Maternal, Behavioral, and Environmental Risk Factors for Gestational Diabetes and Preterm Birth Among Pregnant Women

MATERNAL, BEHAVIORAL, AND ENVIRONMENTAL RISK FACTORS FOR GESTATIONAL DIABETES AND PRETERM BIRTH AMONG PREGNANT WOMEN

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Abstract

Background: Lifestyle changed in Kuwait with the rapid development and economic expansion and the Americanization of the Kuwaiti market. Fast food and sedentary lifestyle have become very prevalent. Environmental exposures such as passive tobacco smoke and extreme temperatures are common in Kuwait where the prevalence of chronic disease is increasing. We describe a Kuwait based pregnancy-birth cohort and examine the associations between perinatal exposures and the risk of chronic disease.

Methods: We recruited women from antenatal clinics in Kuwait and administered baseline questionnaires then followed the women postnatally. We examined maternal and lifestyle risk factors of gestational diabetes mellitus (GDM). We examined the association between passive tobacco smoke exposure and gestational diabetes, and finally we examined the association of preterm delivery with ambient heat and humidity exposures in Kuwait

Results: We successfully enrolled 2,478 women and followed 2,254 to delivery. Overall, frequencies of stillbirth, preterm birth, and small for gestational age were comparable to other developed countries. The incidence of self-reported gestational diabetes was within the expected range worldwide. After past GDM history, pre-pregnancy obesity was the strongest maternal risk factor associated with GDM. We observed patterns suggestive of a positive association between home passive tobacco smoke exposure and GDM among primiparous women. Finally, high relative humidity but not temperature was associated with an increased risk of preterm delivery.

Conclusions: We successfully established a large pregnancy birth cohort in Kuwait. There are several social and environmental challenges in Kuwait that may increase the risk of chronic disease such as diabetes, which is already very prevalent in Kuwait. Understanding the relation of these risk factors with pregnancy health and birth outcomes is important given the potential for early life exposure experience to impact long term health and adult disease risk. Our results should be replicated and the results used to inform interventions to reduce the rates of chronic disease in Kuwait.

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Chapter 1: Introduction

Introduction

Kuwait is a high income middle-eastern country with a 17,818 km^2 area. The country is situated north-east of Saudi Arabia, south of Iraq, and west of Iran across the Arabian Gulf. As of 2013, the Kuwaiti population was 3.45 million of which around 34% were Kuwaiti and 66% were non-Kuwaiti from a range of different nationalities but primarily other Arab nationalities.[1] The Kuwaiti population is fairly young with a median age of 30 years.[2]

The Kuwaiti population faces multiple social and environmental challenges. After the Iraqi war of 1991 the Kuwaiti markets became more open to the American and western markets. Fast-food and western diet became very popular in Kuwait over the past two decades.[3] As a consequence, the Kuwaiti diet has a high calorie, high macronutrient, and low fiber profile with a high frequency of excessive nutrient intake.[4] In general Kuwait is not very walkable because of the car-dependent suburban design of its communities and because of the extreme heat in the summer when temperatures reach a maximum of 52^{o}C in the shade, in effect, forcing most of the population to stay indoors in air conditioned buildings. [5] As a result, physical activity levels are very low where approximately 62% of the Kuwaiti population do not achieve sufficient physical activity according to the World Health Organization standards.[6] Tobacco smoking, another challenge in the country, is very prevalent with 39% of men in Kuwait smoking as of 2014.[6]

Consequences of such a challenging environment are evident in Kuwait. The rates of non-communicable diseases have increased along with modernization and rapid urbanization. Kuwait has one of the world's highest rates of type 2 diabetes where the prevalence of diabetes in adults older than 45 years increases with age from 25% to 37%.[7] When using population overall age standardization, Kuwait ranked ninth worldwide in the prevalence of type 2 diabetes 23.1%. [8] Kuwait also has one of the world's highest rates of obesity. Approximately 77% of the Kuwaiti population is overweight or obese. Obesity and diabetes increase the rates of morbidity and mortality directly and indirectly through heart disease and other health conditions.

Gestational Diabetes Mellitus (GDM) is a condition of impaired glucose tolerance during pregnancy that resolves after delivery. [9] Women who develop GDM during pregnancy are at particularly high risk of subsequent diabetes with 50 to 70% becoming type 2 diabetics within 5 to 10 years after delivery.[10] Important risk factors for GDM such as pre-pregnancy obesity, maternal age, hypertensive disorders, and prior macrosomic birth have been frequently studied in the western world. However, the importance of these GDM risk factors in Kuwait and the Arab world has been significantly understudied. It is important to study these factors because reproductive age women are exposed to such a health challenging environment in Kuwait. We expect that a large number of women are exposed to passive tobacco smoking due to the high prevalence active smoking among men in Kuwait. Preterm delivery (PTD), which is a cause of child morbidity and mortality is also associated with a higher risk of type 2 diabetes in offspring.[11] PTD may be associated with ambient heat and humidity[12–14], which raises the importance of studying such an outcome in relation to Kuwait's extremely hot weather.

In this dissertation we examine the association between maternal and lifestyle risk factors, and the Kuwaiti environment on pregnancy outcomes. The thesis is divided into three parts. The first examines maternal socioeconomic and pregnancy factors in association with GDM. Maternal factors include nationality, age, education, income, and parity. Pregnancy factors are pre-pregnancy body mass index (kg/m^2), gestational weight gain, active pregnancy tobacco smoking, and physical activity. The second part examines maternal home passive tobacco smoke exposure during pregnancy and GDM risk. The third part examines the association between the ambient temperature and humidity in Kuwait and preterm delivery.

Data used for this analysis was obtained from the Transgenerational Assessment of Children's Environmental Risk (TRACER) pregnancy birth cohort. The cohort was established in 2012 to examine the association of social and physical prenatal environments and future childhood chronic disease markers and child development. Because of the importance of diabetes in

Kuwait, we also examined the determinants and risk factors associated with GDM in this pregnancy cohort. We approached 15,469 pregnant women from 9 antenatal clinics spread throughout Kuwait, 10,982 were eligible, and 2478 were enrolled and administered the baseline questionnaire. The pregnant women were followed through birth, and then the mother child pairs were followed up to 3 years after delivery.

The study has been approved by the Harvard T.H. Chan School of Public Health Institutional Review Board (IRB), and the Kuwaiti Dasman Diabetes Institute IRB.

References

1. Central Statistical Bureau. *Kuwait Statical Review*.; 2014.
2. Central Intelligence Agency. The World Fact Book. https://www.cia.gov/library/publications/the-world-factbook/fields/2177.html. Accessed February 23, 2016.
3. FAO. *Nutrition Country Profile*.; 2006. ftp://ftp.fao.org/ag/agn/nutrition/ncp/kwt.pdf.
4. Zaghloul S, Al-Hooti SN, Al-Hamad N, et al. Evidence for nutrition transition in Kuwait: over-consumption of macronutrients and obesity. *Public Health Nutrition*. 2012;16(4):1-12. doi:10.1017/S1368980012003941.
5. Al-Marafie AMR, Suri RK, Maheshwari GP. Energy and power management in air-conditioned buildings in Kuwait. *Energy*. 1989;14(9):557-562. doi:10.1016/0360-5442(89)90027-3.
6. WHO. *Kuwait STEPS Survey 2014*.; 2014. www.who.int/chp/steps .
7. International Diabetes Federation. Kuwait vs World prevalence of diabetes. 2015. http://www.idf.org/membership/mena/kuwait.
8. *International Diabetes Federation Sixth Edition*.; 2013. doi:2-930229-80-2.
9. Buchanan T a., Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? *Diabetes Care*. 2007;30(SUPPL. 2). doi:10.2337/dc07-s201.
10. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes care*. 2002;25(10):1862-1868. http://www.ncbi.nlm.nih.gov/pubmed/12351492.
11. James-Todd TM, Karumanchi SA, Hibert EL, et al. Gestational age, infant birth weight, and subsequent risk of type 2 diabetes in mothers: Nurses' Health Study II. *Preventing chronic disease*. 2013;10(5):E156. doi:10.5888/pcd10.120336.
12. Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. *American Journal of Epidemiology*. 2010;172(10):1108-1117. doi:10.1093/aje/kwq170.

13. Yackerson N, Piura B, Sheiner E. The influence of meteorological factors on the emergence of preterm delivery and preterm premature rupture of membrane. *Journal of perinatology : official journal of the California Perinatal Association*. 2008;28(10):707-711. doi:10.1038/jp.2008.69.

14. Dadvand P, Basagaña X, Sartini C, et al. Climate extremes and the length of gestation. *Environmental Health Perspectives*. 2011;119(10):1449-1453. doi:10.1289/ehp.1003241.

Chapter 2: Birth Outcomes in a Prospective Pregnancy-Birth Cohort Study of Environmental Risk Factors in Kuwait: The TRACER Study

Birth Outcomes in a Prospective Pregnancy-Birth Cohort Study of Environmental Risk Factors in Kuwait: The TRACER Study

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ABSTRACT

Background: Rapid development and westernization in Kuwait and other Gulf states has been accompanied by rising rates of obesity, diabetes, asthma, and other chronic conditions. Prenatal experiences and exposures may be important targets for intervention. We undertook a prospective pregnancy birth cohort study in Kuwait, the TRansgenerational Assessment of Children's Environmental Risk (TRACER) Study, to examine prenatal risk factors for early childhood obesity. This paper describes the methodology and results of follow-up through birth.

Methods: Women were recruited at antenatal clinical visits. Interviewers administered questionnaires during the pregnancy and collected and banked biological samples. Children are being followed-up with quarterly maternal interviews, annual anthropometric measurements, and periodic collection of biosamples. Frequencies of birth outcomes (i.e. stillbirth, preterm birth, small and large for gestational age, and macrosomia) were calculated as a function of maternal characteristics and behaviors.

Results: 2,478 women were enrolled and 2,254 were followed to delivery. Overall, frequencies of stillbirth (0.6%), preterm birth (9.3%), and small for gestational age (7.4%) were comparable to other developed countries, but not strongly associated with maternal characteristics or behaviors. Macrosomia (6.1%) and large for gestational age (23.0%) were higher than expected, and positively associated with pre-pregnancy maternal overweight/obesity.

Conclusions: A large birth cohort has been established in Kuwait. The collected risk factors and banked biosamples will allow examination of the effects of prenatal exposures on the development of chronic disease in children. Initial results suggest that maternal overweight/obesity before pregnancy should be targeted to prevent macrosomia and its associated sequelae of childhood overweight/obesity.

INTRODUCTION:

Both developed and developing countries are experiencing a rise in complex chronic non-communicable diseases.[1, 2] This is particularly evident in the Gulf Cooperation Council (GCC) countries which have experienced dramatic economic and lifestyle changes over the last few generations, along with a dramatic rise in obesity, diabetes, asthma, neurodevelopmental disorders, and cardiovascular disease.[3-5]

Lifestyle and personal behaviors have been suggested as important factors in this transition. The diet in these countries has changed from the traditional high-fiber, low-fat Arab diet to a western diet high in unhealthy fast food and sugar-sweetened beverages, with low intake of fruits and vegetables.[5, 6] The rates of physical inactivity are very high.[5, 6] Cigarette smoking rates are high among men, although not as frequent among women, but hookah (water pipe) smoking is increasingly common.[5, 7]

Along with this rapid transition in lifestyle and behaviors, there is growing evidence that these chronic diseases have roots early in the developmental process. Adverse health trajectories established in early life may have long-term consequences, a notion grounded in the theory of the early life origins of chronic disease.[8] Characteristics of the *in utero* environment, independent of genetic susceptibility, influence fetal development that then sets the stage for chronic disease expression across the life course.[9-12]

The *in utero* and neonatal developmental periods are important “critical windows” during which the rapidly growing fetus and newborn are particularly susceptible to nutritional, chemical, and psychosocial toxins.[13, 14] Environmental exposures during these periods may enhance vulnerability to a number of leading maternal and child health problems, including adverse pregnancy outcomes, neurodevelopmental outcomes, allergic sensitization, respiratory disorders, and obesity and other metabolic disorders.

A number of environmental exposures linked to child health and developmental outcomes[15] are prevalent in Kuwait and other GCC countries. These include dietary deficiencies (e.g., vitamin D) [16, 17] and elevated body burdens of environmental contaminants, such as heavy metals,[18] persistent organics,[19, 20] and pesticides.[21-23] In addition, environmental exposures, such as tobacco smoke,[24] indoor aeroallergens,[25] outdoor air pollution,[26] and psychosocial stress[27] are prevalent in Kuwait and have been linked to chronic conditions of adults and children. Other environmental exposures of potential regional concern include chlorination disinfection by-products (DBPs) and desalination of drinking water.[28] All have the potential to influence developmental processes beginning in pregnancy.

Numerous birth cohorts have been established in Europe and North America,[29, 30] but in Arab countries, despite increasing public health research,[31] there are few, if any, such studies. Yet, exposures unique to this region of the world, coupled with the dramatic increase in chronic diseases, make it imperative to evaluate the impact of these environmental factors on this increasingly high-risk population.

The TRansgenerational Assessment of Children's Environmental Risk (TRACER) Study is a longitudinal Kuwait-based prospective cohort study designed to examine the influence of ongoing environmental exposures (including physical, chemical, and psychosocial factors) on early life programming of chronic disease risk. The study is a pregnancy - birth cohort with data being gathered prospectively over the course of pregnancy with follow-up of children up to age 3 years. The primary hypothesis is that prenatal exposures to environmental contaminants are associated with increased risk of adiposity of infants at 3 years of age. Secondarily, we hypothesize that prenatal environmental exposures are associated with early phenotypes of allergy and asthma of infants at 3 years of age. Environmental factors that are prevalent in Kuwait and have been previously implicated in early-life programming of costly chronic diseases in other studies around the world include environmental contaminants, including methyl mercury, arsenic, and other metals, pesticides, and persistent organics; dietary factors, including vitamin D deficiency; indoor and outdoor air pollution; indoor allergens; and stress.

In this paper, we describe the recruitment and follow-up of this pregnancy - birth cohort, present the distribution of maternal characteristics, and prevalence of preterm birth, low and high birth weight in follow-up between May 2012 and August 2015.

METHODS:

Recruitment, Prenatal Evaluation and Follow-up: The TRACER study was open to both Kuwaiti and non-Kuwaiti women attending the primary public health clinics in each of the six Kuwaiti governorates and three additional private clinics/hospitals. In Kuwait, the government provides antenatal healthcare at primary health care clinics in each governorate. Many Kuwaiti pregnant women elect to receive antenatal health care at public clinics but give birth at private hospitals. Non-Kuwaiti pregnant women tend to utilize the public clinics and hospitals for both antenatal care and delivery. Medical records may be kept by the health care clinic, but are often kept by the patients. Medical records are generally not shared between clinics or between antenatal clinics and delivery hospitals. Therefore, TRACER research assistants were placed in each participating clinic and hospital to collect data from the participants and their medical records.

Permission to recruit participants, to collect data and to collect biological samples was obtained from the administration and the obstetricians at each health center. The study was reviewed and monitored by institutional review boards at both the Harvard T.H. Chan School of Public Health and the Dasman Diabetes Institute.

Obstetric clinic staff provided a project brochure to women attending the antenatal clinics, and referred interested women to our onsite research assistant. The research assistant explained the study, determined eligibility (pregnant, 18 to 45 years old, fluent in Arabic or English, and willing to participate), and provided informed consent documents for the pregnant woman and her husband. Upon completion of the informed consent by both the woman and her husband, the woman was enrolled, often at a following clinic visit, and collection of data and biological samples would begin.

Prenatal risk factors were measured via interviewer-administered questionnaires and biological samples were collected at the participants' regular clinical visits (Figure 1.1). On enrollment, an interviewer administered a questionnaire, which obtained information about demographics, socioeconomic status, family structure, household characteristics, reproductive history, and medical history. Women reported their height and weight before pregnancy. In addition, the mother's current measured weight with clothes and standing height were extracted from the medical record.

Personal smoking and exposure to environmental tobacco smoke during pregnancy were assessed by a questionnaire. The participants were asked "Have you ever smoked tobacco products?" and "Do you currently smoke tobacco products" to define past and current smoking during pregnancy. Women were asked to quantify the number of hours of exposure to environmental tobacco smoke exposure per week at home and outside of home separately for cigarettes and hookah (also known as shisha, narghile, and hubble-bubble). We defined home environmental tobacco smoke as 1 hour or more exposure to cigarettes or hookah per week.

At the second follow-up clinical visit (median 29 weeks gestation), participants completed a Kuwait-specific food frequency questionnaire (Kuwait FFQ 2009, ©Hamilton Health Sciences Corporation)[i]

[i] Provided by Hamilton Health Sciences Corporation through its Population Health Research Institute. Adapted and reproduced with permission of publisher, PHRI.

and a stress questionnaire that included four global and seven pregnancy perceived stress questions.[32, 33]

During the clinical visit for glucose tolerance testing (22-28 weeks) participants were administered a structured questionnaire on their physical activity. Women were asked if they regularly participated in specific exercises (slow to moderate walking, brisk walking, jogging, running, aerobic exercise,

Figure 1.1. Schematic representation of data collection activities

		PRE-NATAL FOLLOW-UP			BIRTH	POST-NATAL FOLLOW-UP								
	Enrollment	2nd Follow-up	GTT	3rd Follow-up		Home/ Clinic Visit	Phone Check	Postnatal Visit	Phone Check	Phone Check	Postnatal Visit	Phone Check	Phone Check	Postnatal Visit
			22-28 wk			*0-3 mo*	*3-6 mo*	*9-12 mo*	*15-18 mo*	*18-21 mo*	*21-24 mo*	*24-26 mo*	*26-30 mo*	*30-36 mo*
	1	2	3	4		5	6	7	8	9	10	11	12	13
Recruitment	**Mom**													
Enrollment	**Mom**													
Baseline Questionnaire	**Mom**													
Bloodspot Spec	**BM1 Mom** (←→)		**BM2 Mom** (←→)			**Baby 1**		**Baby 2**			**Baby 3**			**Baby 4**
Urine Spec	**U1 Mom** (←→)		**U2 Mom** (←→)											
Diet Qs		**Food Freq**		**Vitam-Fish-Exercise**		**Diet Q Baby**		**Diet Q Baby**			**Diet Q Baby**			**Diet Q Baby**
Venous Blood Spec			**Mom**											
Stress Q			**Mom**											
PostNatal Check						⌂	✆	⌂	✆	✆	⌂	✆	✆	⌂
Saliva Spec Collection			**Sv Mom**					Sv Mom						
Hair Spec				**Mom**		Baby 1		Baby 2			Baby 3			Baby 4
Anthropometry						Baby & Mom		Baby & Mom			Baby & Mom			Baby & Mom

⌂ is home visit and ✆ is a phone check.

During phone checks the mother is asked about symptoms of upper respiratory tract infections, diagnosed lower respiratory tract infections (pneumonia & bronichitis), asthma and wheezing, and eczema along with physician visits, hospital stay, and list of medications used for each condition. In addition, we inquired about maternal smoking, the child's environmental tobacco smoke exposure, maternal stress, the child's feeding history, and the child's day car sports, or lifting weights), including frequency and duration per week. They were also asked if they were employed in a physically demanding job and the intensity and duration per week.

At the third follow-up clinical visit (median 33 weeks gestation), participants completed a questionnaire on vitamin supplements and Kuwait-specific fish consumption.[18]

Multiple biological samples were collected during pregnancy and banked for future analyses at the Dasman Diabetes Institute (Figure 1.1). Blood spots were collected at enrollment and at the third follow-up clinic visits. Venous blood collected during the glucose tolerance test (22-28 weeks) was separated, aliquoted, and stored at -80°C for future analyses. Lead exposure was measured with a spot blood sample (LeadCare® II Blood Lead Test). A maternal hair sample was collected during the third trimester visit.

On the morning of the second and third follow-up visits, participants collected first void urine samples at home which they brought to the clinic. These urine samples were aliquoted and stored at -80 °C.

During the clinic visit for glucose tolerance testing, participants were instructed on the collection of repeated saliva samples (upon waking up, 45 minutes, 4 hours, and 10 hours after waking up, and before retiring to bed) on two separate days. These samples were stored in the home freezer until picked up by the study staff, and then stored at -80 °C.

The status of the pregnancy was recorded at each follow-up encounter. Weeks of gestation at each encounter were estimated using the interview date and date of last menstrual cycle. Stillbirth was defined as pregnancy loss after 20 weeks, and preterm birth as birth before 37 weeks of gestation.

Post-Natal Follow-up: Within three months following the expected delivery the mother was called to obtain the baby's birth date, birth weight and length, and mode of delivery. The mother was asked to recall her last measured weight at the end of her pregnancy and any diagnosis and treatment for gestational diabetes and gestational hypertension.

Babies were excluded from follow-up if a fetal chromosomal abnormality was reported which may influence outcomes being studied or if the baby required care in the neonatal intensive care unit (NICU), which included mechanical ventilation or high-level oxygen therapy at time of birth.

The mother and newborn were visited at home within 3 months of delivery, where blood spot, hair, and anthropometric measures of the child were collected. A repeat maternal saliva sample was collected as described above.

The World Health Organization (WHO) birthweight percentile for gestational week calculator was used to define small for gestational age (below the 10th percentile, SGA) and large for gestational age (above the 90th percentile, LGA). Babies with a birth weight of 4000g or more were classified as high birth weight (macrosomia).

In continuing follow-up, the mother and newborn are being telephoned quarterly from birth to age 3 years (Figure 1.1), to ascertain respiratory symptoms (e.g., wheezing, eczema, allergic rhinitis), and the child's diet (transition from breast milk or formula to solid food). Each post-natal telephone interview includes administration of the Edinburgh Postnatal Depression Scale (EPDS) to the mother.[34]

Annual in-person follow-up includes interviews to obtain interval exposure assessments (e.g., parental and child diet, behavioral assessments) and outcomes of interest, as well as anthropometric measurement of the child (Figure 1.1). Blood spot and hair samples from the child are collected. During the child's first annual visit, mothers again provide repeated saliva samples (five over one day) on two separate days. Blood lead of the child (LeadCare® II Blood Lead) is measured at the child's first and second annual visits.

Statistical Analysis:

We examined the frequency of maternal characteristics (nationality, age, parity, income, and education), maternal risk factors (pre-pregnancy overweight/obesity, smoking, environmental tobacco smoke exposure, and physical activity), and the frequency and associations with birth outcomes (preterm birth, SGA, LGA, and macrosomia). Continuous characteristics with symmetric distributions are presented as means (± SD) and those with non-symmetric distributions are presented as median (lower - upper quartile). Categorical variables are presented as frequencies (%). Characteristics are presented overall and by nationality and by birth outcomes and compared using the chi-square test. We further used the Cochrane-Armitage test to evaluate trends in ordinal variables. We calculated the 95% confidence interval (95% CI) for the prevalence of preterm birth; macrosomia, large for gestational age, and small for gestational age. Analyses were performed using SAS 9.4 (SAS Institute Inc., USA).

