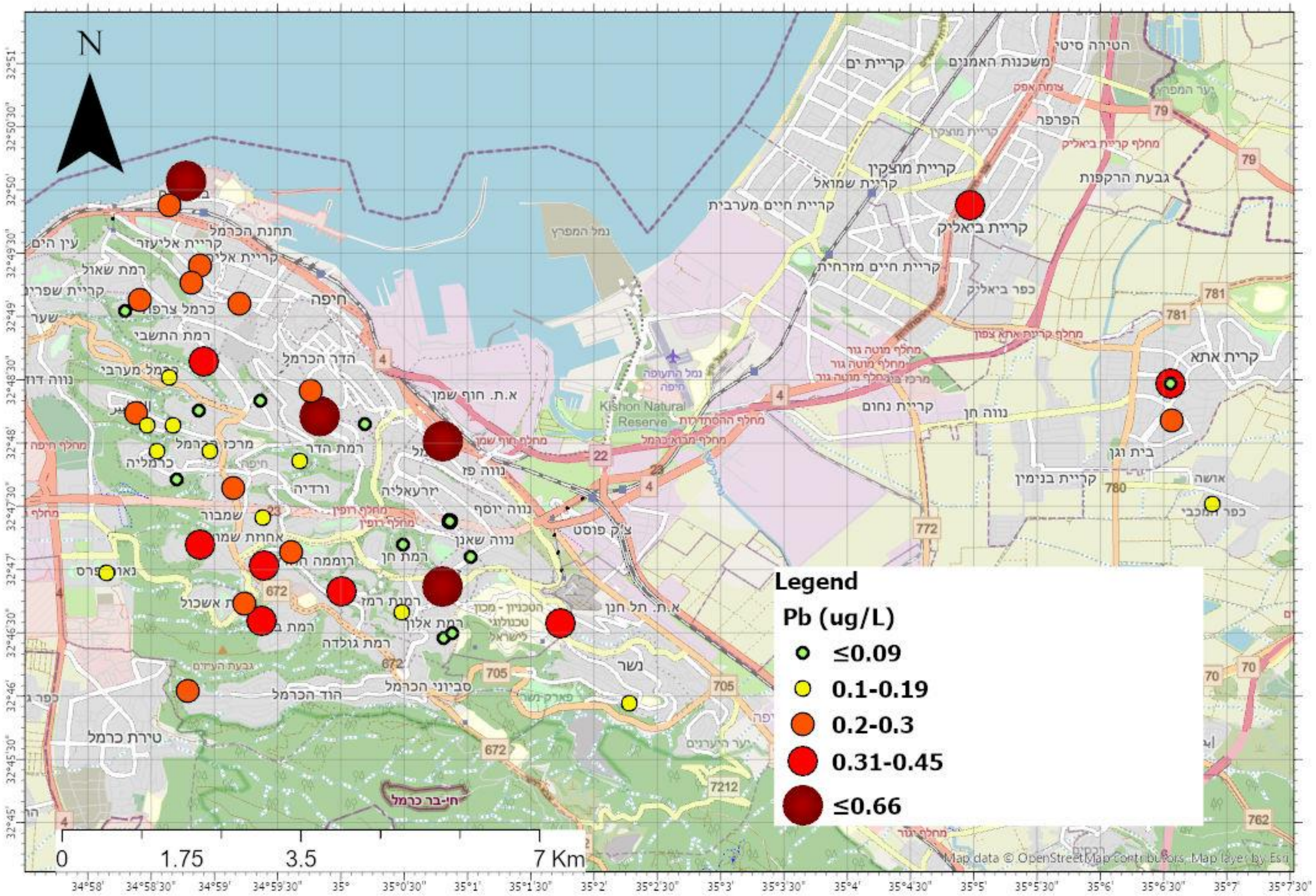


Figure 8. Indoor mean exposure to PM2.5 during day hours.