RESULTS:

Study Population: A total of 15,469 women were approached at the maternity clinics between May 2012 and May 2015 (Figure 1.2) out of whom 10,982 (71%) were eligible. Of these, 2,723 (25%) agreed to participate and 91% of those (2,478 women) were enrolled and completed the baseline questionnaire. The women that agreed to participate were similar in age distribution to the ones eligible that did not agree to participate (Table 1.1); however, they were more likely to be non-Kuwaiti, with a greater proportion recruited at public clinics rather than private clinics (Table 1.1). In our study, 32% of Kuwaiti women attended public antenatal clinics, but 86% gave birth in private hospitals, while 91% of non-Kuwait women attended public antenatal clinics, but only 9% gave birth in private hospitals.

Most women were enrolled in the second trimester (1112 women, 48%), with 387 women (17%) enrolled in the first trimester, 832 (36%) in the third trimester. In addition 147 women completed the baseline questionnaire after delivery and had missing gestational age information. There were 2,254 (83%) women followed through August 2015. Of the women who dropped out, the most common reasons given were “does not wish to participate” (51%), “husband refused” (17%), and “unavailable (14%). During this pregnancy follow-up there were 91 pregnancy losses (miscarriages or stillbirth), 19 twin pregnancies, and one maternal death which excluded participants from further follow up.

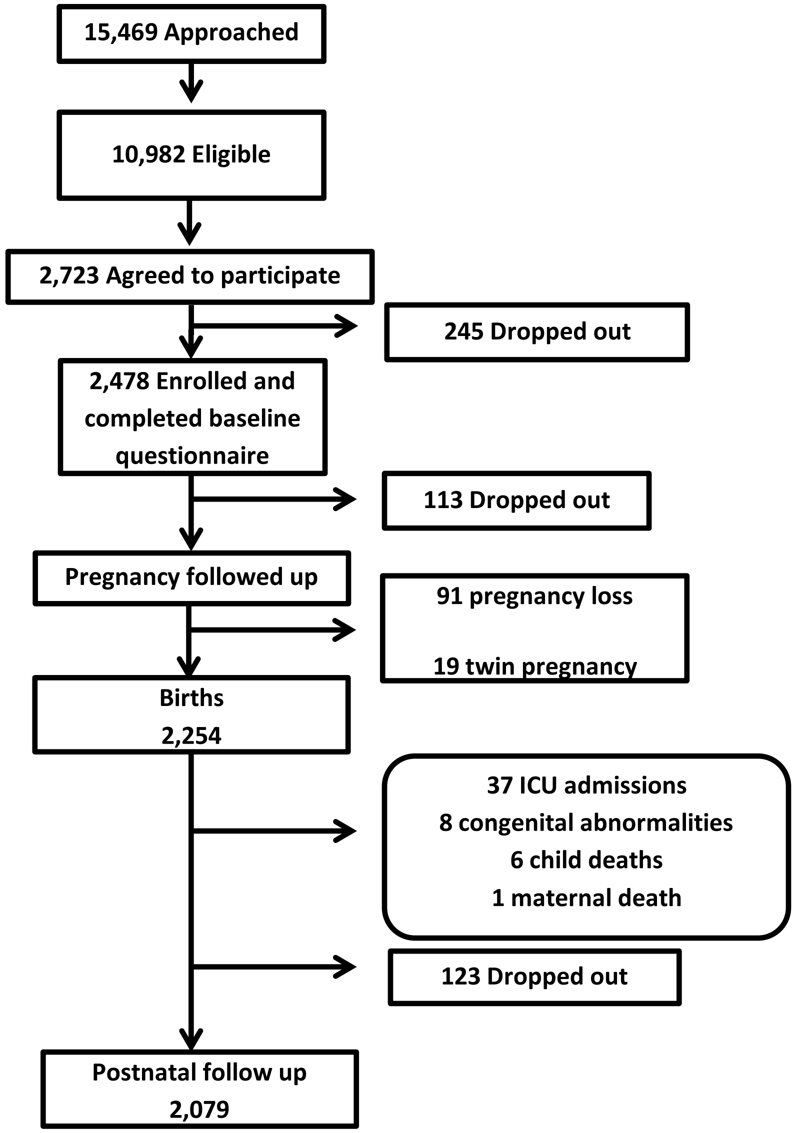
Through August 2015 there were 2254 deliveries and birth data were collected on 2,245 children. In post-natal follow-up, 37 infants have been dropped for Neonatal Intensive Care Unit admissions, eight for congenital abnormalities, six child deaths, and one for maternal death after birth of the child.

Table 1.2 presents the numbers of questionnaire and biological samples collected for the participating women during their follow-up visits while pregnant, through birth as of the end of August 2015.

Table 1.1: Comparison of pregnant women approached, eligible, and enrolled (% of eligible) into the TRACER study

Characteristic	Approached	Eligible	Enrolled	(% Eligible)
Total	15,469	10,982	2,478	23
Age group				
<25	3,362	2,414	577	24
25-30	5,281	3,590	930	26
30-35	3,579	2,426	641	26
35+	1,827	1,288	314	24
Missing	1,420	1,264	16	1
Nationality				
Kuwaiti	8,791	5,723	739	13
Non-Kuwaiti	6,573	5,168	1739	34
Missing	105	91	0	-
Clinic				
Private	5,045	4,210	585	14
Public	7,762	6,287	1740	28
Other	2,657	485	153	32
Missing	5	0	0	-

Figure 1.2. Flow chart showing the participation in the TRACER study.



Maternal Characteristics: The majority of women enrolled (70%) were non-Kuwaiti (n=1,739) while 30% were Kuwaiti nationals (n=739). The mean age of the women was 28.4 years ($\pm$5.02) and the median parity was 1.0 (Interquartile range 0 to- 2). The average pre-pregnancy BMI was 26.4 ($\pm$5.1) kg/m^2. Age at enrollment, active smoking, and home exposure to ETS were similar in Kuwaiti and non-Kuwaiti women (Table 1.3). However, a higher proportion of Kuwaitis compared to non-Kuwaitis had 3 or more children, higher monthly income, and education beyond high school.

Overall, more than half of the women were overweight (33%) or obese (22%) before they became pregnant (Table 1.3). Only 6% (n=143) participants reported smoking before becoming pregnant. Current smoking during this pregnancy was very rare (2%), however exposure to home ETS was common (30%, Table 1.3). Only 26% of women reported any type of regular exercise (slow walking or more) and only 12% reported regular exercise as strenuous as brisk walking or vigorous work (Table 1.3).

Stillbirth and Preterm Deliveries: Among women recruited before 20 weeks of gestation (n=1,275) the frequency of stillbirth was 0.6% (95% CI: 0.2% - 0.8%). The proportion of women with preterm deliveries was 9.3% (95% CI: 8.1 – 10.5%). Preterm birth was more frequent among Kuwaiti women (12.6%) compared to non-Kuwaitis (8.0%, Table 1.4). Preterm births were more frequent among women who were active smokers (19.2%) compared to nonsmokers (9.1%, Table 1.4). There was no difference in preterm delivery by maternal age, parity, weight, physical activity, or home ETS exposure (Table 1.3).

Table 1.2: Counts of measures and biological samples at each study encounter.

PRENATAL MATERNAL FOLLOW-UP			
Measures	**Timing**	**Count**	%
Questionnaires			
Baseline Questionnaire	Enrollment	2,478	100
Food Frequency	2nd Trimester	2,161	87
Stress Questionnaire	2nd Trimester	2,080	84
Fish, Vitamin, Exercise	3rd Trimester	2,121	86
Bio-Samples			
Mother Blood Spot	2nd Trimester	1,250	50
	3rd Trimester	2,060	83
Mother Venous Blood	24-28 weeks	1,465	59
Mother Hair	3rd Trimester	1,826	74
Mother Urine	2nd Trimester	1,222	49
	3rd Trimester	1,680	68
Mother Blood Lead	3rd Trimester	1,577	64
Mother Saliva	24-28 weeks	1,006	41

Table 1.3. Maternal baseline characteristics by nationality.

	TOTAL		Kuwaiti		Non-Kuwaiti		
	N	%	N	%	N	%	p-value
	2478		739		1739		
MATERNAL CHARACTERISTICS							
Ethnicity							<0.001
Arab	2275	92	679	94	1596	92	
Iranian	56	2	45	6	11	1	
Asian	121	5	0	0	121	7	
Other	11	0.4	0	0	11	1	
Age (years)							
<25	578	24	180	25	398	23	0.11
25 to 30	930	38	261	36	669	39	
30 to 35	641	26	178	25	463	27	
35+	315	13	108	15	207	12	
Parity							
0	819	34	219	31	600	35	<0.001
1 to 2	1155	48	305	44	850	50	
3 or more	437	18	173	25	264	15	
Monthly Income in KD							
<400	676	28	13	2	663	39	<0.001
400-800	791	33	77	11	714	42	
800-1600	547	23	279	41	268	16	
1600<	371	16	319	46	52	3	
Education							
HS or less	735	30	144	20	591	34	<0.001
2 Yr Diploma	384	16	198	27	186	11	
4 Yr College+	1341	55	381	53	960	55	
MATERNAL RISK FACTORS							
Pre-Pregnancy BMI Group							
Normal or less	1099	45	346	49	753	44	0.06
Overweight	802	33	211	30	591	34	
Obese	526	22	153	22	373	22	
Smoking during Pregnancy							
No	2375	98	691	98	1684	98	0.90
Yes	53	2	15	2	38	2	
Home Environmental Tobacco smoke							
No	1674	70	494	72	1180	69	0.14
Yes	717	30	190	28	527	31	
Physical Activity							
None	1562	74	407	71	1155	75	0.056
Mild	300	14	86	15	214	14	
Mod/Vigorous	254	12	84	15	170	11	

Table 1.4. Proportion of infants with preterm delivery, Small for Gestational Age (SGA), Large for Gestational Age (LGA), and macrosomia by maternal characteristics and risk factors.

	Preterm			SGA			LGA		Macrosomia		
	N	%	p-value	N	%	p-value	%	p-value	N	%	p-value
Total	2115	9.3		2035	7.4		23.0		2140	6.1	
Nationality											
Kuwaiti	597	12.6	0.001	585	7.7	0.77	19.2	0.01	636	3.5	0.0008
Non-Kuwaiti	1518	8.0		1450	7.3		24.5		1504	7.3	
Age group											
18-24	486	8.6	0.82	464	8.4	0.16	16.2	<0.001	472	5.3	0.13
25-29	809	9.0		787	8.4		23.0		807	5.3	
30-34	550	9.8		528	5.3		25.6		538	6.1	
35+	268	10.5		256	7.0		29.7		262	9.2	
Parity											
0	709	8.9	0.66	685	8.2	0.36	16.6	<0.001	694	3.8	0.002
1+	1403	9.5		1349	7.0		26.2		1270	7.2	
Pre-Pregnancy BMI Group											
Underweight	30	10.0	0.45	31	6.5	0.18	6.5	<0.0001	32	0.0	0.0002
Normal	909	8.3		876	8.6		18.4		893	3.7	
Overweight	697	10.6		671	6.9		26.4		686	7.4	
Obese	453	9.5		434	5.3		28.1		441	9.1	
Smoking during Pregnancy											
No	2066	9.1	0.02	1990	7.4	0.70	22.9	0.55	2022	6.1	0.63
Yes	47	19.2		45	8.9		26.7		46	4.4	
Home Environmental Tobacco Smoke											
No	1477	9.3	0.86	1427	7.2	0.50	22.8	0.77	1447	5.9	0.63
Yes	626	6.8		599	8.0		23.4		607	6.4	
Physical Activity											
None	1452	8.8	0.47	1406	7.2	0.87	22.4	0.56	1428	6.2	0.96
Mild	281	6.8		273	8.1		23.8		277	5.8	
Mod/Vigorous	232	9.5		228	7.0		25.4		233	6.0	

Birthweight: Small for gestational age (SGA) was reported for 7.4% (95% CI:6.4% - 8.6%) of births. There was no difference in the frequency of SGA among Kuwaiti and non-Kuwaiti mothers, by age, or parity (Table1. 4). Overweight and obese women had lower frequencies of SGA babies.

Large for their gestational age (LGA) was reported in 23.0% (95% CI: 21.1 - 24.8%) of births and macrosomia in 6.1% (95% CI: 5.1% - 7.1%, Table 4). LGA and Macrosomia were more frequent among non-Kuwaitis, mothers who were older, who were overweight or obese prior to pregnancy, and for second and later (parity 1+) births (Table 1.4).

DISCUSSION

The TRACER study successfully recruited a large number of pregnant women into a prospective pregnancy birth cohort in Kuwait. TRACER is one of the largest pregnancy birth cohorts in the region and the only one, to our knowledge, in the Arabian Gulf countries. While more Kuwaitis were approached than non-Kuwaitis, we had higher recruitment among non-Kuwaitis leading to final distribution of nationalities similar to the Kuwaiti general population. Long-term retention until delivery was fairly good among the non-Kuwaitis and Kuwaitis (76% and 89%, respectively). The reasons most commonly stated for dropping from the study were lack of interest, lack of time, or husband refusal. Dropping out of the study is not unexpected as the Kuwait population is not accustomed to prospective research studies. However, the fairly high retention rates suggest that this is changing and the value of local scientific studies is being appreciated. The value of this study will grow as follow-up of these children continues.

Comparing the frequency of birth outcomes in this sample to regional and international data is useful in understanding the comparability of the TRACER sample to other populations and cohorts. Stillbirth rate was 6 per 1000 births, which is higher than but consistent with the 2009 estimated rate of 5 per 1000 births for Kuwait.[35] The 9.3% proportion of preterm birth from our study was slightly lower than the 9.7% among singleton births in the USA in 2013.[36] The 7.4% proportion of SGA was similar to the 6.3% among singleton births in the USA in 2013.[36] However, LGA was found in about 23% of infants which is higher than the expected 10% using WHO standards, or rates among whites in the USA (11.7%) in the late 1990's.[37]

We found higher frequencies of preterm birth among Kuwaiti women, and higher frequencies of macrosomia and LGA among non-Kuwaiti women. Kuwaiti women had a higher socioeconomic status and more children than non-Kuwaiti women. The non-Kuwaiti women are predominantly from other Arab and Asian countries. The maternal age distribution was similar for Kuwaiti and non-Kuwaiti women. The frequency of pre-pregnancy obesity was also similar. Maternal age, especially being >35 years, was associated with increased adverse pregnancy outcomes, such as macrosomia, which is consistent with literature.[38] We found that pre-pregnancy overweight/obesity was associated with increased risk of high birthweight.

The majority of women were recruited in the second trimester (48%) and a significant proportion (35%) in the third. This limits our ability to evaluate pregnancy outcomes such as miscarriage and stillbirth, which may have occurred before a woman enrolled. For outcomes assessed later in pregnancy or post-delivery, such as preterm birth and birthweight, this is less of a concern. Compared to Kuwaiti women, non-Kuwaitis were less likely to be recruited earlier in the pregnancy, but when we compared some of the baseline characteristics by trimester of recruitment we did not find any differences. Another concern is the response rate of only 23% overall, and only 13% among Kuwaitis. This response rate is lower than other birth cohort studies such as 45% in the Norwegian Mother and Child (MoBa)[39] and 64% in the VIVA cohorts.[40] The low response rate in our study may affect the external generalizability of our results, but is less likely to affect the internal validity of our future analyses if confounders are adjusted for adequately.

Strengths of the TRACER study include the relatively large sample size for a prospective birth, and the unique ability to evaluate environmental health questions and pregnancy, as well as child health outcomes, using urine, blood, saliva, and hair samples collected at multiple time points across pregnancy in the understudied population of the Gulf countries. We have collected detailed information about birth weight and pregnancy conditions within 3 months of delivery. The interviewer-administered questionnaire provides consistency and clarity in the administration and understanding of questions by our participants, unlike self-administered questionnaires. The TRACER design and measurements are consistent with that of many other pregnancy cohorts in the USA and European populations. To the extent that common design elements facilitate comparisons across and within these studies, the power to detect environmental risk factors will be significantly improved.

In conclusion, our study provides baseline maternal characteristics for a prospective pregnancy birth cohort that has the potential for a unique contribution to the environmental risk factors of maternal and child health outcomes. The present findings suggest that LGA and macrosomia are relatively common adverse pregnancy outcomes, with implications for future maternal and child risk of chronic diseases, including type 2 diabetes and cardiovascular disease. The prospective collection of maternal behaviors and biospecimens during pregnancy in this population sample allows TRACER to evaluate environmental factors unique to this region of the world that could be contributing to the increasing prevalence of chronic diseases in Kuwait and other Arab countries. As such, TRACER can fill a major research gap and has the potential to provide needed information about pregnancy and early life environmental risk factors of chronic diseases.

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References

1. Kelishadi R. Childhood overweight, obesity, and the metabolic syndrome in developing countries. *Epidemiologic Reviews*. 2007; 29:62-76.

2. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015; 385:117-171.

3. Brown DW, Mokdad AH, Walke H, As'ad M, Al-Nsour M, Zindah M, et al. Projected burden of chronic, noncommunicable diseases in Jordan. *Preventing Chronic Disease*. 2009; 6:A78.

4. Mokdad AH, Jaber S, Aziz MI, AlBuhairan F, AlGhaithi A, AlHamad NM, et al. The state of health in the Arab world, 1990-2010: an analysis of the burden of diseases, injuries, and risk factors. *Lancet*. 2014; 383:309-320.

5. Rahim HF, Sibai A, Khader Y, Hwalla N, Fadhil I, Alsiyabi H, et al. Non-communicable diseases in the Arab world. *Lancet*. 2014; 383:356-367.

6. Mehio Sibai A, Nasreddine L, Mokdad AH, Adra N, Tabet M, Hwalla N. Nutrition transition and cardiovascular disease risk factors in Middle East and North Africa countries: reviewing the evidence. *Ann Nutr Metab*. 2010; 57:193-203.

7. Akl EA, Gunukula SK, Aleem S, Obeid R, Jaoude PA, Honeine R, et al. The prevalence of waterpipe tobacco smoking among the general and specific populations: a systematic review. *BMC Public Health*. 2011; 11:244.

8. Barker DJ. The origins of the developmental origins theory. *Journal of Internal Medicine*. 2007; 261:412-417.

9. Kuh D, Ben-Shlomo Y. *A Life Course Approach to Chronic Disease Epidemiology: Tracing the Origins of Ill-Health from Early to Adult Life. 2nd Edition*. 2 ed. London: Oxford University Press; 2004.

10. Muhlhausler B, Smith SR. Early-life origins of metabolic dysfunction: role of the adipocyte. *Trends in Endocrinology and Metabolism*. 2009; 20:51-57.

11. Solomons NW. Developmental origins of health and disease: concepts, caveats, and consequences for public health nutrition. *Nutrition Reviews*. 2009; 67 Suppl 1:S12-16.

12. Vrijlandt EJ, Gerritsen J. The womb and lung function later in life. *European Respiratory Journal*. 2004; 24:722-723.

13. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine*. 2008; 359:61-73.

14. Wright RJ. Moving towards making social toxins mainstream in children's environmental health. *Current Opinion in Pediatrics*. 2009; 21:222-229.

15. Wigle DT, Arbuckle TE, Walker M, Wade MG, Liu S, Krewski D. Environmental hazards: evidence for effects on child health. *Journal of Toxicology and Environmental Health Part B, Critical Reviews*. 2007; 10:3-39.

16. el-Sonbaty MR, Abdul-Ghaffar NU. Vitamin D deficiency in veiled Kuwaiti women. *European Journal of Clinical Nutrition*. 1996; 50:315-318.

17. Molla AM, Al Badawi M, Hammoud MS, Shukkur M, Thalib L, Eliwa MS. Vitamin D status of mothers and their neonates in Kuwait. *Pediatr Int*. 2005; 47:649-652.

18. Evans JS, Vorhees DJ, Hussain A, Al-Zenki S, Cooper MA. Fish Consumption, Mercury Intake, and the Associated Risks to the Kuwaiti Population. *Human and Ecological Risk Assessment: An International Journal*. 2012; 18:1014-1035.

19. Guo Y, Alomirah H, Cho HS, Minh TB, Mohd MA, Nakata H, et al. Occurrence of phthalate metabolites in human urine from several Asian countries. *Environmental Science and Technolology*. 2011; 45:3138-3144.

20. Zhang Z, Alomirah H, Cho HS, Li YF, Liao C, Minh TB, et al. Urinary bisphenol A concentrations and their implications for human exposure in several Asian countries. *Environ Sci Technol*. 2011; 45:7044-7050.

21. Saeed T, Sawaya WN, Ahmad N, Rajagopal S, Al-Omair A, Al-Awadhi F. Chlorinated pesticide residues in the total diet of Kuwait. *Food Control*. 2001; 12:91-98.

22. Saeed T, Sawaya WN, Ahmad N, Rajagopal S, Dashti B, al-Awadhi S. Assessment of the levels of chlorinated pesticides in breast milk in Kuwait. *Food Additives and Contaminants*. 2000; 17:1013-1018.

23. Sawaya WN, et al. Dietary intake of organophosphate pesticides in Kuwait. *Food Chemistry*. 2000; 69:331-338.

24. El-Nasser S, El Aziz Fakher O. Report on Results of the Global Youth Tobacco Survey (GYTS) 2009. Kuwait 2009: WHO Regional Office for the Eastern Mediterranean2010.

25. Al-Mousawi MS, Lovel H, Behbehani N, Arifhodzic N, Woodcock A, Custovic A. Asthma and sensitization in a community with low indoor allergen levels and low pet-keeping frequency. *Journal of Allergy and Clinical Immunology*. 2004; 114:1389-1394.

26. Brown KW, Bouhamra W, Lamoureux DP, Evans JS, Koutrakis P. Characterization of particulate matter for three sites in Kuwait. *Journal of the Air & Waste Management Association*. 2008; 58:994-1003.

27. Wright RJ, et al. War-related stressors are associated with asthma risk among older Kuwaitis following the 1990 Iraqi invasion and occupation. *Journal of Epidemiology and Community Health*. 2009; In Press.

28. Kozisek F. Health Risks from Drinking Demineralized Water. *Rolling Revision of the WHO Guielines for Drinking Water Quality by World Health Organization*. 2004.

29. Vrijheid M, Casas M, Bergstrom A, Carmichael A, Cordier S, Eggesbo M, et al. European birth cohorts for environmental health research. *Environ Health Perspect*. 2012; 120:29-37.

30. Bousquet J, Gern JE, Martinez FD, Anto JM, Johnson CC, Holt PG, et al. Birth cohorts in asthma and allergic diseases: report of a NIAID/NHLBI/MeDALL joint workshop. *Journal of Allergy and Clinical Immunology*. 2014; 133:1535-1546.

31. Sweileh WM, Zyoud SH, Al-Jabi SW, Sawalha AF. Public, environmental, and occupational health research activity in Arab countries: bibliometric, citation, and collaboration analysis. *Archives of Public Health*. 2015; 73:1.

32. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA. Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. *Health Psychology*. 1999; 18:333-345.

33. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. *American Journal of Obstetrics and Gynecology*. 1993; 169:858-865.

34. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry*. 1987; 150:782-786.

35. Cousens S, Blencowe H, Stanton C, Chou D, Ahmed S, Steinhardt L, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet*. 2011; 377:1319-1330.

36. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. *National Vital Statistics Reports*. 2015; 64:1-65.

37. Ananth CV, Wen SW. Trends in fetal growth among singleton gestations in the United States and Canada, 1985 through 1998. *Semin Perinatol*. 2002; 26:260-267.

38. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ*. 2000; 320:1708-1712.

39. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2006; 35:1146-1150.

40. Gillman MW, Rich-Edwards JW, Rifas-Shiman SL, Lieberman ES, Kleinman KP, Lipshultz SE. Maternal age and other predictors of newborn blood pressure. *J Pediatr*. 2004; 144:240-245.

Chapter 3: Risk Factors Associated with Gestational Diabetes Among Women in Kuwait: the TRACER Study

Risk Factors Associated with Gestational Diabetes Among Women in Kuwait: the TRACER Study

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ABSTRACT:

Background: With rapid westernization, type 2 diabetes has increased markedly in Kuwait and other Gulf Council Countries (GCC). Gestational diabetes (GDM) is a potent risk factor for type 2 diabetes. While the associations between maternal lifestyle factors and GDM have been studied in Western populations, little is known about these associations in rapidly westernizing Middle Eastern populations.

Methods: Among women in a Kuwait-based pregnancy cohort , we examined the risk of GDM for four potentially modifiable lifestyle risk factors -- pre-pregnancy obesity, tobacco smoking, physical inactivity, and excessive gestational weight gain. Maternal characteristics and self-reported GDM were collected by questionnaires at pre-natal clinical/home visits and via post-natal home visits or phone interviews. We used multivariable logistic regression to calculate odds ratios and 95% confidence intervals, and adjusted for potential confounders to evaluate the associations between risk factors and GDM.

Results: In our sample of 1627 women, 8.1% reported a diagnosis of GDM. Pre-pregnancy obesity was associated with a 1.75 relative odds of GDM (95% CI:1.01 - 3.04). We found non-significant increased risk of GDM among the 41% of women with excessive reported weight gain (OR =1.43, 95% CI: 0.82 - 2.49), and the 75% of women with reported physical inactivity (OR= 1.42, 95% CI 0.81 - 2.50). There was suggestive evidence of a protective association with higher education. In primiparous women, GDM associations with excessive gestational weight gain were stronger (OR= 2.51, 95% CI: 0.94 – 6.72) than among parous women (OR= 1.03, 95% CI: 0.51-2.09) consistent with the potential for prior pregnancy experience to alter behavior. Among the primiparous women who were overweight or obese before pregnancy, we found larger but very imprecise odds ratios for the association of physical inactivity with GDM (OR= 4.08, 95% CI: 0.53 – 31.47).

Conclusion: Pre-pregnancy obesity was significantly associated with GDM in this sample of women. While excessive gestational weight gain and physical inactivity were not significantly

associated with GDM in this sample, the positive associations suggest attention should be given to these modifiable risk behaviors in Kuwait.

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INTRODUCTION:

Gestational diabetes mellitus (GDM) affects approximately 7% of pregnant women worldwide. [1] GDM is associated with a higher risk of subsequent type 2 diabetes (T2DM) and cardiovascular disease for mothers, as well as obesity and adverse cardio-metabolic conditions for children that result from GDM-complicated pregnancies. [2, 3] GDM is associated with pregnancy complications such as cesarean delivery and preterm delivery. [4] Pre-pregnancy maternal characteristics, and maternal lifestyle and behaviors during pregnancy may be associated with a higher risk of GDM. For instance, pre-pregnancy obesity and overweight have been reported to be a risk for GDM.[5],[6] Furthermore, women with lower levels of physical activity are more likely to have GDM.[7]

These potential maternal risk factors for GDM are growing in Kuwait. The Kuwaiti Ministry of Health's 2006 National Non-Communicable Disease Survey reported that 77% of Kuwaiti women were either overweight or obese.[8] Only 22% of women reported regular to moderate intensity physical activity, and only 8% reported vigorous physical activity. If these findings hold true for women of reproductive age in Kuwait, then a large proportion of pregnant women may be at risk for GDM and other adverse conditions during pregnancy.

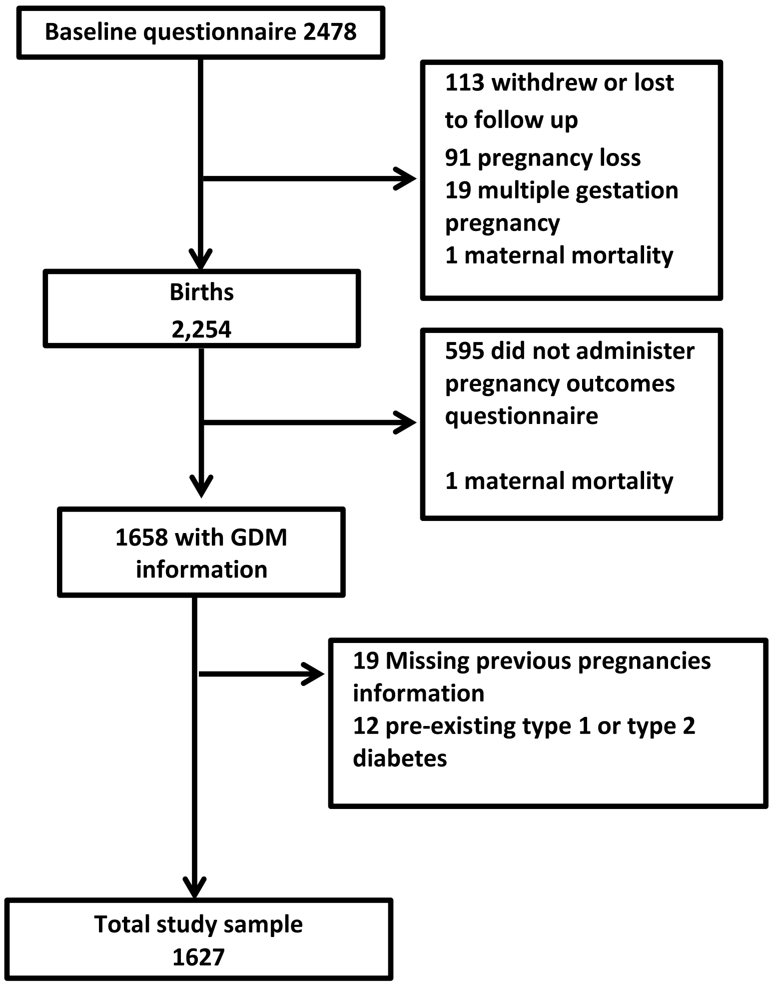
We examined the associations between GDM and maternal characteristics pre-pregnancy (i.e. age, nationality, income, education, parity, and obesity) and behaviors during pregnancy (i.e. gestational weight gain, physical activity, and smoking) among women living in Kuwait. We analyzed data from the TRansgenerational Assessment of Children's Environmental Risk (TRACER), a longitudinal prospective birth cohort study designed to evaluate lifestyle, behavioral, and environmental risk factors of adverse reproductive and child health outcomes in Kuwait.

METHODS:

Study Population: The TRACER study has been described previously [9]. Briefly, the study was open to all pregnant female Kuwaiti residents aged 18 to 45 years old, who were fluent in Arabic or English, and who were attending one of the study antenatal clinics between 2012 and 2015. The study clinics included six primary public health clinics, one in each Kuwaiti governorate (South Hawalli Clinic, West Farwaniya Clinic, Subah Al Naser Clinic, Jahraa Clinic, Al-Sager Clinic, and Al-Qurain Health Clinic) ,and three private clinics/hospitals (Al-Hakim Clinic, New Mowasat Hospital, and Royale Hayat Hospital). We obtained permission to recruit from the health center administrator and the obstetricians at each health center. During the antenatal visits, obstetricians and clinic staff referred pregnant women to the study's field investigator who provided patients with a brochure describing the study and asked if they were interested in participating. The trained field staff explained the study details to women who were interested and obtained written informed consent from them and their husbands. Participants were recruited across pregnancy with 30%, 48%, and 21%, respectively, in their first, second and third trimesters. After consent, participants were followed periodically for the remainder of their pregnancy with up to 4 assessments (for questionnaire and biospecimen collection) scheduled during prenatal clinic or study home visits, depending on the mother's availability. Over the course of these follow up assessments, 2,478 women completed baseline questionnaires. From this group, women were excluded from further study if they were found to have a multiple gestation (e.g. twins or triplets, n=19), experienced pregnancy loss (n=91) or maternal mortality (n=1). An additional 113 withdrew or were lost to follow up prior to birth leaving a total of 2,254 followed through birth. For this analysis, we selected those women followed through birth with information regarding past or current GDM diagnosis (n=1658), excluding one case of postnatal maternal mortality. We excluded those with a history of type 1 or type2 diabetes (n=12) and those missing previous pregnancy information (n-19), leaving a total of 1627 for these analyses (Figure 2.1).

The study was reviewed, approved, and monitored by the IRBs at the Dasman Diabetes Institute and the Harvard T.H. Chan School of Public Health.

Figure 2.1. Flow chart of study sample selection.



Baseline questionnaire: Participating mothers completed an interviewer-administered baseline questionnaire with the majority (58%) completed within one month of recruitment. The questionnaire collected information on age, nationality, pre-pregnancy weight, height, number of live children (used to approximate parity), number of previous pregnancies, date of last menstrual period (used to calculate weeks of gestation), education level (high school or less, 2-year diploma, and 4-year college or higher), household total monthly income in Kuwaiti Dinars (less than 400 KD, 400-800 KD, 801-1600 KD, and more than 1600 KD)[ii] , pre-pregnancy and pregnancy smoking habits and type of tobacco smoking (cigarettes or water pipe, i.e., hookah), and medical/reproductive history ("*ever*" diagnosed with type 1 and 2 diabetes, gestational diabetes, or chronic hypertension). We calculated pre-pregnancy body mass index (BMI) as reported pre-pregnancy weight (kg) divided by height (m) squared. Pre-pregnancy overweight was defined as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2.[10]

Follow up data collection: In follow-up clinic visits (primarily during second or third trimester, although some after birth), we administered a physical activity questionnaire and semi-quantitative food frequency questionnaire adapted and validated for the region[11]. The physical activity questionnaire collected data on frequency and duration of physical activity (minutes of physical activity/day), and specific types of exercises (slow to moderate walking, brisk walking, jogging, running, aerobic exercise, sports, lifting weights). The questionnaire also included questions about participants' jobs; if they reported holding a physically demanding job, they were asked to report the intensity and duration of such work days and hours per week.

Postnatal data collection: In a postnatal phone interview, we collected information on key pregnancy outcomes including recall of final pre-delivery weight and diagnosis and treatment of

[ii] Kuwaiti Dinar (KD) exchanges for 3.3 Dollars as of 2016

GDM. Note that GDM was not a primary outcome of the TRACER birth cohort study, and the pregnancy outcomes questionnaire was introduced later in the study. Thus, collection of study pregnancy outcome data extended over several years of follow-up (58% answered in the first year, 34% in the second year, and 8% in the third year following birth).

Gestational weight gain (GWG) was calculated as the reported last pre-delivery weight minus reported pre-pregnancy weight. We classified the GWG over the pregnancy as inadequate, normal, or excessive according to the Institutes of Medicine (IOM) guidelines based on the gestational age at delivery and pre-pregnancy BMI [12]. Participants whose GWG exceeded the upper limit IOM guidelines were classified as "excessive" GWG, and participants whose GWG was below the lower IOM recommendation limit were classified as "inadequate" GWG.

Gestational Diabetes: We defined GDM as maternal reported physician diagnosed GDM and maternal report of a prescription for a diet, dietitian referral, or medication for diabetes. Of note, 97% of women reporting a GDM diagnosis also reported a prescription for treatment by diet or medication.

In Kuwait, pregnant women typically receive an Oral Glucose Tolerance Test (OGTT) between 24 and 28 weeks gestation. In public clinics the screening for GDM follows the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria.[13] Some private clinics use alternative criteria. Patients are given the clinical diagnoses, but the quantitative OGTT screening results usually are not given to the patient and are not uniformly recorded in the patient records.

To validate the self-report of GDM, we extracted OGTT results from medical records for a sub-sample of 281 study women who consented to review of their medical records. After excluding those with a history of type 1 or 2 diabetes (n=12), we were able to retrieve OGTT results from medical records for 19 women with self-reported GDM and 131 who reported no GDM in this pregnancy. For the balance, either the medical record was not available or there was no information regarding OGTT testing. All received a 75-gram glucose challenge and evaluation of blood glucose while fasting pre-challenge and 2-hours post-challenge. Among women who reported GDM, 13 met the IADPSG criteria for GDM with fasting glucose of >=5.1 mmol/L or 2-hour of >=8.5 mmol/L (68 % positive predictive value). Among 131 women who reported no GDM, 118 had OGTT results below the criteria for GDM (90% negative predictive value). In a post-hoc analysis, we noted that two women had 2-hour glucose >=8.3 mmol/L. With relaxed OGTT criteria for these 2 women and assuming their physicians had also used other information in making their diagnosis, 15 of 19 reported GDM cases would be classified as GDM (positive predictive value 79%) while 116 of 131 reported non-cases would be classified as non-GDM (negative predictive value 89%).

Statistical analysis: We examined the distribution of maternal characteristics in the sample. For continuous variables with symmetric distributions, we calculated the mean plus/minus standard deviation (±SD). For categorical variables we calculated the percent (%) reported for each category. We tabulated the frequency of GDM by baseline demographic characteristics (age, nationality, parity, income, and education) and history of GDM in a prior pregnancy. We then calculated the frequency of GDM by categories of pre-pregnancy weight, gestational weight gain, physical activity, and smoking. To validate the postnatal maternal reported final pregnancy weight we examined medical records for a subsample of 96 women who had pregnancy weight measurements between 37 weeks and delivery. There was a strong correlation between recalled final pregnancy weight and the weight recorded in the medical record (R^2=96%) with a root mean square error of 2.12.

We examined the association of pre-pregnancy factors (age, nationality, income, education, parity, pre-pregnancy BMI, and prior GDM) and pregnancy factors (gestational weight gain, physical inactivity, and tobacco smoking) with GDM by calculating the odds ratio (OR) and associated 95% confidence intervals (CIs) using logistic regression models. We did not include diet data in our analyses because it was generally ascertained after GDM would have been diagnosed. We compared women with excessive or inadequate total pregnancy GWG to those with normal GWG. We evaluated the risk of physical inactivity by comparing women who did not report any workplace or recreational physical activity to those with any physical activity (mild, moderate, or vigorous). We compared active tobacco smokers (cigarettes or hookah) to non-smokers during pregnancy.

To investigate potential effect measure modifications we ran interaction models for the risk factor associations stratified by parity (0 vs 1 or more). We then assessed associations in primiparous women stratified by pre-pregnancy overweight/obesity (BMI ≥25 kg/m^2 vs <25kg/m^2). We report the statistical significance of the interaction, and odds ratios and 95% CI for each level of the modifier obtained from a single model using linear combinations of the independent variable of interest and the effect modifier variable.

We imputed missing covariates in all multivariable logistic regression models using a Markov Chain Monte Carlo (MCMC) multiple imputation for a total of 50 datasets. We report the pooled odds ratio and 95% confidence interval estimates for all imputed datasets for all the above models using the MIANALYZE procedure in SAS. Statistical significance was set at 0.05 and all p-values reported were two-sided. The Statistical Analysis Software SAS 9.4 (SAS Inc., Cary, NC) was used for all analyses.

RESULTS

Study population: The 1627 women in this analysis, were similar to those excluded (n=851) in age, education, and prevalence of pre-pregnancy overweight and obesity (Supplementary Table 2.1). However, excluded women were more likely to be Kuwaitis (33% vs.28%), to be having their first child (39% vs 32%), and to be physically active (31% vs 25%).

The majority of the sample were non-Kuwaiti (72%) with most of the non-Kuwaiti's from other Arab countries. In addition, most of our participants were younger than 30 years old (61%), and had a total household income of less than or equal to 800KDs (61%). The prevalence of pre-pregnancy obesity and overweight (55%), inappropriate (excessive or inadequate) total GWG (68%), and lack of physical activity (75%) were high in our study sample (Table 2.1). Active smoking during pregnancy was rare (2%).

Table 2.1 Distribution of gestational diabetes by pre-pregnancy and pregnancy risk factors for TRACER participants (N=1627)

	Total		**No GDM**		**GDM**		χ^2 p-value
	N	%	N	%	N	%	
Nationality							0.82
Non-Kuwaiti	1166	71.7	1071	71.6	95	72.5	
Kuwaiti	461	28.3	425	28.4	36	27.5	
Age (Years)							0.22
<25	376	23.1	349	23.3	27	20.6	
25 to 29	617	37.9	575	38.4	42	32.1	
30 to 35	425	26.1	385	25.7	40	30.5	
35+	209	12.8	187	12.5	22	16.8	
Monthly income KD							0.74
<400KD	431	27.3	395	27.3	36	28.1	
400-800KD	535	33.9	490	33.8	45	35.2	
801-1600KD	380	24.1	354	24.5	26	20.3	
1601+	230	14.6	209	14.4	21	16.4	
Missing	51		48		3		
Education							0.08
HS or less	495	30.4	450	30.1	45	34.4	
2 Yr Diploma	255	15.7	228	15.2	27	20.6	
4 Yr College+	877	53.9	818	54.7	59	45.0	
Parity							0.06
0	515	31.7	483	32.3	32	24.4	
1+	1112	68.3	1013	67.7	99	75.6	
Pre-Pregnancy BMI							<0.0001
Normal or less	731	45.5	687	46.5	44	34.1	
Overweight	530	33.0	494	33.4	36	27.9	
Obese	347	21.6	298	20.2	49	38.0	
missing	19		17		2		
Past GDM							
No	1535	94.3	1465	97.9	70	53.4	<0.0001
Yes	92	5.7	31	2.1	61	46.6	
Gestational weight gain*							0.69
Below	376	27.0	345	26.9	31	27.9	
Within	452	32.5	420	32.8	32	28.8	
Above	564	40.5	516	40.3	48	43.2	
Missing	235		215		20		
Physical Activity							0.03
Any	389	24.6	368	25.3	21	16.5	
None	1190	75.4	1084	74.7	106	83.5	
Missing	48		44		4		
Cigarette or hookah smoker							0.67
No	1594	98.0	1465	97.9	129	98.5	
Yes	33	2.0	31	2.1	2	1.5	

GDM: Gestational Diabetes Mellitus
*Gestational weight gain classification is according to the Institute of Medicine recommendations.

The average gestational age at baseline questionnaire administration was 28.4 ±5.0 weeks. The median time between birth and administration of the pregnancy outcomes questionnaire was 9.8 months (IQR: 2.6, 17.5).

Pre-pregnancy risk factors for GDM: Overall, 8.1% (95% CI: 6.7 – 9.4) of the women in this sample reported incident GDM. There was a higher prevalence of GDM among non-Kuwaitis (8.2%) than Kuwaitis (7.8%), and we found borderline statistically significant decreased odds of GDM among Kuwaiti women after adjustment for multiple factors (Table 2.2). In adjusted models, the odds of GDM were lower, but not statically significant, among parous compared to primiparous women, and those with college or more education (Table 2.2). There was no association with income. Pre-pregnancy obesity was associated with increased risk of GDM, adjusted OR= 1.75 (95% CI: 1.01 - 3.04).

Pregnancy factors risk for GDM: Excessive total gestational weight gain was positively associated with increased risk of GDM (OR=1.43, 95% CI: 0.82 - 2.49, Table 2). Women who were physically inactive also had a higher risk of GDM (OR=1.42, 95% CI: 0.81 - 2.50, Table 2). Active smoking was not associated with adverse odds of GDM (Table 2.2) but the small number of women who reported smoking makes these results very uncertain.

In analyses of the 515 primiparous women (Table 2.3) we found a stronger association of excessive gestational weight gain with GDM (OR=2.51, 95% CI: 0.94 - 6.72) than was observed in the overall population (Tables 2.2 and 2.3). Among the 1112 multiparous women, physical inactivity was associated with increased risk of GDM (OR= 1.76, 95% CI: 0.86 – 3.60) (Table 2.3).

Results of sensitivity analyses of primiparous women stratified by pre-pregnancy BMI (Table 2.4) showed suggestive evidence that women who are overweight or obese prior to pregnancy may have greater susceptibility to some risk factors than women who were normal weight prior to pregnancy. Although confidence limits were wide (and included the null) primiparous women who were overweight or obese prior to pregnancy had increased odds of GDM with physical

Table 2.2 Unadjusted and adjusted logistic regression models of gestational diabetes as a function of potential pre-pregnancy and pregnancy risk factors among 1627 participants in TRACER

			Unadjusted				Adjusted			
	Count	% GDM	OR	(95%	CI)	p-value	OR	(95%	CI)	p-value
Nationality										
Non-Kuwaiti	1166	8.2	1.00				1.00			
Kuwaiti	461	7.8	0.96	0.64	1.42	0.82	0.55	0.27	1.11	0.10
Age (Years)										
<25	376	7.2	1.00				1.00			
25 to 29	617	6.8	0.94	0.57	1.56	0.82	0.85	0.46	1.57	0.61
30 to 35	425	9.4	1.34	0.81	2.24	0.26	0.82	0.41	1.62	0.56
35+	209	10.5	1.52	0.84	2.74	0.16	1.16	0.52	2.58	0.72
Monthly income KD										
<400KD	431	8.4	1.00				1.00			
400-800KD	535	8.4	1.01	0.64	1.59	0.97	1.17	0.67	2.05	0.59
801-1600KD	380	6.8	0.81	0.48	1.36	0.42	0.99	0.49	2.02	0.98
1601+	230	9.1	1.10	0.63	1.94	0.73	1.41	0.54	3.70	0.48
Education										
HS or less	495	9.1	1.00				1.00			
2 Yr Diploma	255	10.6	1.18	0.72	1.96	0.51	1.17	0.62	2.21	0.63
4 Yr College+	877	6.7	0.72	0.48	1.08	0.11	0.62	0.37	1.05	0.07
Parity										
0	515	6.2	1.00				1.00			
1+	1112	8.9	1.48	0.98	2.23	0.07	0.54	0.31	0.94	0.03
Pre-Pregnancy BMI										
Normal or less	731	6.0	1.00				1.00			
Overweight	530	6.8	1.14	0.72	1.79	0.58	0.85	0.49	1.47	0.57
Obese	347	14.1	2.57	1.67	3.94	<.0001	1.75	1.01	3.04	0.05
Past GDM										
No	1535	4.6	1.00							
Yes	92	66.3	41.18	25.12	67.51	<.0001	56.64	31.74	101.06	<.0001
Gestational weight gain*										
Below	376	8.2	1.18	0.71	1.97	0.53	1.26	0.67	2.38	0.48
Within	452	7.1	1.00				1.00			
Exceed	564	8.5	1.22	0.77	1.95	0.40	1.43	0.82	2.49	0.21
Physical activity										
Any	389	5.4	1.00				1.00			
None	1190	8.9	1.71	1.06	2.78	0.03	1.42	0.81	2.50	0.22
Cigarette or hookah smoker										
No	1594	8.1	1.00				1.00			
Yes	33	6.1	0.73	0.17	3.10	0.68	0.88	0.19	4.11	0.87

The models are simultaneously adjusted for all the variables in the table
For adjusted models, missing covariates were imputed using Markov Chain Monte Carlo multiple imputation (50 sets).
*Gestational weight gain classification is according to the Institute of Medicine recommendations.