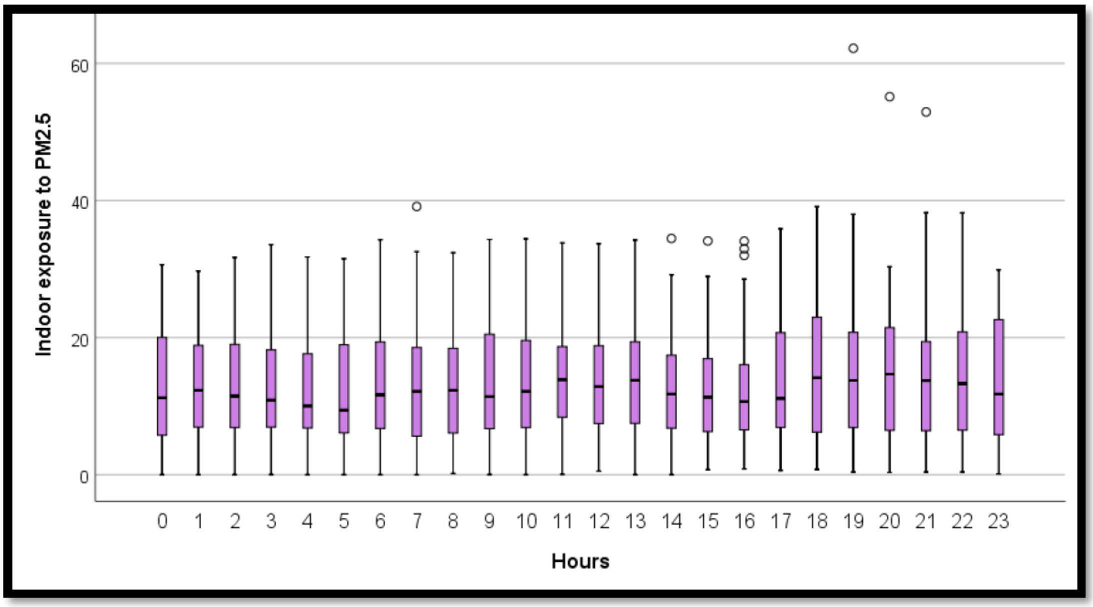


Figure 9. Personal mean exposure to PM2.5 during day hours.

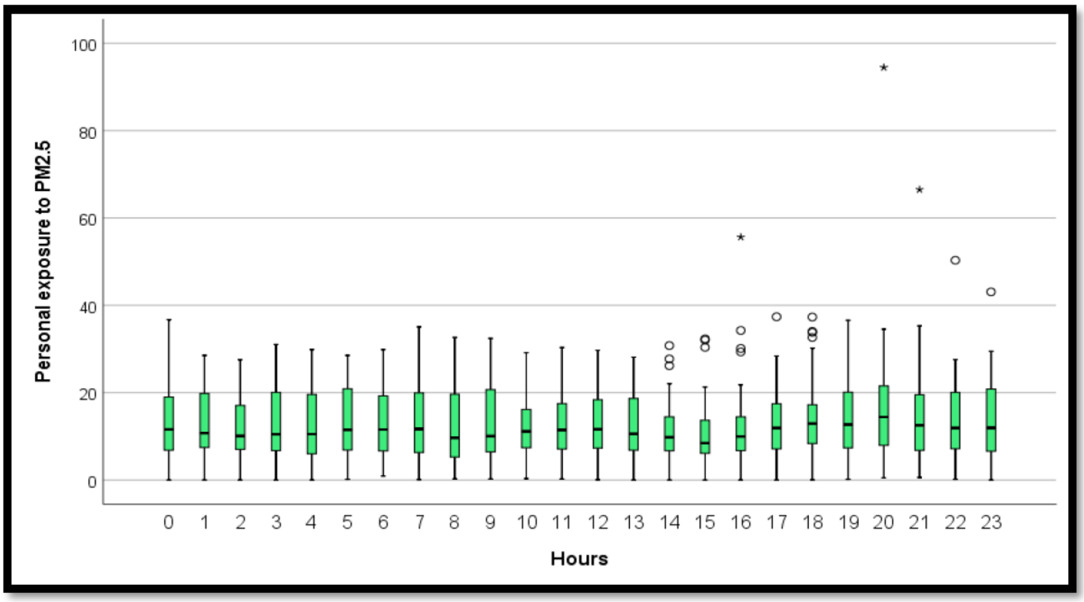


Figure 10. Associations between first and fifth quintiles of mean $PM_{2.5}$ and $PM_{10\text{-}2.5}$ over the entire pregnancy and preterm birth in fully adjusted model.