Table 2.3. Multivariable logistic regression models of gestational diabetes as a function of potential risk factors stratified by parity

	Parity 0 (n=515)						Parity 1 + (n=1112)						
	Count	**% GDM**	**OR**	**(95%**	**CI)**	**p-value**	**Count**	**% GDM**	**OR**	**(95%**	**CI)**	**p-value**	p-value*
Nationality													
Non-Kuwaiti	387	7.2	1.00				779	8.6	1.00				
Kuwaiti	128	3.1	0.42	0.11	1.59	0.20	333	9.6	0.54	0.23	1.26	0.15	0.77
Age (Years)													
<25	241	6.6	1.00				135	8.2	1.00				
25 to 29	192	6.3	1.06	0.46	2.45	0.89	425	7.1	0.78	0.31	1.98	0.60	0.63
30 to 35	64	4.7	0.55	0.14	2.11	0.38	361	10.3	0.90	0.35	2.30	0.82	0.56
35+	18	5.6	1.11	0.12	9.76	0.93	191	11.0	1.24	0.44	3.51	0.69	0.93
Monthly income (KD)													
<400KD	175	6.9	1.00				256	9.4	1.00				
400-800KD	167	8.4	1.61	0.68	3.83	0.28	368	8.4	0.94	0.44	1.98	0.87	0.35
801-1600KD	105	5.7	1.25	0.36	4.28	0.72	275	7.3	0.85	0.35	2.06	0.72	0.62
1601+	51	0.0	--	--	--	--	179	11.7	1.70	0.54	5.37	0.36	0.95
Education													
HS or less	131	9.2					364	9.1					
2 Yr Diploma	79	7.6	1.17	0.39	3.53	0.78	176	11.9	1.30	0.59	2.87	0.51	0.88
4 Yr College+	305	4.6	0.44	0.18	1.06	0.07	572	7.9	0.72	0.37	1.37	0.31	0.39
Pre-Pregnancy BMI													
Normal or less	288	5.6					443	6.3					
Overweight	154	5.2	0.74	0.29	1.87	0.52	376	7.5	0.90	0.45	1.79	0.77	0.73
Obese	69	11.6	1.80	0.67	4.85	0.24	278	14.8	1.68	0.85	3.30	0.14	0.90
Past GDM													
No	515	6.2					1020	3.7					
Yes	0	0.0	--	--	--	--	92	66.3	53.75	29.96	96.06	<.0001	
Gestational Weight Gain													
Below	79	5.1	1.23	0.34	4.45	0.75	297	9.1	1.22	0.58	2.55	0.60	0.99
Within	152	4.0					300	8.7					
Exceed	217	9.2	2.51	0.94	6.72	0.07	347	8.1	1.03	0.51	2.09	0.93	0.15

Table 2.3 (Continued)

Physical activity													
Any	116	6.0					273	5.1					
None	377	6.6	0.93	0.37	2.32	0.87	813	10.0	1.76	0.86	3.60	0.12	0.28
Cigarette or Hookah Smoker													
No	500	6.2					1094	9.0					
Yes	15	6.7	1.34	0.15	11.92	0.79	18	5.6	0.71	0.07	6.94	0.77	0.69

The models are simultaneously adjusted for all the variables in the table

The estimates among parous women were also adjusted for history of GDM in a prior pregnancy.

Missing covariates were imputed using Markov Chain Monte Carlo multiple imputation (50 sets).

*Interaction p-value

Table 2.4. Multivariable logistic regression models of gestational diabetes as a function of potential risk factors among primiparous women (parity=0) stratified by pre-pregnancy BMI

	Pre-pregnancy BMI < 25 kg/m^2 (n=288)						Pre-pregnancy BMI $\geq$ 25kg/m^2 (n=223)						
	N	**%GDM**	**OR**	**(95%**	**CI)**	**p-value**	**N**	**%GDM**	**OR**	**(95%**	**CI)**	**p-value**	p-value*
Nationality													
Non-Kuwaiti	212	6.6	1.00				173	8.1	1.00				
Kuwaiti	76	2.6	0.26	0.05	1.47	0.13	50	4.0	0.44	0.07	2.74	0.38	0.65
Age (Years)													
<25	150	6.7	1.00				89	6.7	1.00				
25 to 29	106	5.7	1.65	0.50	5.46	0.41	85	7.1	1.12	0.33	3.78	0.86	0.76
30 to 35	26	0.0	--	--	--	--	37	8.1	0.90	0.18	4.45	0.90	--
35+	6	0.0	--	--	--	--	12	8.3	1.60	0.16	16.17	0.69	--
Monthly income (KD)													
<400KD	91	7.7	1.00				83	6.0	1.00				
400-800KD	97	6.2	1.20	0.37	3.89	0.76	67	11.9	2.87	0.84	9.85	0.09	0.21
801-1600KD	60	5.0	1.63	0.32	8.32	0.56	45	6.7	1.93	0.37	10.18	0.44	0.79
1601+	32	0.0	--	--	--	--	19	0.0					
Education													
HS or less	76	7.9	1.00				53	11.3	1.00				
2 Yr Diploma	38	10.5	1.72	0.43	6.91	0.45	40	5.0	0.51	0.08	3.23	0.47	0.38
4 Yr College+	174	3.5	0.33	0.09	1.27	0.11	130	6.2	0.43	0.13	1.42	0.17	0.69
Gestational Weight Gain**													
Below	53	5.7	1.43	0.34	6.08	0.63	26	3.9	0.95	0.10	9.30	0.97	0.93
Within	112	4.5	1.00				40	2.5	1.00				
Exceed	90	8.9	2.27	0.72	7.22	0.16	127	9.5	2.13	0.50	9.14	0.31	0.59
Physical activity													
Any	71	8.5	1.00				45	2.2	1.00				
None	202	5.0	0.45	0.14	1.38	0.16	172	8.7	4.08	0.53	31.47	0.18	0.07
Cigarette or Hookah Smoking													
No	281	5.7	1.00				216	6.9	1.00				
Yes	7	0.0	--	--	--	--	7	14.3	2.00	0.18	22.53	0.58	--

The models are simultaneously adjusted for all the variables in the table
For adjusted models, missing covariates were imputed using Markov Chain Monte Carlo multiple imputation (50 sets).
*Interaction p-value
**Gestational weight gain classification is according to the Institute of Medicine recommendations.

inactivity (OR= 4.08, 95% CI: 0.53 – 31.5) and with smoking (OR= 2.00, 95% CI: 0.18 – 22.5) while there was no positive association among normal weight women (Table 2.4).

DISCUSSION

In this sample of pregnant women in Kuwait we found a high prevalence of many modifiable behaviors and personal characteristics traditionally associated with a western life-style (pre-pregnancy obesity, excessive gestational weight gain, and physical inactivity). In our study 55% of participating women were overweight or obese before becoming pregnant. Pre-pregnancy obesity is consistently reported to be one of the most important risk factors for GDM. [5, 6] In our sample, pre-pregnancy obesity was the most significant modifiable risk factor of GDM (Table 2.2), with 75% increased odds of GDM after adjusting for other maternal characteristics or risk factors. This suggests that 16% (population attributable risk %) of the GDM among obese women in this sample is attributable to their obesity.

Excessive gestational weight gain has been associated with subsequent development of GDM.[14, 15] In our sample 68% of the women had inappropriate total gestational weight gain (either excessive or inadequate) compared to Institute of Medicine recommendations. [16] Although effect estimates were imprecise, excess gestational weight gain was associated with GDM, particularly among primiparous women (Table 2.3). Although we found excessive gestational weight gain was positively associated with GDM, we were not able to separate gestational weight gain before the diagnosis of GDM from gestational weight gain post-diagnosis. Although the confidence limits were very wide and included the null, we also saw a positive association of inadequate total GWG, which may be due to reverse causation, that is women with a GDM diagnosis may limit their subsequent GWG.

Although we had very limited power to detect any benefits from physical activity as only 25% of women reported even minimal physical activity, we did find suggestive evidence of increased odds of GDM among the inactive woman (Table 2.2). The potential protective association of physical activity with GDM is consistent with a recent meta-analysis of randomized control trials which showed 31% reduction of GDM risk due to physical activity.[17]

England and colleagues reported a significant association between smoking among primiparous women and GDM.[18] Although we had limited power to assess this exposure with only 15 smokers among 515 primiparous women, we found an association in the same direction.

Among primiparous women, whose findings would not be confounded or modified by prior pregnancy experience, there also was evidence that smoking and physical inactivity might be particularly deleterious among women who were obese or overweight prior to pregnancy (Table 4). This suggests that overweight or obese women might be a target for enhanced interventions if they are considering becoming pregnant.

Obesity is a hyper-inflammatory state[19, 20] which may be associated with increased vulnerability to a wide range of other risk factors for adverse health. For example, GDM is associated with a higher risk of cardiovascular disease in the future among obese women compared to normal weight women.[21] High BMI was also found to increase the risk of coronary heart disease due to exposure to high blood lipids.[22] This may support our findings of possible effect modification. However, it is important to acknowledge that the relationship between active smoking and obesity is a complex and the interaction between obesity and long term smoking may not be consistent with all health outcomes. For example studies show an inconsistent interaction between smoking and all-cause mortality [23, 24].

Among maternal socioeconomic characteristics, higher education, which is likely a proxy for other health behaviors unmeasured in our analysis, had a protective association with GDM. This is consistent with findings from the Pregnancy Risk Assessment System (PRAMS).[25] After adjustment for prior GDM, we also found an inverse relationship between parity and risk of

GDM, as has been reported previously.[26, 27] This finding suggests that women who “survived” previous pregnancies without developing GDM are less likely to develop it in future pregnancies which may partially explain attenuation of some associations in parous compared with primiparous women (Table 2.3).

Our findings support the public health importance of addressing the unhealthy pregnancy profiles among women in Kuwait. Overweight and obesity are very prevalent in this population, which puts a large proportion of women at risk of pregnancy complications related to obesity, such as gestational diabetes, gestational hypertension, and cesarean deliveries. [6] The IOM recommends lower total GWG among those who are overweight or obese compared to normal weight women because pre-pregnancy obesity also increases pregnancy risks associated with excessive gestational weight gain.[12] A large portion of our study population (41%) had excessive gestational weight gain which increases the risk of labor and delivery complications, excessive post-delivery maternal weight retention, future maternal obesity and its attendant cardiovascular disease risks.[16]

Physical activity plays an important role in pre-pregnancy weight control, which may help reduce the risk of GDM, with implications for high birth weight, and cesarean deliveries.[7, 28] A very high proportion of women reported physical inactivity (75%) with very few women (11.5%) reporting physical activity that was at least as vigorous as brisk walking. The majority of women reporting physical activity did not reach the recommended level of intensity associated with benefits to general health. The American College of Obstetricians and Gynecologists (ACOG) recommends 30 minutes or more of moderate intensity physical activity on most days of the week among pregnant women who are free from obstetric complications.[29] The ACOG recommended intensity is equivalent to brisk walking at a pace of 3 to 4 miles per hour. Even studies that describe health protective effects of “light” physical activity during pregnancy include activities that are more intense than slow walking, such as aerobics and whole body resistance training.[17, 30, 31] Therefore, most of our participants, even those reporting slow walking, were not engaging in an effective level of physical activity. Our results among primiparous women suggest that women who become pregnant when they are overweight or obese may be particularly at risk for adverse effects of excessive gestational weight gain, lack of physical activity, and smoking.

In considering these findings, it is important to keep in mind that the TRACER study was designed to examine effects of prenatal exposures on the health of newborns and children. [9] Examining pregnancy outcomes in this cohort was a secondary objective defined after data collection was well underway. Therefore, indicators and risk factors for GDM in many cases were collected retrospectively. Many women were asked to recall their pre-delivery weight and gestational diabetes diagnosis many months after delivery. Nevertheless, our validation analyses suggest good concordance between self-reported weight compared with medical record weights, and self-reported GDM compared to OGTT results. There may have been misclassification of our measure of GDM measure due to physician diagnostic practices. For example, in our validation study, some women appeared to have been diagnosed with GDM with glucose elevations that did not meet the strict IADPSG diagnostic criteria. In general, misclassification in an outcome due to random error may result in loss of precision and attenuation of estimates. [32]

We did not include or adjust for nutrient or caloric intake in our analysis because we did not obtain information about diet until after the usual time of GDM diagnosis. In this circumstance, GDM dietary recommendations may have significantly altered dietary intake and/or dietary recall on the study's food frequency questionnaire. Indeed, in a preliminary analysis we observed a positive association between low caloric intake and GDM (data not shown).

Potential confounding from previous pregnancy experiences, especially prior GDM, was one limitation of our data. Prior GDM is a strong predictor of subsequent GDM. We assessed previous GDM retrospectively by asking if the participant had "ever" had GDM in the baseline questionnaire. Adjusting for past GDM history in our models may result in bias due to incomplete adjustment for the outcome, or loss of power due to the strong correlation with current GDM.[33] To assess associations without this potential limitation, we conducted sensitivity analyses stratified by parity. Stronger associations in primiparous compared to parous women provides at least indirect evidence that health behaviors and other GDM risk factors may have been influenced by prior pregnancies in parous women (Table 2.3).

Finally, our study was underpowered to assess a number of associations such as smoking and physical activity in which the number of participants reporting these activities was very low.

Our study is unique in examining maternal lifestyle and pregnancy risk factors for GDM in the Kuwait and Gulf region population. Kuwait has some of the highest rates of obesity and type 2 diabetes in the world,[8] making these analyses particularly informative for this high risk population. The findings highlight the relative importance of previously identified risk factors for GDM among this understudied population. For example, our study suggests that pre-pregnancy obesity is a strong GDM risk factor in Kuwait. In addition, this study helps fill a significant gap in the literature due to the scarcity of population based epidemiological studies about GDM prevalence and risk factors in the region.

In conclusion, our study suggests that pre-pregnancy obesity is a significant health risk for women planning to become pregnant in Kuwait. Although our study suffered from lack of statistical power for some risk factors, we see suggestive evidence of increased risk of GDM with pregnancy smoking, excessive gestational weight gain, and lack of physical activity. Among primiparous women, the effect of these modifiable risk factors was more pronounced among women who were overweight or obese prior to their pregnancy. Women who expect to become pregnant should be encouraged to undertake a healthier lifestyle that targets a normal BMI prior to the pregnancy. Programs should educate women that having an unhealthy lifestyle, especially obesogenic behaviors, puts their future pregnancies at risk of GDM. We suggest that gestational weight gain be monitored in antenatal clinics of Kuwait according to the recommended IOM range. Smoking was very rare in our population and we were not able to see any significant associations. However, smoking remains a very important public health problem that needs to be monitored especially if the prevalence of smoking should increase among women with more westernization of the society. Similarly, the importance of physical activity among pregnant women should not be overlooked especially when the prevalence of physical activity is so low in this population. We recommend future research using a larger sample of the Kuwaiti population examine the results with reliable power. Future research should also explore potentially modifiable determinants of pre-pregnancy obesity, lack of physical activity, and excessive gestational weight among populations in the region.

References

1. Agarwal MM, Dhatt GS, Shah SM: **Gestational diabetes mellitus**. *Nippon Rinsho* 2010, **115**:2018–2020.

2. Hillier T, Pedula K, Schmidt M: **Childhood obesity and metabolic imprinting the ongoing effects of maternal hyperglycemia**. *Diabetes …* 2007, **30**.

3. Bellamy L, Casas J-P, Hingorani AD, Williams D: **Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis.** *Lancet* 2009, **373**:1773–1779.

4. Mocarski M, Savitz D a: **Ethnic differences in the association between gestational diabetes and pregnancy outcome.** *Maternal and child health journal* 2012, **16**:364–73.

5. Abenhaim H a, Kinch R a, Morin L, Benjamin A, Usher R: **Effect of prepregnancy body mass index categories on obstetrical and neonatal outcomes.** *Archives of gynecology and obstetrics* 2007, **275**:39–43.

6. Doherty D a, Magann EF, Francis J, Morrison JC, Newnham JP: **Pre-pregnancy body mass index and pregnancy outcomes.** *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2006, **95**:242–7.

7. Sanabria-Martínez G, García-Hermoso A, Poyatos-León R, Álvarez-Bueno C, Sánchez-López M, Martínez-Vizcaíno V: **Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis.** *BJOG : an international journal of obstetrics and gynaecology* 2015.

8. MOH KM of H: **Kuwait STEPS Report**. 2008.

9. Alseaidan M, Al Wotayan R, Christophi CA, Al-Makhseed M, Abu Awad Y, Nassan F, Ahmed A, Abraham S, Boley RB, James-Todd TM, Wright RJ, Dockery DW, Behbehani K: **Birth Outcomes in a Prospective Pregnancy-Birth Cohort Study of Environmental Risk Factors in Kuwait: The TRACER Study**. *Paediatric and perinatal epidemiology* 2016:(In

press).

10. Who: **Physical Status: the Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. Technical Report Series No. 854.** *Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Technical Report Series No. 854*. 1995:1–452.

11. Dehghan M, Al-Hamad N, McMillan CR, Prakash P, Merchant AT: **Comparison of a semi-quantitative food frequency questionnaire with 24-hour dietary recalls to assess dietary intake of adult Kuwaitis**. *Saudi Medical Journal* 2009, **30**:159–161.

12. Yaktine A, Rasmussen K: *Weight Gain During Pregnancy:: Reexamining the Guidelines*. 2009.

13. Metzger BE, Gabbe SG, Persson B, Buchanan T a, Catalano P a, Damm P, Dyer AR, Leiva A De, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJN, Omori Y, Schmidt MI: **International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy.** *Diabetes care* 2010, **33**:676–82.

14. Saldana TM, Siega-Riz AM, Adair LS, Suchindran C: **The relationship between pregnancy weight gain and glucose tolerance status among black and white women in central North Carolina**. *American Journal of Obstetrics and Gynecology* 2006, **195**:1629–1635.

15. Brunner S, Stecher L, Ziebarth S, Nehring I, Rifas-Shiman SL, Sommer C, Hauner H, von Kries R: **Excessive gestational weight gain prior to glucose screening and the risk of gestational diabetes: a meta-analysis**. *Diabetologia* 2015, **58**:2229–2237.

16. Olson CM: **Achieving a healthy weight gain during pregnancy.** *Annual review of nutrition* 2008, **28**:411–23.

17. Sanabria-Martínez G, García-Hermoso a, Poyatos-León R, Álvarez-Bueno C, Sánchez-López M, Martínez-Vizcaíno V: **Effectiveness of physical activity interventions on preventing**

gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology* 2015:n/a–n/a.

18. England LJ, Levine RJ, Qian C, Soule LM, Schisterman EF, Yu KF, Catalano PM: **Glucose tolerance and risk of gestational diabetes mellitus in nulliparous women who smoke during pregnancy**. *American Journal of Epidemiology* 2004, **160**:1205–1213.

19. Revelo XS, Luck H, Winer S, Winer DA: **Morphological and inflammatory changes in visceral adipose tissue during obesity**. *Endocrine Pathology* 2014, **25**:93–101.

20. DeLoach S, Keith SW, Gidding SS, Falkner B: **Obesity associated inflammation in African American adolescents and adults.** *The American journal of the medical sciences* 2014, **347**:357–63.

21. Fadl H, Magnuson A, Östlund I, Montgomery S, Hanson U, Schwarcz E: **Gestational diabetes mellitus and later cardiovascular disease: a Swedish population based case-control study.** *BJOG : an international journal of obstetrics and gynaecology* 2014, **121**:1530–6.

22. Hirakawa Y, Lam T-H, Welborn T, Kim HC, Ho S, Fang X, Ueshima H, Suh I, Giles G, Woodward M, Asia Pacific Cohort Studies Collaboration: **The impact of body mass index on the associations of lipids with the risk of coronary heart disease in the Asia Pacific region.** *Preventive medicine reports* 2016, **3**:79–82.

23. Spijkerman AMW, Van Der A DL, Nilsson PM, Ardanaz E, Gavrila D, Agudo A, Arriola L, Balkau B, Beulens JW, Boeing H, De Lauzon-Guillain B, Fagherazzi G, Feskens EJM, Franks PW, Grioni S, Huerta JM, Kaaks R, Key TJ, Overvad K, Palli D, Panico S, Redondo ML, Rolandsson O, Roswall N, Sacerdote C, S??nchez MJ, Schulze MB, Slimani N, Teucher B, Tjonneland A, et al.: **Smoking and long-term risk of type 2 diabetes: The EPIC-InterAct study in European populations**. *Diabetes Care* 2014, **37**:3164–3171.

24. Banack HR, Kaufman JS: **Estimating the Time-Varying Joint Effects of Obesity and Smoking on All-Cause Mortality Using Marginal Structural Models**. *American*

Journal of Epidemiology 2015, **183**:kwv168.

25. DeSisto CL, Kim SY, Sharma AJ: **Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010.** *Preventing chronic disease* 2014, **11**:E104.

26. Nanda S, Savvidou M, Syngelaki A, Akolekar R, Nicolaides KH: **Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks.** *Prenatal diagnosis* 2011, **31**:135–41.

27. Savvidou M, Nelson SM, Makgoba M, Messow CM, Sattar N, Nicolaides K: **First-trimester prediction of gestational diabetes mellitus: Examining the potential of combining maternal characteristics and laboratory measures**. *Diabetes* 2010, **59**:3017–3022.

28. Wiebe HW, Boulé NG, Chari R, Davenport MH: **The Effect of Supervised Prenatal Exercise on Fetal Growth: A Meta-analysis.** *Obstetrics and gynecology* 2015, **125**:1185–94.

29. Artal R, O'Toole M: **Guidelines of the American College of Obstetricians and Gynecologists for exercise during pregnancy and the postpartum period**. *Obstetrics & Gynecology* 2002, **99**:171–173.

30. Barakat R, Cordero Y, Coteron J, Luaces M, Montejo R: **Exercise during pregnancy improves maternal glucose screen at 24-28 weeks: a randomised controlled trial**. *British Journal of Sports Medicine* 2012, **46**:656–661.

31. Barakat R, Ruiz JR, Stirling JR, Zakynthinaki M, Lucia A: **Type of delivery is not affected by light resistance and toning exercise training during pregnancy: a randomized controlled trial**. *American Journal of Obstetrics and Gynecology* 2009, **201**:209–210.

32. Copeland KT, Checkoway H, Mcmichael AJ, Holbrook RH, Checkoway H, Mcmichael AJ: **Bias due to misclassification in the estimation of relative risk.** 1977, **105**:488–495.

33. Schisterman EF, Cole SR, Platt RW: **Overadjustment bias and unnecessary**

adjustment in epidemiologic studies. *Epidemiology (Cambridge, Mass)* 2009, **20**:488–95.

Supplementary Table 2.1. Characteristics of participants included in the analysis (n=1627) vs those not included (n=851)

	Not analyzed		Analyzed		X^2 p-value
	n	%	n	%	
Nationality					
Non-Kuwaiti	573	67.3	1166	71.7	0.025
Kuwaiti	278	32.7	461	28.3	
Age group					
<25	201	24.1	376	23.1	0.94
25-29	313	37.5	617	37.9	
30-35	216	25.9	425	26.1	
35+	105	12.6	209	12.9	
Missing	16		0		
Income					
<400	245	30.3	431	27.3	0.043
401-800	255	31.6	535	33.9	
801-1600	167	20.7	380	24.1	
1601+	141	17.5	230	14.6	
Missing	43		51		
Education					
High school or less	239	28.8	495	30.4	0.65
2 yr Diploma	128	15.4	255	15.7	
4 year college or more	463	55.8	877	53.9	
Missing	21		0		
BMI					
Normal or less	367	45.0	731	45.5	0.98
Overweight	271	33.3	530	33.0	
Obese	177	21.7	347	21.6	
Missing	36		19		
Parity					
0	304	38.8	515	31.7	0.0005
1+	480	61.2	1112	68.4	
Past GDM					
No	743	94.9	1535	94.4	0.58
Yes	40	5.1	92	5.7	
Missing	37		0		
Active smoker					
No	780	97.5	1594	98.0	0.45
Yes	20	2.5	33	2.0	
Missing	14		0		
Gestational Weight Gain**					
Below	2	16.7	376	27.0	0.68*
Within	5	41.7	452	32.5	
Exceed	5	41.7	564	40.5	
Missing	825		235		
Physical Activity					
Any	167	31.4	389	24.6	<0.01
None	365	68.6	1190	75.4	
Missing	319		48		

*Fisher's exact test

**Gestational weight gain classification is according to the Institute of Medicine recommendations.

Chapter 4: Home Passive Tobacco Smoke Exposure and Gestational Diabetes Risk in Kuwait: the TRACER Study

Home Passive Tobacco Smoke Exposure and Gestational Diabetes Risk in Kuwait: the TRACER Study

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ABSTRACT:

Background: Gestational diabetes mellitus (GDM) is a strong risk factor of type 2 diabetes (T2DM), which is prevalent in approximately 25% of the Kuwaiti population. Previous studies suggest an association between passive tobacco smoke (PTS) exposure and T2DM. PTS is significantly understudied in Kuwait, where tobacco about half of men smoke (42%) while smoking among women is rare. Little is known about the association between PTS and GDM.

Methods: We investigated the association between pregnancy home exposure to PTS and risk of GDM among primiparous women enrolled in the TRansgenerational Assessment of Children's Environmental Risks (TRACER) study. We investigated the association of PTS exposure with GDM among 395 pregnant women with no reported exposure to PTS outside of home. PTS was obtained by interviewer administered questionnaires prenatally, while GDM was self-reported via postnatal questionnaire. We used multivariable binomial regression models to estimate the relative risk (RR) and 95% confidence intervals (CI).

Results: The incidence of GDM was 7.6%, and 25% of participants were exposed to at least 1 hour a week of home passive smoke during pregnancy. Exposure to any PTS was suggestively associated with 1.45 (95%CI: 0.69, 3.03) increased GDM risk. Exposure to passive smoking from cigarettes was associated with a 1.17 (95%CI: 0.52, 2.61) increased GDM risk, while exposure to passive smoking from hookah use was associated with a 2.21 (95%CI: 0.56, 8.73) increased GDM risk.

Conclusion: Our study was underpowered to examine the association between GDM and PTS. However, our results show patterns suggestive of deleterious associations between PTS and incident GDM. The results suggest a deleterious pattern of association with hooka exposure that may be at least as harmful as cigarette PTS. The health associations with PTS should be further studied and efforts to control tobacco smoke in the region should be made.

INTRODUCTION:

Gestational diabetes mellitus (GDM) affects approximately 7% of all pregnancies, with an incidence ranging from 1 to 14% depending on the population.[1] GDM is associated with a higher risk of developing type 2 diabetes mellitus (T2DM), with 50-70% of women going on to develop T2DM in the years following pregnancy .[2–4] Certain populations are at particularly high risk of T2DM, including individuals living in Kuwait, which ranks among the top nine countries in the world for T2DM prevalence.[5] Given that GDM is the strongest predictor of future of T2DM,[6] identifying modifiable factors for GDM could help reduce the burden of T2DM in this high-risk population.

While diet and physical inactivity are well studied risk factors for T2DM, several studies have reported that active tobacco smoking is a risk factor for T2DM.[7] Tobacco smoking is a significant public health issue in Middle-Eastern countries like Kuwait. Almost a quarter of the Kuwaiti population are active smokers, with approximately half of men reporting active smoking .[8] While the vast majority of women are not active smokers, passive tobacco smoke (PTS) exposure may contribute to a number of adverse health outcomes, including metabolic disturbances related to diabetes. Pregnancy may be a particularly vulnerable period, as exposure to PTS may be associated with pregnancy complications, such as GDM through chemicals contained in PTS. These chemicals, including nicotine, are associated with increased beta cell loss, systemic inflammation, and oxidative stress.[9–13] While numerous studies have evaluated PTS and T2DM, little is known about PTS and GDM, particularly in high-exposure, high-risk populations. Furthermore, little is known about the association between GDM risk and different types of PTS exposure, especially the association with hookah (i.e., water pipe) smoke exposure, a growing form of tobacco use that is common in the Middle East.

We examined the risk of GDM as a function of PTS exposure among pregnant women participating in the Kuwait-based TRansgenerational Assessment of Children's Environmental

Risks (TRACER) study. Specifically, we evaluated home PTS exposures from both cigarette and hookah PTS and their associations with GDM. By evaluating the association between PTS and GDM, we can provide needed evidence for a potentially modifiable risk factor, with implications for future development of interventions that could reduce this pregnancy complication and subsequent risk of T2DM in this high-risk population.

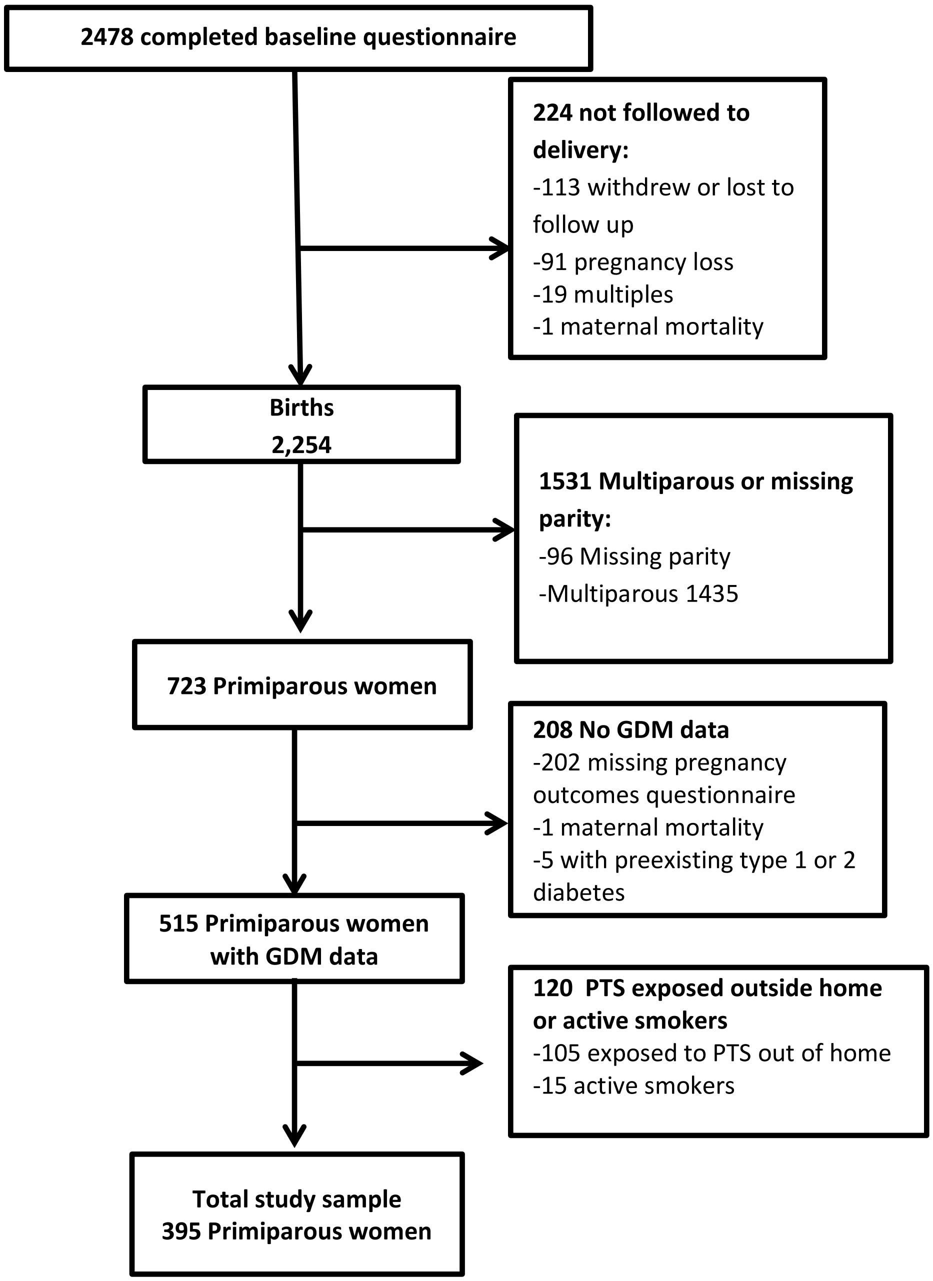
METHODS:

Study Population: The TRACER study has been described previously. [14] Briefly, pregnant women between 18 and 45 years of age, of any nationality who were fluent in Arabic or English were recruited from 9 prenatal clinics (6 public and 3 private) located in the 6 Kuwaiti governorates. Permission to recruit subjects was obtained from the health center administration and the obstetricians at each health center. The study was reviewed and monitored by institutional review boards at the Harvard T.H. Chan School of Public Health and the Dasman Diabetes Institute. During regular antenatal visits, the obstetricians referred potential participants to the TRACER study staff who provided them with brochures and explained the study to the participants. We obtained written consent from the participant and her husband if they were interested in joining the study.

A total of 2,478 participants consented and completed baseline questionnaires in TRACER. Of these, 30% were recruited in their first trimester, 48% in the second trimester, and 21% in third trimester. During pregnancy follow-up, 113 women withdrew or were lost to follow-up prior to delivery, and we excluded 91 women with pregnancy loss, 19 multiple gestation pregnancies, and one maternal deaths during pregnancy. There were a total of 2,254 births. Women were followed-up after delivery to collect birth data and pregnancy outcomes including a diagnosis of GDM.[15] To avoid confounding by prior pregnancy experiences we excluded a total of 1531 women--1435 multiparous women and 96 women who were missing parity information. We also excluded 208 women with missing GDM data. In addition, 120 women with outside of home

PTS exposure or who reported being active smokers were excluded (105 women and 15 women, respectively). The former group (i.e. women with outside of home PTS exposure) was excluded to avoid confounding by the social circumstances that may be related to both out of home exposure and GDM. After exclusions, a total of 395 primiparous women were included in the analysis (more details in Figure 3.1).

Figure 3.1. Flow chart of study sample selection.



Data collection: The baseline questionnaire collected information on lifestyle, socio-demographic, anthropometric, and reproductive factors. In addition, information on medical history and environmental exposures, such as prior GDM and smoking history, including PTS exposure was collected. The baseline questionnaire was administered within a month of recruitment for approximately half (58%) of the participants, while the remainder answered it during the rest of the pregnancy (43%) and a small minority (6%) after delivery. GDM information was collected by the pregnancy outcomes questionnaire, which was introduced later in the study. Collection of these pregnancy outcome data extended over several years of follow-up (58% answered in the first year, 34% in the second year, and 8% in the third year following birth).

Gestational Diabetes: We defined GDM as maternal self-report of physician diagnosed GDM and maternal self-report of a prescription for a diet, dietitian referral, or medication for diabetes. Of note, 97% of women reporting a GDM diagnosis also reported a prescription for treatment by diet or medication. To validate the self-report of GDM, we extracted OGTT results from medical records for a sub-sample of 281 study participants who consented to review of their medical records. Of those 150 participants had OGTT information and were non-missing self-reported GDM. Nineteen (n=19) women reported GDM and 131 reported no GDM in this pregnancy. All received a GDM screening test consisting of a 75-gram glucose challenge and evaluation of blood glucose while fasting pre-challenge and 2-hours post-challenge. Among women who reported GDM, 13 met the International Association of Diabetes and Pregnancy Study Groups criteria for GDM with fasting glucose of >=5.1 mmol/L or 2-hour of >=8.5 mmol/L (68 % positive predictive value). Among 131 women who reported no GDM, 118 had OGTT results below the criteria for GDM (90% negative predictive value). In a post-hoc analysis, we noted that two women had 2-hour glucose >=8.3 mmol/L. With relaxed OGTT criteria for these 2 women and assuming their physicians had also used other information in making their diagnosis, 15 of 19 reported GDM cases would be classified as GDM (positive predictive value 79%) while 116 of 131 reported non-cases would be classified as non-GDM (negative predictive value 89%).

Passive tobacco smoke exposure: Study participants responded to the question "Since you became pregnant, on average, how many hours per week have you been exposed to cigarette smoke at home?" with categories of "less than 1 hour per week, 1 to 4 hours per week, 5 to 8, 9 to 12 hours a week, and more than 12 hours a week". The questions were repeated for hookah (also known as shisha, narghile, waterpipe, or hubble-bubble) PTS. A similar set of questions was asked for outside of home exposure to PTS. However, given that a previous study showed low correlations (r=0.01) of biomarkers of exposure to PTS with self-report of public PTS exposure, we restricted our analysis to home PTS exposure.[16] In our analysis, we assessed 3 types of exposure: 1) any type of home PTS exposure (i.e. cigarette or hooka), 2) home cigarette PTS exposure, and 3) home hookah PTS exposure. For each of these types of PTS exposure, we defined a dichotomous indicator of PTS exposure (> 1 hour per week). Women who reported less than 1 hour per week for home exposure were considered to not be exposed to home PTS.

Covariates: Several variables collected from the baseline questionnaire were considered as potential confounders. Specifically, we assessed maternal age, nationality, income, completed education, and monthly income in Kuwaiti Dinars (KD)[3]. We calculated pre-pregnancy body mass index (BMI) from the reported pre-pregnancy weight (kg) divided by collected height (m) squared. We then categorized pre-pregnancy weight as overweight if BMI $\geq$ 25 kg/m^2 and obese if BMI $\geq$ 30 kg/m^2.[17] During study follow up (primarily during the second or third trimester, although some after birth), we administered a physical activity questionnaire, which collected data on frequency and duration of physical activity.

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[3] 1 KD is equivalent to 3.3 US dollars.

Statistical analysis

Continuous variables with symmetrical distribution are presented as mean and standard deviation (SD). We report frequency of GDM and its 95% confidence interval among our study sample. We examined the distribution of nationality, age, education, income, pre-pregnancy weight, current GDM, and housing characteristics (single family versus apartment building, central versus room air conditioning, and number of rooms) by dichotomous PTS exposure (less than 1 versus 1 hour or more of smoke exposure per week).

We used multivariable binomial regression to calculate risk ratios and 95% confidence intervals. For this, we used the PROC GENMOD procedure in SAS with a poisson distribution, log link, and an unstructured variance-covariance matrix.[18] We estimated the unadjusted relative risks of GDM associated with exposure to PTS at home (more than 1 hour per week). Then we estimated the relative risks using a 3 level categorical exposure comparing any PTS of 1 to 12 hours per week, and 12+ hours per week to those with no PTS exposure during pregnancy. In multivariable models, we adjusted risk ratios for nationality (Kuwaiti versus non-Kuwaiti), age, education, pre-pregnancy BMI, and physical activity. We did not adjust for income as there was not associated with GDM in this sample after adjusting for other variables.

In further analysis we examined the association between GDM and home passive smoke exposure assessing PTS exposure from cigarettes versus hookah separately using dichotomous variables. For analyses, we defined three different measures of PTS exposure and compared each to those with no PTS exposure (n=297). The three groups were women with any PTS exposure (cigarette, hookah, or both, n=98), those with PTS exposure via cigarettes only (n=86), and those with PTS exposure via hookah only (n=7). The latter two groups were used to evaluate potential differential associations by smoking type.

For sensitivity analyses we examined effect measure modification of the association between PTS and GDM by nationality (Kuwaiti and non-Kuwaiti), type of building (single family house, apartment building), type of air conditioning (central AC, room AC), and number of rooms (2 rooms or less, 3 or more rooms). We stratified the data by each of the 4 potential effect modifying variables using separate models then estimated the odds ratio for each stratum. We present the stratum-specific results of the association between any home PTS exposure and GDM risk.

We used Monte Carlo Markov Chain to impute missing covariates by imputing 50 datasets. Statistical significance was set at 0.05 and all p-values reported were two-sided. The Statistical Analysis Software SAS 9.4 (SAS Inc., Cary, NC) was used for all analyses.

RESULTS

Study population

A total of 395 primaparous women were included in this analysis (Figure 1). Approximately 25% of the women reported PTS exposure at home (Table 3.1). The overall incidence of GDM in this sample was 7.6% (95% CI :5.0, 10.2%). The mean maternal age was 25.5 years (SD: 4.1 years) was the same among women with and without home PTS exposure. Women exposed to PTS had similar BMI (mean 25.6, 95% CI: 24.7, 26.5) compared to those unexposed (mean 25.3, 95%CI: 24.8, 25.8) kg/m^2 (Table 3.1). Overall, more than half (61%) of the participants reported 4 or more years of college, and this frequency was slightly lower among the exposed compared to the non-exposed. There was slightly higher home PTS exposure among those who lived in homes with central air conditioning compared to those with room air conditioning (71% versus 62%, respectively). There were no clear differences in other maternal sociodemographic, housing characteristics, or reproductive factors by PTS exposure (Table 3.1).

Table 3.1. Distribution of maternal characteristics by home passive tobacco smoke exposure among primiparous women in TRACER (N=395)

	Total		Any passive tobacco smoke exposure per week				
			No		Yes		
	n	(%)	n	(%)	n	(%)	x^2 p-value
Maternal sociodemographic characteristics							
Age							
<25	180	45.6	139	46.8	41	41.8	0.78
25-29	152	38.5	110	37.0	42	42.9	
30-35	51	12.9	39	13.1	12	12.2	
35+	12	3.0	9	3.0	3	3.1	
Nationality							
Non-Kuwaiti	305	77.2	228	76.8	77	78.6	0.71
Kuwait	90	22.8	69	23.2	21	21.4	
Education							
High school or less	96	24.3	68	22.9	28	28.6	0.45
2 year diploma	57	14.4	42	14.1	15	15.3	
College or higher	242	61.3	187	63.0	55	56.1	
Housing characteristics							
Type of building							
Single Family house	86	21.8	61	20.5	25	25.5	0.30
Apartment bldg	309	78.2	236	79.5	73	74.5	
Air Conditioning							
Room	142	35.9	114	38.4	28	28.6	0.08
Central	253	64.1	183	61.6	70	71.4	
Number of rooms							
1 & 2	233	59.0	177	59.6	56	57.1	0.62
3	94	23.8	72	24.2	22	22.5	
4+	68	17.2	48	16.2	20	20.4	
Reproductive factors							
Pre-Pregnancy BMI							
Normal or less	221	56.2	172	58.1	49	50.5	0.41
Overweight	116	29.5	83	28.0	33	34.0	
Obese	56	14.2	41	13.9	15	15.5	
GDM							
No	365	92.4	277	93.3	88	89.8	0.26
Yes	30	7.6	20	6.7	10	10.2	

Association between any passive tobacco smoke exposure and GDM

Participants with any home PTS exposure had a higher incidence of GDM (10.2%) compared to those without PTS exposure (6.7%, Table 2). After adjusting for age, nationality, education, pre-pregnancy BMI, and physical activity, there was a suggestive association of home PTS exposure with an increased risk of GDM (RR= 1.45, 95% CI: 0.69, 3.02, Table 2). When we examined the association of GDM with type of tobacco exposure compared to the non-exposed group, we found a significant association with passive smoke exposure from hooka (RR= 3.96, 95%CI: 0.1.37, 11.46, Table 2), and a suggestion of a positive association with passive smoking from cigarettes (RR= 1.36, 95%CI: 0.61, 3.02); although the small sample size meant these results had wide confidence intervals (Table 3.2).

We observed a pattern suggestive of effect modification by nationality , type of housing, number of rooms, and type of air conditioning but, in our relatively modest sample, these interactions were not statistically significant (Table 3.3). Specifically, there was a suggestively stronger association between any PTS exposure and GDM among non-Kuwaitis (RR= 1.52, 95%CI: 0.70, 3.29) than Kuwaitis (RR= 0.93, 95% CI: 0.06, 15.11, Table 3.3). There was a suggestion of a stronger association of PTS with GDM for those with central air conditioning (RR=1.55, 95% CI: 0.64, 3.80) than among those with room air conditioners (RR=1.27, 95% CI: 0.32, 5.07). Women who lived in apartment buildings or homes with 2 rooms or less also showed a pattern of higher associations between home PTS exposure and GDM (table 3.3). Due to the small sample size we were unable to analyze the stratified samples by type of tobacco PTS.

Table 3.2. Associations between passive tobacco smoke (PTS) exposure and GDM among primiparous women in TRACER (N=395)

	N	%GDM	Adjusted			
			RR	95%	CI	p-value
Any Passive Tobacco Smoke						
No	297	6.7	1.00			
Yes	98	10.2	1.45	(0.69,	3.02)	0.33
Type of tobacco						
Cigarette PTS*						
No	297	6.7	1.00			
Yes	86	9.3	1.36	(0.61,	3.02)	0.46
Hookah PTS**						
No	297	6.7	1.00			
Yes	7	28.6	3.96	(1.37,	11.46)	0.01

Models have been adjusted for maternal age, nationality, education, pre-pregnancy BMI, and physical activity

*Exposure to cigarette passive tobacco smoke (PTS) after excluding 7 participants with only Hooka PTS and 5 with both hooka and cigarette PTS

**Distribution of exposure to Hooka smoke after excluding 86 participants with only cigarette tobacco smoke, and 5 participants with both hooka and cigarette PTS.

Table3.3. Association between Passive Tobacco Smoking (PTS) and GDM stratified by nationality and housing characteristics among primiparous women in TRACER (n=395)

Stratification variable	Home PTS	Number	% GDM	RR	(95%	CI)	model p-value
Nationality							
Kuwaiti	No	69	4.4	1.00			
	Yes	21	4.8	0.93	0.06	14.93	0.96
Non-Kuwaiti	No	228	7.5	1.00			
	Yes	77	11.7	1.52	0.70	3.29	0.29
Type of building							
Apartment bldg	No	236	6.8	1.00			
	Yes	73	11	1.47	0.64	3.40	0.37
Family house	No	61	6.6	1.00			
	Yes	25	8	1.10	0.27	4.58	0.89
Type of Air conditioning							
Central AC	No	183	7.1	1.00			
	Yes	70	11.4	1.55	0.64	3.80	0.33
Room AC	No	114	6.1	1.00			
	Yes	28	7.1	1.27	0.32	5.07	0.73
Number of rooms							
2 or less	No	177	7.3	1.00			
	Yes	56	8.9	1.47	0.48	4.44	0.5
3 or more	No	120	5.8	1.00			
	Yes	42	11.9	1.22	0.46	3.27	0.69

Models have been adjusted for maternal age, nationality, education, pre-pregnancy BMI, and physical activity

DISCUSSION

Our study of home PTS exposure and risk of GDM among primiparous women living in Kuwait provides suggestive findings that PTS exposure, particularly hookah exposure, could be associated with an increased risk of GDM. Patterns of association also suggested a potential increased risk of GDM with any type of cigarette PTS exposure. Further, in exploratory analyses, we found that non-Kuwaitis and those using central air conditioning had suggestively higher risk of GDM compared to Kuwaitis and those with room air conditioning. While our findings were non-precise, the patterns of exposure suggest the need for future studies evaluating PTS and GDM.

Previous studies have evaluated PTS and T2DM. For example, a recent meta-analysis by Wei et al (2014) examining seven studies found PTS exposure was associated with a moderate increased risk of T2DM.[19] In middle age women participating in Nurses' Health Study II (age ranging between 41 and 55 years), there was a weak to borderline significant association between PTS and T2DM.[20] Women in the European Prospective Investigation into Cancer and Nutrition study (40 and 65 years of age) showed 36% increased risk of T2DM associated with PTS.[21] Our study is among the first to look at pregnant women for the association between PTS exposure and GDM. We found suggestive associations that were similar to associations seen between PTS and T2DM in the European Prospective Investigation into Cancer and Nutrition study. Given that GDM is a strong predictor of future T2DM, with up to 70% of women develop T2DM in the following 10 years, the present study's findings may extend previous work by evaluating an important time period—pregnancy, as GDM has important implications for future maternal and child health.[22]

While studies have not evaluated passive tobacco smoke exposure and GDM, a number of studies have evaluated active smoking and GDM risk. For example, England et al examined the association among 3,602 primiparous women and found a significant association of nearly two fold increased odds of GDM among actively smoking pregnant women.[3] Other studies found no associations between passive smoke and GDM[23–25] or inverse relationships.[26] These inconsistent findings may suggest different types and patterns of smoking, as well as differences in baseline GDM risk. Furthermore, unmeasured confounding may be an issue when evaluating smoking and GDM risk in many of these studies. Our study, which only examines the association with passive smoke is not precluded from unmeasured confounding, however we adjusted for several sociodemographic factors in addition to physical activity.

GDM and T2DM have similar pathophysiological mechanisms.[22] GDM is thought to be a result of chronic pancreatic beta cell dysfunction and the inability to handle the increasing insulin resistant state of pregnancy.[22] Exposure to tobacco smoke is associated with increased beta cell loss, systemic inflammation, oxidative stress, and endothelial disfunction,[9] which is associated with increased insulin resistance in the liver, skeletal muscles, and other tissues.[10] Nicotine has been associated with insulin function impairment[11] as well as pancreatic beta cell loss,[12] and chronic pancreatic inflammation .[13] Therefore the increased risk of GDM due to exposure to tobacco smoke is biologically plausible. While we did not look at mechanisms in the present study, we did evaluate type of PTS finding hookah PTS to have a stronger association than cigarette PTS, albeit statistically there was no difference between the two due to the very wide and somewhat overlapping confidence limits. That said, mechanistically, compared to a single cigarette, a single session of hookah smoke produces many multiples of total particulate matter (up to 250-fold) and carbon monoxide (up to 30 fold).[27,28] Consequently, women exposed to PTS from a single session of hookah are likely to get a substantially higher dose of the harmful components in PTS, which would normally be delivered from hours of cigarette PTS exposure.

There was a suggestion of different patterns by nationality and home environments (i.e. type of air conditioning). Specifically, we found potentially positive associations among non-Kuwaiti women but a null association among Kuwaiti women. There are substantial socioeconomic differences between the Kuwaiti and non-Kuwaiti populations which might affect housing characteristics and thereby the level of PTS exposure in the home. It is also possible that this effect modification by nationality is due to cultural differences. Many Kuwaiti homes have a separate room, a diwaniah, where men socialize and preferentially smoke. [29] Thus, Kuwaiti women are unlikely to be in direct PTS exposure from either cigarettes or hookah. The diwaniah is unique to Kuwatiti homes. Non-Kuwaiti homes do not have a specific diwaniyah and the women are more likely to be exposed to smoking by men in the home. Therefore, non-Kuwaiti women may be more likely to be directly exposed to PTS at home, with implications for increased GDM risk. However, it is unclear how this unique environment might affect women's perception of exposure and subsequently their reporting.

In the present study, we also found suggestive differences in the patterns of PTS and GDM by type of air conditioning, which serves as the ventilation system. We found a positive association in homes with central air conditioning but weaker association for homes with room air conditioners, albeit substantially underpowered. Because of the high outdoor temperatures, the practice in Kuwaiti homes is to maximize the recirculation of indoor air, which minimizes the dilution of indoor air with fresh outdoor air. For homes with central air conditioning, this means that the indoor generated tobacco smoke is circulated throughout the house. However, for homes with room air conditioning, there would be less room-to-room circulation of air and therefore potentially less indoor tobacco smoke exposure. The pattern of higher association among those living in smaller homes or apartments may be suggestive that the housing size may play a role in the increasing levels of exposure. Apartment buildings had lower number of rooms (69% less than 3 rooms) compared to family houses (only 22% had less than 3 rooms), which is consistent with the pattern of higher associations. On the other hand homes with more room were more likely to have central air conditioning (75% vs 54%), which indicates that the pattern observed with central air conditioning may not be due to housing size.

There are some limitations to our study. Half of the participants (50%) responded to PTS exposure questions at 24 weeks gestation or later when typically GDM screening and diagnosis is between 24 and 28 weeks. As such, recall bias could affect estimates if PTS exposure was differentially reported based on GDM status where it would be overestimating the association if women with GDM tend to recall more exposure than non-cases. However, we conducted a sensitivity analysis among women reporting PTS exposure prior to GDM screening and found similar associations (data not shown). Second, our validation study of the self-reported GDM suggests there could be some misclassification our measure of GDM, when comparing self-report to glucose levels from the GDM screening tests. It is likely that such GDM misclassification is random which would lead to less precise and possibly attenuated estimates.[30] Third, PTS exposure also could be affected by random misclassification. However, we restricted our analysis to home PTS exposure, which has been shown to be a more valid assessment of true exposure to PTS, with a modest correlation of 0.41 for home PTS exposure and serum nicotine concentrations .[16] Finally, this study is substantially underpowered; however, the patterns of associations suggest that PTS exposure and the novel exposure of hookah, might increase the risk of GDM. These findings are inconclusive and will require further investigation in a larger study population.

While our study has a number of limitations, there are several strengths. First, this study provides new information about the association between PTS and GDM on which very little is published. Second, this study evaluated PTS exposure and GDM in a high-exposure, high T2DM prevalent population—those living in Kuwait. Moreover, this study provides unique examination of hookah PTS exposure, an increasingly prevalent form of tobacco exposure, and GDM. Not only is hookah common to the Middle East, but it is also growing in popularity worldwide with possible implications for adverse pregnancy outcomes, including GDM. Finally, we conducted the analyses in primiparous women to evaluate incident GDM, as well as restricted to home PTS exposure to ensure a better measure of valid self-report of PTS exposure.

In summary, while our study was limited by small sample size, the results suggest a positive association between home PTS exposure and GDM. Passive hookah exposure was associated with a significant increased risk of GDM among primiparous women in this cohort. Future studies will need to evaluate this question in a larger population to more definitively determine these associations. If positive and more precise associations are found, then reduction in PTS exposure, particularly hookah exposure, may aid in reducing the burden of GDM, with implications for subsequent reductions in T2DM in this high-risk population.

References

1. Agarwal MM, Dhatt GS, Shah SM. Gestational diabetes mellitus. *Nippon Rinsho*. 2010;115:2018-2020. doi:10.4103/2230-8210.85580.

2. Doherty D a, Magann EF, Francis J, Morrison JC, Newnham JP. Pre-pregnancy body mass index and pregnancy outcomes. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2006;95(3):242-247. doi:10.1016/j.ijgo.2006.06.021.

3. England LJ, Levine RJ, Qian C, et al. Glucose tolerance and risk of gestational diabetes mellitus in nulliparous women who smoke during pregnancy. *American Journal of Epidemiology*. 2004;160(12):1205-1213. doi:10.1093/aje/kwh340.

4. Jovanovic L, Pettitt DJ. Gestational diabetes mellitus. *JAMA*. 2001;286(20):2516-2518. http://www.ncbi.nlm.nih.gov/pubmed/11722247.

5. IDF. International Diabetes Federation. Diabetes prevalence refers to the percentage of people ages 20-79 who have type 1 or type 2 diabetes. 2016. http://data.worldbank.org/indicator/SH.STA.DIAB.ZS.

6. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes care*. 2002;25(10):1862-1868. http://www.ncbi.nlm.nih.gov/pubmed/12351492.

7. CDC. Health Effects of Cigarette Smoking. 2014. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/. Accessed August 17, 2015.

8. MOH KM of H. Kuwait STEPS Report. 2008. http://www.who.int/chp/steps/STEPS_Report_Kuwait.pdf.

9. Yanbaeva DG. Systemic Effects of Smoking<xref rid="AFF1">[*]</xref> *CHEST Journal*. 2007;131(5):1557. doi:10.1378/chest.06-2179.

10. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory Markers and Risk of Developing Type 2 Diabetes in Women. *Diabetes*. 2004;53(3):693-700. doi:10.2337/diabetes.53.3.693.

11. Xie X, Liu Q, Wu J, Wakui M. Impact of cigarette smoking in type 2 diabetes development. *Acta pharmacologica Sinica*. 2009;30(6):784-787. doi:10.1038/aps.2009.49.

12. Bruin JE, Petre MA, Raha S, Morrison KM, Gerstein HC, Holloway AC. Fetal and neonatal nicotine exposure in Wistar rats causes progressive pancreatic mitochondrial damage and beta cell dysfunction. *PloS one*. 2008;3(10):e3371. doi:10.1371/journal.pone.0003371.

13. Wittel U a., Pandey KK, Andrianifahanana M, et al. Chronic pancreatic inflammation induced by environmental tobacco smoke inhalation in rats. *American Journal of Gastroenterology*. 2006;101(1):148-159. doi:10.1111/j.1572-0241.2006.00405.x.

14. Alseaidan M, Al Wotayan R, Christophi CA, et al. Birth Outcomes in a Prospective Pregnancy-Birth Cohort Study of Environmental Risk Factors in Kuwait: The TRACER Study. *Paediatric and perinatal epidemiology*. 2016:(In press).

15. Alseaidan M, Korrick SA, James-Todd TM, et al. Risk Factors Associated with Gestational Diabetes Among Women in Kuwait: the TRACER Study (Submitted for review). *BMC pregnancy and childbirth*. 2016.

16. Prochaska JJ, Grossman W, Young-Wolff KC, Benowitz NL. Validity of self-reported adult secondhand smoke exposure. *Tobacco control*. 2015;24(1):48-53. doi:10.1136/tobaccocontrol-2013-051174.

17. Who. Physical Status: the Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. Technical Report Series No. 854. *Physical status: the use and interpretation of anthropometry Report of a WHO Expert Committee Technical Report Series No 854*. 1995:1-452. doi:854.

18. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *American Journal of Epidemiology*. 2004;159(7):702-706. doi:10.1093/aje/kwh090.

19. Wei X, E. M, Yu S. A meta-analysis of passive smoking and risk of developing Type 2 Diabetes Mellitus. *Diabetes Research and Clinical Practice*. 2015;107(1):9-14. doi:10.1016/j.diabres.2014.09.019.

20. Zhang L, Curhan GC, Hu FB, Rimm EB, Forman JP. Association between passive and active smoking and incident type 2 diabetes in women. *Diabetes Care*. 2011;34(4):892-897. doi:10.2337/dc10-2087.

21. Lajous M, Tondeur L, Fagherazzi G, De Lauzon-Guillain B, Boutron-Ruaualt MC, Clavel-Chapelon F. Childhood and adult secondhand smoke and type 2 diabetes in women. *Diabetes Care*. 2013;36(9):2720-2725. doi:10.2337/dc12-2173.

22. Buchanan T a., Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? *Diabetes Care*. 2007;30(SUPPL. 2). doi:10.2337/dc07-s201.

23. Xiong X, Saunders LD, Wang FL, Demianczuk NN. Gestational diabetes mellitus: prevalence, risk factors, maternal and infant outcomes. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2001;75(3):221-228. http://www.ncbi.nlm.nih.gov/pubmed/11728481.

24. Moore Simas TA, Szegda K, Liao X, Markenson G, Chasan-Taber L. Cigarette smoking and risk of gestational diabetes mellitus in a cohort of hispanic women. *American Journal of Epidemiology*. 2011;173(2):S42. doi:10.1016/j.diabres.2014.04.026.

25. Hosler AS, Nayak SG, Radigan AM. Stressful events, smoking exposure and other maternal risk factors associated with gestational diabetes mellitus. *Paediatric and Perinatal Epidemiology*. 2011;25:566-574. doi:10.1111/j.1365-3016.2011.01221.x.

26. Wendland EMDR, Duncan BB, Belizán JM, Vigo A, Schmidt MI. Gestational diabetes and pre-eclampsia: common antecedents? *Arquivos brasileiros de endocrinologia e*

metabologia. 2008;52(6):975-984. doi:10.1590/S0004-27302008000600008.

27. Katurji M, Daher N, Sheheitli H, Saleh R, Shihadeh a. Direct measurement of toxicants inhaled by water pipe users in the natural environment using a real-time in situ sampling technique. *Inhalation toxicology*. 2010;22(13):1101-1109. doi:10.3109/08958378.2010.524265.

28. Schubert J, Hahn J, Dettbarn G, Seidel A, Luch A, Schulz TG. Mainstream smoke of the waterpipe: Does this environmental matrix reveal as significant source of toxic compounds? *Toxicology Letters*. 2011;205(3):279-284. doi:10.1016/j.toxlet.2011.06.017.

29. Memon A, Moody PM, Sugathan TN, et al. Epidemiology of smoking among Kuwaiti adults: Prevalence, characteristics, and attitudes. *Bulletin of the World Health Organization*. 2000;78(11):1306-1315. doi:10.1590/S0042-96862000001100005.

30. Copeland KT, Checkoway H, Mcmichael AJ, Holbrook RH, Checkoway H, Mcmichael AJ. Bias due to misclassification in the estimation of relative risk. 1977;105(5):488-495.

Chapter 5: Association of High Temperature and Humidity with Preterm Delivery in Extreme Climate: A TRACER Study

Association of High Temperature and Humidity with Preterm Delivery in Extreme Climate: A TRACER Study

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ABSTRACT

Introduction: Preterm delivery (PTD) contributes to significant neonatal morbidity and mortality. There is some evidence associating PTD with extreme climate, especially temperature. We examined PTD in relation to the temperature and humidity in a region where extreme heat is common.

Methods: We assessed 1893 pregnant women enrolled in a prospective study in Kuwait designed to assess the relation of environmental exposures in pregnancy with pregnancy and child health. We investigated the association of singleton PTD with the pre-delivery 7-day mean temperature (T_m), Heat Index (HI), relative humidity (RH), Dew Point (T_d), and Specific Humidity (SH) obtained from the national airport's weather station. We defined PTD as birth prior to 37 weeks gestation based on the maternal last menstrual period. We used a logistic regression time series and case-crossover models to estimate the odds ratio (OR) and 95% confidence intervals (CI) for PTD per standard deviation change in exposure.

Results: The incidence of PTD was 9.3%. During the weeks around delivery, the average T_m was 26.7 ^oC (range: 9.7 - 41) and average RH was 34.2% (range: 7.4 - 83.7). PTD was not associated with the T_m (OR: 0.94, 95% CI: 0.46 - 1.91), but there was a suggestive, albeit not statistically significant, association with RH (OR: 1.34, 95% CI: 0.94 - 1.89). During the hot season (T_m>22^oC), RH was associated with PTD (OR: 1.52, 95% CI: 1.02 - 2.29). Associations with other humidity variables were also positive but lacked statistical significance and remained the same regardless of season. Results from the case-crossover analysis were similar to those from the time-series analysis.

Conclusion: Our findings suggest that high humidity during the hot season in the week prior to birth may increase the odds of PTD. Direct associations with T_m were not observed in this climate where extreme high temperatures are frequent. Public health advisories for pregnant women to avoid the outdoors should be considered during extremely humid and hot conditions.

INTRODUCTION

Significant neonatal morbidity and mortality can be attributed to preterm delivery (PTD) (Martin et al., 2005). Neonates born preterm, especially those with low birth weight, are subject to organ immaturity and bronchopulmonary dysplasia (Smith et al., 2005), visual impairment (Repka, 2002), and cerebral palsy (Wu & Colford, 2000). Compared to regular term born children, preterm born children are more likely to have learning, social, and behavioral difficulties later in life (Marlow, Wolke, Bracewell, Samara, & EPICure Study Group, 2005). Furthermore, PTD leads to longer hospitalization and increased financial costs for families of the newborn (Goldenberg & Culhane, 2007). Preterm delivery in Kuwait is reported in approximately 10.5% of deliveries in Kuwait (Blencowe et al., 2012), which is comparable to 12% in the United States (Blencowe et al., 2012), and 11.1% worldwide (Blencowe et al., 2013). Factors associated with the risk of preterm delivery include maternal demographics, nutritional status, pregnancy history, smoking, stressful work conditions, and infections (Goldenberg, Culhane, Iams, & Romero, 2008). The risk of preterm delivery has also been associated with air pollution episodes and extreme weather conditions have also been associated with risk (Rupa Basu, Malig, & Ostro, 2010; Goldenberg et al., 2008; Ritz, Wilhelm, Hoggatt, & Ghosh, 2007; Wilhelm & Ritz, 2002).

Climate change has led to increased frequency, length and intensity of extreme weather events (Meehl & Tebaldi, 2004). To understand the health implications of these extreme events, it would be informative to examine experiences of populations which experience these events routinely. Kuwait has one of the hottest climates in the world and has extremely variable weather patterns (Nasrallah, Nieplova, & Ramadan, 2004; Shaker, 1966). The mean daily temperature typically ranges from 7^{o}C to 43^{o}C. Humidity also varies from extremely dry to very humid with mean daily relative humidity ranging from 6% to 93%. Weather stressors such as excessive heat or humidity episodes may increase maternal physiological stress because pregnant women may have a lower ability to mitigate heat due to physiological changes such as fat deposition and lower body surface area to mass ratio (Wells & Cole, 2002).

Several studies have suggested that the risk of PTD might be linked to weather exposures such as high heat and humidity (Dadvand et al., 2011; Kent, McClure, Zaitchik, Smith, & Gohlke, 2014; Lajinian, Hudson, Applewhite, Feldman, & Minkoff, 1997; Schifano et al., 2013; Vicedo-Cabrera, Iñíguez, Barona, & Ballester, 2014). However, none of the studies evaluated the association of PTD with temperature and humidity in the Middle-East specifically the Arab Gulf region (Kuwait, Saudi, Bahrain, UAE, Qatar, and Oman) where the temperature reaches extreme highs and the humidity is highly variable. In these countries high humidity frequently coincides with high temperatures which may trigger heat stress decompensation mechanisms (Coris, Ramirez, & Van Durme, 2004). In this paper, we examined the association of PTD with temperature and humidity in a population of pregnant women from Kuwait. We used data collected prospectively from the TRansgenerational Assessment of Children's Environmental Risks (TRACER) pregnancy birth cohort.

METHODS

Pregnant women were recruited at nine prenatal clinics (6 public and 3 private) covering all 6 governorates of Kuwait between June 2012 and January 2015. Kuwait and non-Kuwaiti women between 18 and 45 years of age with confirmed singleton pregnancies were invited to participate. After the study details were explained, informed consent was obtained from the pregnant woman and her husband. The TRACER study has been described in more detail previously (Alseaidan et al., 2016).

After enrollment, the TRACER field staff administered a baseline questionnaire the participant's home or the clinic based on the participant's convenience. The questionnaire included self-reported information on date of last menstrual period (LMP), age, number of live children (used to approximate parity), income, education, weight prior to the pregnancy, and height. The questionnaires also asked participants about their active smoking behaviors and their exposure to second hand smoke during pregnancy. We followed the participants throughout their pregnancy. Women were followed up post-delivery to determine birth date, complications, and characteristics of the newborn. We included all the births from the start of study recruitment (June 2012) through the end of pregnancy follow up in August 2015.

A total of 2723 participants consented to participate in the TRACER study and 2478 completed baseline questionnaires necessary for final enrollment. Of those 2254 were followed until birth. For this analysis we excluded those who were missing information about LMP or child date of birth (n=113), answered the baseline questionnaire after 36 weeks of pregnancy (n=197), had missing weather variables around the time of birth (n=2), had missing covariates such as nationality, age, income, education, pre-pregnancy BMI, and tobacco smoke exposure (n=29), or had inconsistent (transcription errors) reported last menstrual period (n=18).

The study was reviewed and monitored by the Institutional Review Boards at both the Harvard T.H. Chan School of Public Health and the Dasman Diabetes Institute.

<u>Exposure ascertainment:</u> Daily mean temperature (°C), Dew Point temperature (°C), relative humidity (%) and atmospheric pressure measured at the Kuwait International Airport for the period between June 2012 to August 2015 were retrieved from the Weather Underground Website (Weather Undeground, 2015) . We used the mean daily temperature, mean daily Dew Point temperature to calculate the Heat Index (°C) using the US National Weather Service's algorithm (Brooke Anderson, Bell, & Peng, 2013). Specific Humidity (SH), a measure of mass of water vapor per kilogram of air (g/kg), was calculated from mean Dew Point temperature and atmospheric pressure (Saucier, 2003) using the following equation:

$$SH\ (g/kg) = 1000*(0.622 \times e)/[P - (0.378 \times e)] \text{ and } e=6.11 \times 10^{(7.5+Td)/(237.7+Td).}$$

where e is the vapor pressure (mb), T_d is the Dew Point temperature (^oC), and P is the atmospheric pressure (mb).

The Kuwait International airport is centrally located, south of the Kuwaiti residential areas (Figure 4.1). The clinics are generally close to the airport (4.3km to West Farwaniya clinic, 8.3km to Sabah Al-Nasser clinic, 9.2km to Qurain clinic, 10.3km for Al-Saqer Clinic, 10.4km to South Hawalli clinic, 10.9km to Royal Hayat hospital, 11.1km to Al-Hakeem clinic, and 16km to New Muwasat clinic), except for the Jahra clinic which is 31.2km away (Figure 4.1).

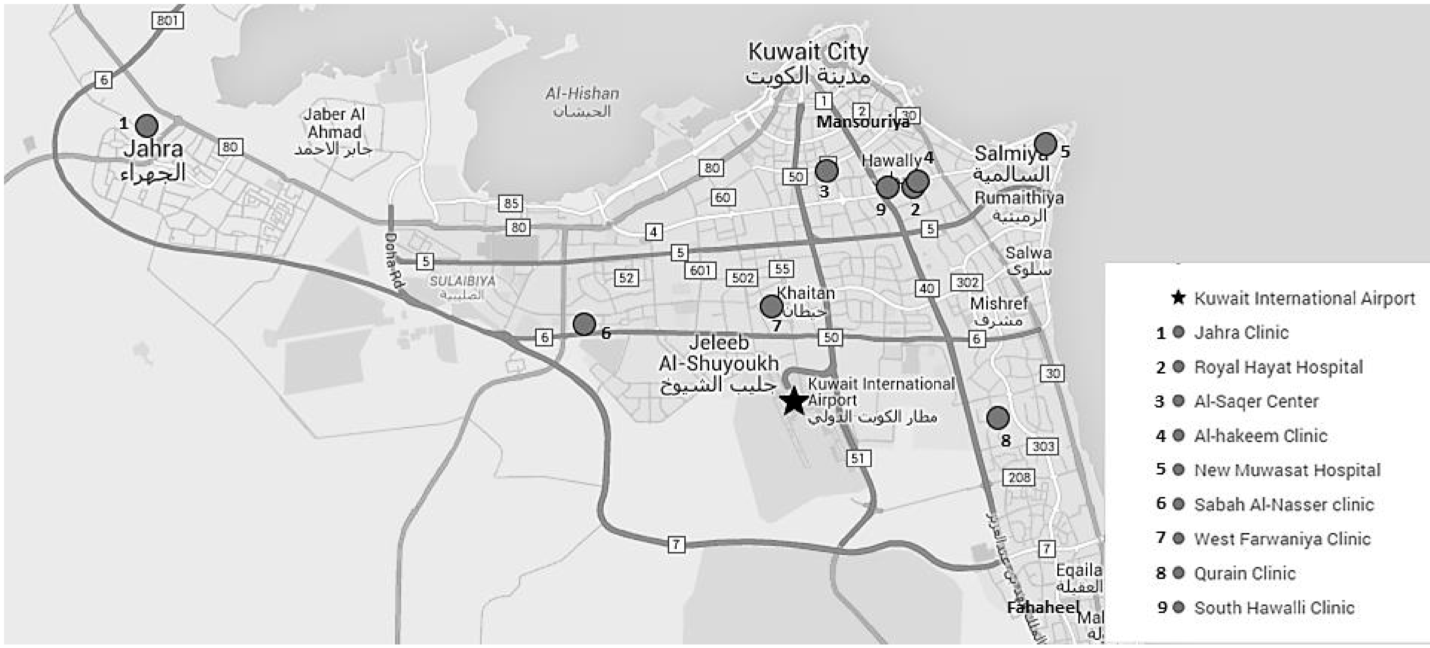
PreTerm Delivery: The baby's gestational age at birth was calculated in completed weeks using the participants' reported last menstrual period and the child's date of birth. We defined PTD as delivery prior to 37 weeks of gestation.

Maternal characteristics: Maternal characteristics considered as potential confounders included maternal age (years), nationality (Kuwaiti vs non-Kuwaiti), parity, pre-pregnancy BMI (Normal, Overweight, or Obese), monthly income in (<400, 400-800, 801-1600, and 1601+ Kuwaiti Dinars), education (high school or less, 2 year diploma, and 4 years of college or more), active smoking (yes vs no), and home passive smoke exposure (more than 1 hour per week, or less than 1 hour).

Time varying covariates: To model the associations with season, we parameterized the models with categorical indicators of month and calendar year of birth. We also adjusted for Ramadan and other religious and national holidays, but these were not predictive after adjustment for month and calendar year.

Air pollution levels are potentially time varying confounders of interest. Daily concentrations of Sulfur Dioxide (SO_2), Nitrogen Dioxide (NO_2), Ozone (O_3), Carbon Monoxide (CO), Particulate matter <10μm aerodynamic diameter (PM_{10}), and particulate matter <2.5μm aerodynamic diameter ($PM_{2.5}$) were available from the Kuwait Environmental Public Authority for the period from June 2012 to June 2014. We estimated the daily average for SO_2, NO_2, O_3, CO, and PM_{10} from the 4 stations (Fahaheel, Mansouriya, Al-Jahra, and Al-Rumaithiya) that had the most complete air pollution measurements collected and that were situated close to the densely populated areas of Kuwait. Only one station (Jahra) had $PM_{2.5}$ data but the data was incomplete and very limited in daily coverage, therefore, it was not used for this analysis.

Figure 4.1: Map of Kuwait City showing the TRACER study clinic locations



Statistical Analysis:

Time series analysis: We examined the association between the 2, 4, and 7 day moving averages (including day of birth) of weather variables with PTD (Supplementary table 4.1). We found stronger associations with the 7 day averages which we present in this paper (other durations of exposure are presented in the Supplementary Table 4.1). In addition to the mean daily Heat Index (HI) we examined PTD with the average daily mean temperature (T_m), mean relative humidity (RH), mean Specific Humidity (SH), and mean Dew Point temperature (T_d). We used logistic regression models for each exposure controlling for month of birth and year of birth.

Nguyen and Dockery (2015) showed that residential indoor temperature in Kuwait correlated with outdoor (airport) measurements up to approximately 22°C, but were not correlated at higher outside temperature (see Supplemental Figure 4.1). We examined effect modification by temperature in an interaction model. We included an interaction term with PTD for average daily temperature above 22°C, and estimated the associations above and below 22°C for the different weather variables with PTD using linear combinations.

To examine the shape of the dose-response relationship between these exposures and PTD, we used Generalized Additive Modeling with penalized cubic splines. We compared the spline models to the linear models using an analysis of deviance where the spline models were considered the saturated models. We reported the Odds Ratio (OR) and 95% Confidence Intervals (95% CI) for the linear models if the spline model did not fit the data significantly better. We considered a p-value of 0.1 for the test of deviance as the cutoff point for non-linearity when the linear models were compared to the spline models. We considered all the aforementioned potential confounders in our models.

Case-Crossover analysis: To intrinsically adjust for confounding by maternal characteristics, we analyzed the data using a time-stratified case-crossover design, in which exposure on the days prior to a PTD case are compared to exposures on days for non-case (control) days. Control days were selected as the same day of the week within the same calendar month (Janes, Sheppard, & Lumley, 2005; Levy, Lumley, Sheppard, Kaufman, & Checkoway, 2001). Figure 4.2 shows the selection scheme for this study with 4 to 5 selected control periods per case. The case-crossover design eliminates confounding by maternal characteristics because each case serves as her own control (Maclure, 1991). Potential confounding by seasonality is reduced because we are comparing case and bidirectional control periods within the same month.

Exposures during case periods were compared to control periods with conditional logistic regression. We used the PROC PHREG procedure in SAS 9.4 with BRESLOW method for ties, to create risk-sets using the participant's ID in the Strata statement. Each of the weather measures was modelled as a linear function. Adjusting for Ramadan and other holidays did not affect the estimates as there was no discordance within case-control sets therefore holiday and Ramadan indicator variables were not included in our case-crossover models. We assessed whether the associations for each weather variable differed according to average temperature in our case-crossover models by including the 22°C T_m indicator variable as an interaction term and created linear combinations for our estimates.

In a subset of our data where air pollution variable are available (n=1549) we compared the results before and after adjusting for the air pollution variables to assess confounding.

Figure 4.2. Describing the controls selection for each case within the same month and same day of the week.

Case control Set	Week1	Week2	Week3	Week4	Week5*
Type 1	Case	Control	Control	Control	Control
Type 2	Control	Case	Control	Control	Control
Type 3	Control	Control	Case	Control	Control
Type 4	Control	Control	Control	Case	Control
Type 5	Control	Control	Control	Control	Case

***Cases occurring in the first week of the month may be assigned an additional control from the 5th week if the month had a fifth week with the same day of the week as the case occurrence.**

RESULTS

Among the 1893 births in these analyses, the incidence of preterm delivery was 9.3% (95% CI: 8.0 – 10.6). Kuwaiti women had a significantly ($p < 0.001$) higher incidence of PTD (13.2%) compared to non-Kuwaiti women (7.9%, Table 4.1). There were no significant differences by other maternal characteristics (Table 4.1). The occurrence of PTD was higher in the warmer months (March to August) than at other times of the year (Table 4.1).

Seven day mean temperature for the 7 days prior to birth was 26.7 ^{o}C among term births, with a range from 9.7 ^{o}C to 41.9 ^{o}C (Table 4.2). Mean relative humidity was very low (34.2%) but with a range from 7.4% to 83.7%. Mean temperature was almost perfectly correlated with Heat Index (Pearson correlation 0.99), but inversely correlated with Relative Humidity (Pearson correlation -0.79). Temperature was not correlated with Dew Point ($r=-.05$) or Specific Humidity ($r=-.03$). Dew Point and Specific Humidity were highly correlated with each other ($r=0.97$), but only modestly with Relative Humidity ($r = 0.58$ and 0.56 respectively).

We found a large variation in Temperature, Heat Index, and Relative Humidity by month (Figure 4.3). Mean daily temperature ranged from 7^{o} to 43^{o}C with the highest in June, July, and August. RH ranged from 5% to 93% with the lowest values in June and July. Dew Point temperature and Specific Humidity did not have such a strong seasonal pattern, but were highly variable except in the summer months (Figure 4.3).

Time series analysis

After adjusting for seasonality and maternal characteristics we found that the 7 day average Dew Point temperature, Specific Humidity, and Relative Humidity prior to birth were positively associated with PTD, but the associations lacked statistical significance (Table 4.3).

The shape of exposure response association of PTD with 7 day averages of mean daily temperature and mean daily Heat Index appeared to be non-linear, with positive below 25^{o}C and negative above that (Figure 4.4). In contrast the non-parametric fitted data for Relative

Humidity, Dew Point, and Specific Humidity did not significantly deviate from linearity (ANOVA test of difference chi-square p-values of 0.63, 0.28, and 0.18, respectively). Therefore we used linear models or piecewise linear models for all the weather variables.

There was no clear association between temperature or Heat Index above or below the 22°C T_m (Table 4.3). Relative Humidity had a statistically significant association with PTD above the 22°C mean daily temperature (OR 1.52, 95%CI: 1.02 – 2.29, p-value 0.04), but a weaker association below that temperature (Table 4.3). Dew Point had a weaker and non-significant association that was the same above and below the 22°C T_m cutoff (Table 4.3). Specific Humidity also had a positive but non-statistically significant association with PTD above the 22°C mean temperature cutoff (Table 4.3).

Case-crossover analysis

In case-crossover analyses we found results very similar to those in the time-series analysis (Table 4.4). Above the 22°C mean daily temperature, we found Relative Humidity had a strong and statistically significant positive association (OR1.73, 95% CI: 1.08 – 2.78, p-value 0.02, Table 4.4).

In sensitivity analysis, the results were not materially altered upon adjustment for Ozone, Sulfur Dioxide, Nitrogen Dioxide, Carbon Monoxide, or PM_{10} (Data not shown).

Table 4.1. Sample characteristics, numbers and % preterm stratified by 7 day average of mean daily temperature N=1893, with 176 cases and 1717 non-cases)

	N	% Preterm	χ^2 p-value
Total	1893	9.30	
Nationality			
non-Kuwaiti	1386	7.90	0.0004
Kuwaiti	507	13.20	
Age (years)			
<25	445	8.76	0.92
25-30	715	9.09	
30-35	500	9.60	
35+	233	10.3	
Parity			
None	640	8.75	0.23
1 to 2	902	8.76	
3 or more	351	11.68	
Pre-pregnancy BMI			
Underwt or Normal	855	8.19	0.31
Overweight	626	10.38	
Obese	412	9.95	
Education			
High school or less	584	9.25	0.1
2 year diploma	286	12.59	
College or more	1023	8.41	
Child Sex			
Female	888	9.00	0.68
Male	1005	9.60	
Month of birth			
DJF	465	8.82	0.26
MAM	464	9.89	
JJA	474	9.92	
SON	490	8.57	
7 Day Mean Temperature (^oC)			
9.7 – 18.6	471	8.28	0.63
18.7 – 26.6	475	8.84	
26.7 – 36.0	488	9.43	
36.1 – 41.9	459	10.68	

Table 4.2. Distribution of pre-delivery 7 day average weather variables by outcome

Weather variable	N	Mean (SD)	Min	P25	Median	P75	Max
Temperature (^{o}C)							
Term	**1717**	26.7 (9.3)	9.7	18.6	26.4	36.0	41.9
Preterm	**176**	27.5 (9.2)	10.6	19.6	28.0	36.5	41.3
Heat Index (^{o}C)							
Term	**1717**	25.3(8.7)	7.9	17.9	25.7	33.1	42.6
Preterm	**176**	26.1(8.6)	9.3	19.1	27.2	34.1	42.3
Relative Humidity (%)							
Term	**1717**	34.2 (20.9)	7.4	16.3	27.9	52.4	83.7
Preterm	**176**	33.6 (20.9)	8.3	15.1	26.9	52.3	82.1
Dew Point (^{o}C)							
Term	**1717**	6.1 (4.5)	-4.7	3.0	5.9	9.0	22.3
Preterm	**176**	6.3 (4.2)	-2.3	3.2	6.4	8.5	22.3
Specific Humidity (g/kg)							
Term	**1717**	6.2 (2.1)	2.7	4.8	5.8	7.4	17.3
Preterm	**176**	6.3 (2.1)	3.3	5.0	6.1	7.1	17.3

Figure 4.3. Distribution of daily weather variables by month (comparing term and preterm deliveries)

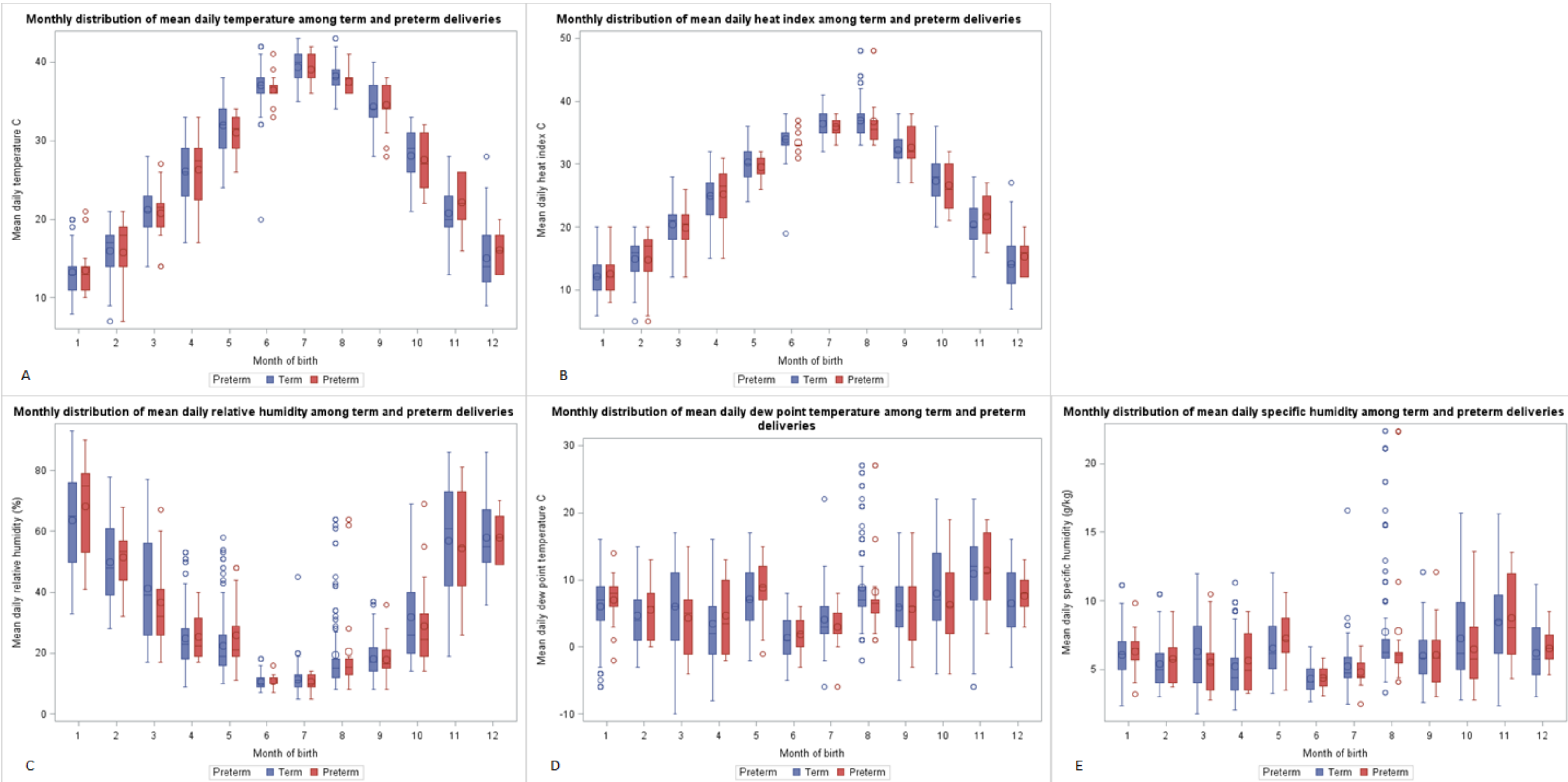
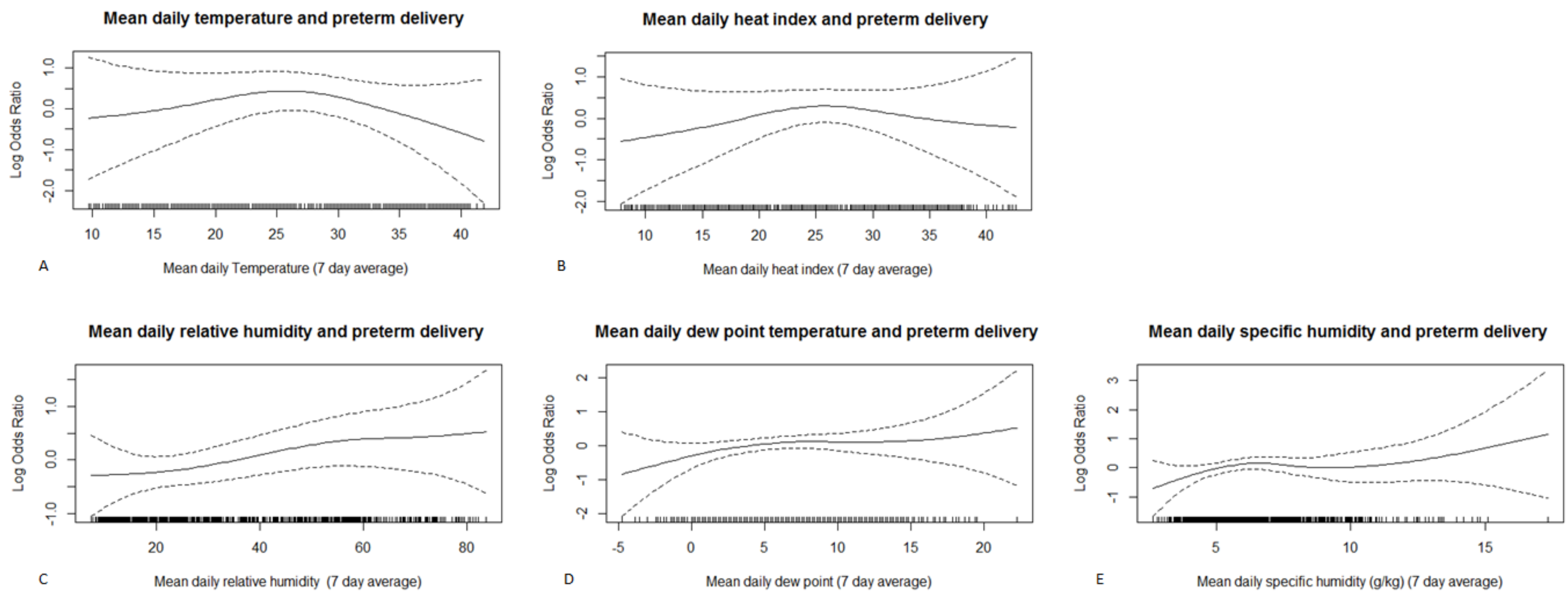


Figure 4.4. Penalized cubic splines for the time series analysis log odds ratio of preterm delivery by weather variables.



A: Daily mean temperature, B: Daily mean Heat Index, C: Daily mean Relative Humidity, D: Daily mean Dew Point temperature, E: Daily mean Specific Humidity.

Table 4.3. Time series logistic regression analysis of preterm delivery (<37 weeks) by atmospheric measures stratified by the 7 day average temperature (Temp<22°C, Temp≥22°C). (Scaled by non-case SD)

	Non-Case (n=1717)	Cases (N=176)	Overall				Below 22°C				Above 22°C			
	Mean (SD)	Mean (SD)	OR	(95%	CI)	p-value	OR	(95%	CI)	p-value	OR	(95%	CI)	p-value
Temperature (°C)	26.70 (9.30)	27.50 (9.20)	0.94	(0.46,	1.91)	0.85	0.71	(0.29,	1.74)	0.46	0.86	(0.41,	1.78)	0.69
Heat Index (°C)	25.29 (8.73)	26.08 (8.63)	1.14	(0.60,	2.16)	0.69	0.95	(0.43,	2.09)	0.90	1.09	(0.57,	2.08)	0.79
Relative Humidity (%)	34.19 (20.85)	33.57 (20.93)	1.34	(0.94,	1.89)	0.11	1.24	(0.86,	1.78)	0.25	1.52	(1.02,	2.29)	0.04
Dew Point (°C)	6.09 (4.48)	6.33 (4.22)	1.16	(0.95,	1.41)	0.15	1.16	(0.88,	1.53)	0.30	1.16	(0.93,	1.46)	0.20
Specific humidity (g/kg)	6.23 (2.07)	6.32 (2.07)	1.13	(0.94,	1.36)	0.20	1.07	(0.84,	1.37)	0.57	1.15	(0.95,	1.39)	0.15

- All odds ratio estimates are scaled using the standard deviation of exposure among non-cases.
- The models have been adjusted for month of conception (categorical variable), age, income, education, nationality, parity, pre-pregnancy BMI, baby's sex, Ramadan (Muslim fasting month), holidays, active smoking, and exposure to second hand smoke at home.

Table 4.4. Mean daily temperature stratified (Temp<22°C & Temp≥22°C) case-crossover analysis of preterm delivery and weather exposures using conditional logistic regression.

	non-case		case		Overall				Below 22°C				Above 22°C			
	Mean	(SD)	Mean	(SD)	OR	(95%	CI)	p-value	OR	(95%	CI)	p-value	OR	(95%	CI)	p-value
Temperature (°C)																
	26.7	9.3	27.5	9.2	0.75	(0.36,	1.56)	0.44	0.5	(0.19,	1.30)	0.16	0.67	(0.31,	1.42)	0.29
Heat Index (°C)																
	25.3	8.7	26.1	8.6	0.94	(0.48,	1.84)	0.87	0.72	(0.31,	1.68)	0.45	0.89	(0.45,	1.76)	0.75
Relative Humidity (%)																
	34.2	20.9	33.6	20.9	1.42	(0.96,	2.08)	0.08	1.31	(0.88,	1.96)	0.19	1.73	(1.08,	2.78)	0.02
Dew Point (°C)																
	6.1	4.5	6.3	4.2	1.16	(0.93,	1.44)	0.19	1.15	(0.86,	1.53)	0.35	1.17	(0.90,	1.51)	0.23
Specific Humidity (g/kg)																
	6.2	2.1	6.3	2.1	1.13	(0.92,	1.40)	0.23	1.07	(0.82,	1.38)	0.63	1.17	(0.94,	1.45)	0.16

All odds ratio estimates are scaled using the standard deviation of exposure among non-cases

All models have been adjusted for age in years, nationality (Kuwaiti vs non-Kuwaiti), education, income, parity, pre-pregnancy BMI, and child sex.

The analysis is restricted to those who answered the baseline questionnaire prior to delivery and were recruited into the study prior to 37 weeks of pregnancy

DISCUSSION

We found that in the very hot and dry climate of Kuwait, the risk of preterm delivery was associated with 7 day average of humidity (Relative Humidity, Dew Point temperature, and Specific Humidity), but not with mean daily temperature or Heat Index. This is in contrast to many previous studies which have reported ambient temperature was positively associated with preterm delivery (Arroyo et al., 2015; Kent et al., 2014; Kloog, Melly, Coull, Nordio, & Schwartz, 2015; Strand, Barnett, & Tong, 2011; Wang, Williams, Guo, Pan, & Tong, 2013; Yackerson, Piura, & Sheiner, 2008). Our findings also contrast with the studies that reported a positive association between PTD and the apparent temperature or heat-humidity Index (Rupa Basu et al., 2010; Dadvand et al., 2011; Kent et al., 2014; Lajinian et al., 1997; Schifano et al., 2013).

This study examined the experiences of pregnant women in a very hot and dry climate (mean temperature 27 ^{o}C, mean Relative Humidity 27%). These conditions are very different from those from almost all other studies, but of interest as evidence of associations which might be experienced under extreme global warming scenarios. Some of the published studies examined the association in mild, Mid-Atlantic coastal climates of the United States, such as Massachusetts (Kloog et al., 2015) and New York (Lajinian et al., 1997). Others studied populations in warm, subtropical climates, such as Barcelona (Dadvand et al., 2011) and Alabama (Kent et al., 2014). One study examined the association in Negev, which is similarly hot (mean temperature 27.5 ^{o}C) but much more humid (mean Relative Humidity 83.4%)(Yackerson et al., 2008).

There is mounting evidence that populations respond to local variation in temperature about the mean rather than mean temperature (Gasparrini et al., 2015; M. Lee et al., 2014). That is, populations adapt to the local climate, although variation from the mean still can produce environmental stress and adverse health events. The high average temperatures in Kuwait are tolerable because of universal reliance on air conditioning for almost the entire year (Al-Marafie, Suri, & Maheshwari, 1989). This adaptation contrasts with other locations where the prevalence of air conditioning is inconsistent (R. Basu & Ostro, 2008; Stafoggia, Schwartz, Forastiere, & Perucci, 2008). There is a disconnect in the associations between heat related health outcomes and temperature in hot cities that is modulated by the prevalence of air conditioning (Braga, Zanobetti, & Schwartz, 2001). The study in the very hot Negev, also failed to find a positive association between ambient temperature and preterm delivery, but reported a strong association with changes (variation) in temperature (Yackerson et al., 2008). An analysis of daily temperature measured in two residences in Kuwait and outdoor temperatures measured at Kuwait International Airport found very poor correlation especially during the hot season (Nguyen & Dockery, 2015). This lack of correlation between temperature in homes and outdoor temperature, may explain the lack of association in Kuwait between outdoor (airport) temperature and preterm delivery. Populations living in hot climates usually adapt by changing their daily and social habits to avoid the heat of the day (Robinson, 2001).

In contrast to the lack of associations of preterm delivery with temperature or Heat Index in Kuwait, we found suggestive, although not statically significant, positive associations between preterm delivery and three measures of the water content of the ambient air – Relative Humidity, Dew Point and Specific Humidity. Very few studies examined humidity as a separate weather variable; two studies found no associations (Hirsch, Lim, Dobrez, Adams, & Noble, 2011; S. J. Lee, Hajat, Steer, & Filippi, 2008) but the study in Negev found a significant positive association (Yackerson et al., 2008). Consistent with the Negev study, we found a positive association with Relative Humidity. While both Negev and Kuwait have hot climates, Negev has much higher average humidity than Kuwait. Indeed, Kuwait has extremely low humidity most of the year and the local population may not rapidly adapt to increases in humidity. Dew Point temperature and Specific Humidity had weaker associations compared to Relative Humidity.

Both Specific Humidity and Dew Point temperature were confined to a narrow range which limits our ability to detect an association. On the other hand Relative Humidity showed a linear relationship over a wide range of exposure.

There are several methodological challenges to be considered when analyzing PTD in relation to weather exposures. Maternal characteristics and behaviors can be strong predictors of preterm delivery, and could confound the associations with weather if these maternal characteristics are correlated with season, for example through seasonality of conception (Darrow et al., 2009). However, when looking at 7 day average weather variables within season maternal characteristics are unlikely to confound the associations. We adjusted for nationality and other maternal characteristics in our time series analyses. On the other hand, the case-crossover analysis greatly reduces such confounding by any non-time varying covariates, thus providing complementary support for our time-series analysis. While adjusting for air pollution variables in our sensitivity analysis did not suggest confounding, residual confounding by these covariates remains a possibility. Seasonal exposures such as infections are less likely to confound the associations in the case-crossover analysis because the case and control periods are within the same month, assuming there is no rapid change within the months. The time-stratified bidirectional sampling of control periods is important in these analyses because the risk of preterm labor increases as the pregnancy progresses (Darrow et al., 2009). However, it is important to appreciate that the case-crossover methods was developed to examine fairly non-changing risk outcomes. Since preterm delivery risk changes in a non-linear fashion over the stratified time periods, the bidirectional sampling scheme may not adjust for time trending within the sampling period. While this method has been used in the prior published analyses , there is the possibility of bias for reproductive outcomes such as preterm delivery.

There are challenges in defining the health outcome preterm birth. We used self-reported date of last menstrual period to define gestational age at delivery and preterm birth, as is common in these studies. However, determination of last menstrual period is subject to error among women who were on birth control or had irregular periods. These conditions may be associated with PTD but are not likely to be associated with weather conditions, resulting in non-differential measurement error. Random misclassification of PTD also is a concern because many women were asked to recall their last menstrual period late in their pregnancy (second and third trimesters). A large proportion of preterm deliveries are expected to be in the 36^{th} week of pregnancy (Carolan-Olah & Frankowska, 2014). A one week random error in calculation of gestational age could result in loss of power and attenuation of the estimated associations. We have information about the mode of delivery for only a subsample of 452 participants in the TRACER cohort. Thirty two percent (32%) of these women who had term deliveries had cesarean deliveries, while 56% of those who had preterm deliveries had cesarean deliveries. It is unlikely that these procedures were conducted electively prior to 37 weeks as it does not comply with medical practices in Kuwait. Therefore, cesarean deliveries, either elective or clinically indicated, are unlikely to affect the incidence of preterm delivery.

There is also the potential for misclassification of the exposure to ambient weather conditions. During periods of extreme heat, pregnant women would spend little time outdoors. The degree to which indoor environment does not reflect the outdoor ambient environment would produce random misclassification of exposure. Measurements of daily indoor temperature and humidity over a year in two Kuwaiti home (one single family home and one apartment) showed airport weather measures were weakly correlated with temperature (r=0.54) and apparent temperature (r=0.56) but more strongly correlated with Relative Humidity (r=0.70), Dew Point (r=0.81), or Specific Humidity (r=0.77)(Nguyen and Dockery 2015).

Pregnancy places an increased metabolic burden on the mother, especially in the late stages just before delivery. It is plausible that environmental stresses late in pregnancy could trigger a cascade of compensatory responses that could trigger preterm labor. Exposure to high temperature can be detrimental to the pregnancy (Duong et al., 2011; Hartgill, Bergersen, & Pirhonen, 2011). Pregnant women have a lower ability to mitigate heat due to physiological changes such as fat deposition and lower body surface area to mass ratio (Wells & Cole, 2002). Evaporation is the primary mechanisms of heat mitigation, and evaporative cooling of the body is reduced in humid conditions (Coris et al., 2004). Weather stressors such as excessive heat or high humidity episodes may increase maternal physiological stress through the adrenocorticotropic hormone axis which in turn may increase the risk of PTD (Lockwood, 1999). The inability to mitigate heat stress may be associated with PTD via increase in antidiuretic hormone and oxytocin secretion as well as reduction in placental blood flow (Dreiling, Carman, & Brown, 1991). Heat stress is associated with the release of heat shock protein 70 which is associated with labor(Chang et al., 2013). Metabolic insufficiency may trigger early parturition (Dunsworth, Warrener, Deacon, Ellison, & Pontzer, 2012) if exposure to heat and humidity increase the mother's metabolic needs at the expense of fetal metabolic needs, especially among those with placental insufficiencies. These mechanisms focus on the association between PTD and heat. However, due to the nature of the hot and dry climate of Kuwait, the Kuwaiti population may be proficient in adapting to heat, but not humid conditions in which may trigger the above heat related mechanisms via decompensation.

Conclusion

We did not find that high temperature or Heat Index in Kuwait was associated with preterm delivery. However, we did find that ambient water content measures (Relative Humidity, Dew Point, and Specific Humidity) were positively associated with preterm delivery. Environmental stress may trigger preterm delivery in pregnant women because of inability to maintain body temperature. Outdoor temperature and Heat Index may not adequately measure this stress, at least in the hot, dry climate of Kuwait where indoor temperatures are controlled all year.

Alternative measures of the water content of air, a key factor in evaporative cooling to maintain body temperature, may be more informative in assessing environmental stress.

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References

Al-Marafie, A. M. R., Suri, R. K., & Maheshwari, G. P. (1989). Energy and power management in air-conditioned buildings in Kuwait. *Energy*, *14*(9), 557–562. doi:10.1016/0360-5442(89)90027-3

Alseaidan, M., Al Wotayan, R., Christophi, C. A., Al-Makhseed, M., Abu Awad, Y., Nassan, F., … Behbehani, K. (2016). Birth Outcomes in a Prospective Pregnancy-Birth Cohort Study of Environmental Risk Factors in Kuwait: The TRACER Study. *Paediatric and Perinatal Epidemiology*, (In press).

Arroyo, V., Díaz, J., Ortiz, C., Carmona, R., Sáez, M., & Linares, C. (2015). Short term effect of air pollution, noise and heat waves on preterm births in Madrid (Spain). *Environmental Research*, *145*, 162–168. doi:10.1016/j.envres.2015.11.034

Basu, R., Malig, B., & Ostro, B. (2010). High ambient temperature and the risk of preterm delivery. *American Journal of Epidemiology*, *172*(10), 1108–1117. doi:10.1093/aje/kwq170

Basu, R., & Ostro, B. D. (2008). A Multicounty Analysis Identifying the Populations Vulnerable to Mortality Associated with High Ambient Temperature in California. *American Journal of Epidemiology*, *168*(6), 632–637. doi:10.1093/aje/kwn170

Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A.-B., … Lawn, J. (2013). Born Too Soon: The global epidemiology of 15 million preterm births. *Reproductive Health*, *10*(Suppl 1), S2. doi:10.1186/1742-4755-10-S1-S2

Blencowe, H., Cousens, S., Oestergaard, M. Z., Chou, D., Moller, A.-B., Narwal, R., … Lawn. Joy E. (2012). Country data and rankings for preterm birth EMBARGO UNTIL MAY 2ND 2012. *"Born Too Soon: The Global Action Report on Preterm Birth,"* 6–9. Retrieved from http://www.who.int/pmnch/media/news/2012/201204_borntoosoon_countryranking.pdf

Braga, A. L., Zanobetti, A., & Schwartz, J. (2001). The time course of weather-related deaths. *Epidemiology (Cambridge, Mass.)*, *12*(6), 662–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11679794

Brooke Anderson, G., Bell, M. L., & Peng, R. D. (2013). Methods to calculate the heat index as an exposure metric in environmental health research. *Environmental Health Perspectives*, *121*(10), 1111–1119. doi:10.1289/ehp.1206273

Carolan-Olah, M., & Frankowska, D. (2014). High environmental temperature and preterm birth: A review of the evidence. *Midwifery*, *30*(1), 50–59. doi:10.1016/j.midw.2013.01.011

Chang, A., Zhang, Z., Jia, L., Zhang, L., Gao, Y., & Zhang, L. (2013). Alteration of heat shock protein 70 expression levels in term and preterm delivery. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *26*(16), 1581–5. doi:10.3109/14767058.2013.795535

Coris, E. E., Ramirez, A. M., & Van Durme, D. J. (2004). Heat Illness in Athletes: The Dangerous Combination of Heat, Humidity and Exercise. *Sports Medicine*, *34*(1), 9–16. doi:10.2165/00007256-200434010-00002

Dadvand, P., Basagaña, X., Sartini, C., Figueras, F., Vrijheid, M., de Nazelle, A., … Nieuwenhuijsen, M. J. (2011). Climate extremes and the length of gestation. *Environmental Health Perspectives*, *119*(10), 1449–1453. doi:10.1289/ehp.1003241

Darrow, L. a, Strickland, M. J., Klein, M., Waller, L. a, Flanders, W. D., Correa, A., … Tolbert, P. E. (2009). Seasonality of birth and implications for temporal studies of preterm birth. *Epidemiology (Cambridge, Mass.)*, *20*(5), 699–706. doi:10.1097/EDE.0b013e3181a66e96

Dreiling, C. E., Carman, F. S., & Brown, D. E. (1991). Maternal endocrine and fetal metabolic responses to heat stress. *Journal of Dairy Science*, *74*(1), 312–27. doi:10.3168/jds.S0022-0302(91)78175-7

Dunsworth, H. M., Warrener, a. G., Deacon, T., Ellison, P. T., & Pontzer, H. (2012). Metabolic hypothesis for human altriciality. *Proceedings of the National Academy of Sciences*, *109*(38), 15212–15216. doi:10.1073/pnas.1205282109

Duong, H. T., Shahrukh Hashmi, S., Ramadhani, T., Canfield, M. A., Scheuerle, A., Kim Waller, D., & National Birth Defects Prevention Study. (2011). Maternal use of hot tub and major structural birth defects. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *91*(9), 836–41. doi:10.1002/bdra.20831

Gasparrini, A., Guo, Y., Hashizume, M., Kinney, P. L., Petkova, E. P., Lavigne, E., ... Armstrong, B. G. (2015). Temporal variation in heat–mortality associations: A multicountry study. *Environmental Health Perspectives*, *123*(11), 1200–1207. doi:10.1289/ehp.1409070

Goldenberg, R. L., & Culhane, J. F. (2007). Low birth weight in the United States. *The American Journal of Clinical Nutrition*, *85*(2), 584S–590S.

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. *Lancet*, *371*(9606), 75–84. doi:10.1016/S0140-6736(08)60074-4

Hartgill, T., Bergersen, T., & Pirhonen, J. (2011). Core body temperature and the thermoneutral zone: A longitudinal study of normal human pregnancy. *Acta Physiologica (Oxford, England)*, *201*(4), 467–474. doi:10.1111/j.1748-1716.2010.02228.x

Hirsch, E., Lim, C., Dobrez, D., Adams, M. G., & Noble, W. (2011). Meteorological factors and timing of the initiating event of human parturition. *International Journal of Biometeorology*, *55*(2), 265–272. doi:10.1007/s00484-010-0332-2

Janes, H., Sheppard, L., & Lumley, T. (2005). Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology (Cambridge, Mass.)*, *16*(6), 717–26. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16222160

Kent, S. T., McClure, L. a., Zaitchik, B. F., Smith, T. T., & Gohlke, J. M. (2014). Heat waves and health outcomes in Alabama (USA): The importance of heat wave definition. *Environmental Health Perspectives*, *122*(2), 151–158. doi:10.1289/ehp.1307262

Kloog, I., Melly, S. J., Coull, B. A., Nordio, F., & Schwartz, J. D. (2015). Research | Children ' s Health Using Satellite-Based Spatiotemporal Resolved Air Temperature Exposure to Study the Association between Ambient Air Temperature and Birth Outcomes in Massachusetts, *123*(10), 1053–1058. doi:10.1289/ehp.1308075

Lajinian, S., Hudson, S., Applewhite, L., Feldman, J., & Minkoff, H. L. (1997). An association between the heat-humidity index and preterm labor and delivery: A preliminary analysis. *American Journal of Public Health*, *87*(7), 1205–1207. doi:10.2105/AJPH.87.7.1205

Lee, M., Nordio, F., Zanobetti, A., Kinney, P., Vautard, R., & Schwartz, J. (2014). Acclimatization across space and time in the effects of temperature on mortality: a time-series analysis. *Environmental Health : A Global Access Science Source*, *13*, 89. doi:10.1186/1476-069X-13-89

Lee, S. J., Hajat, S., Steer, P. J., & Filippi, V. (2008). A time-series analysis of any short-term effects of meteorological and air pollution factors on preterm births in London, UK. *Environ Res*, *106*(2), 185–194. doi:S0013-9351(07)00220-4 [pii]\n10.1016/j.envres.2007.10.003 [doi]

Levy, D., Lumley, T., Sheppard, L., Kaufman, J., & Checkoway, H. (2001). Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology (Cambridge, Mass.)*, *12*(2), 186–92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11246579

Lockwood, C. J. (1999). Stress-associated preterm delivery: the role of corticotropin-releasing hormone. *American Journal of Obstetrics and Gynecology*, *180*, S264–S266. doi:10.1016/S0002-9378(99)70713-1

Maclure, M. (1991). The case-crossover design: a method for studying transient effects on the risk of acute events. *American Journal of Epidemiology*, *133*(2), 144–153.

Marlow, N., Wolke, D., Bracewell, M. A., Samara, M., & EPICure Study Group. (2005). Neurologic and developmental disability at six years of age after extremely preterm birth. *The New England Journal of Medicine*, *352*(1), 9–19. doi:10.1056/NEJMoa041367

Martin, J. a, Hamilton, B. E., Sutton, P. D., Ventura, S. J., Menacker, F., & Munson, M. L. (2005). Births: final data for 2003. *National Vital Statistics Reports : From the Centers for*

Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, *54*(2), 1–116.

Meehl, G. a, & Tebaldi, C. (2004). More intense, more frequent, and longer lasting heat waves in the 21st century. *Science (New York, N.Y.)*, *305*(5686), 994–997. doi:10.1126/science.1098704

Nasrallah, H. A., Nieplova, E., & Ramadan, E. (2004). Warm season extreme temperature events in Kuwait. *Journal of Arid Environments*, *56*(2), 357–371. doi:10.1016/S0140-1963(03)00007-7

Nguyen, J. L., & Dockery, D. W. (2015). Daily indoor-to-outdoor temperature and humidity relationships: a sample across seasons and diverse climatic regions. *International Journal of Biometeorology*. doi:10.1007/s00484-015-1019-5

Repka, M. X. (2002). Ophthalmological problems of the premature infant. *Mental Retardation and Developmental Disabilities Research Reviews*, *8*(4), 249–57. doi:10.1002/mrdd.10045

Ritz, B., Wilhelm, M., Hoggatt, K. J., & Ghosh, J. K. C. (2007). Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. *American Journal of Epidemiology*, *166*(9), 1045–1052. doi:10.1093/aje/kwm181

Robinson, P. J. (2001). On the Definition of a Heat Wave. *Journal of Applied Meteorology*, *40*(4), 762–775. doi:10.1175/1520-0450(2001)040<0762:OTDOAH>2.0.CO;2

Saucier, W. J. (2003). *Principles of Meteorological Analysis*. Dover Publications.

Schifano, P., Lallo, A., Asta, F., De Sario, M., Davoli, M., & Michelozzi, P. (2013). Effect of ambient temperature and air pollutants on the risk of preterm birth, Rome 2001–2010. *Environment International*, *61*, 77–87. doi:10.1016/j.envint.2013.09.005

Shaker, Y. (1966). Thirst fever, with a characteristic temperature pattern in infants in Kuwait. *British Medical Journal*, *1*(5487), 586–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5907317

Smith, V. C., Zupancic, J. A. F., McCormick, M. C., Croen, L. A., Greene, J., Escobar, G. J., & Richardson, D. K. (2005). Trends in severe bronchopulmonary dysplasia rates between 1994 and 2002. *The Journal of Pediatrics*, *146*(4), 469–73. doi:10.1016/j.jpeds.2004.12.023

Stafoggia, M., Schwartz, J., Forastiere, F., & Perucci, C. a. (2008). Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy. *American Journal of Epidemiology*, *167*(12), 1476–85. doi:10.1093/aje/kwn074

Strand, L. B., Barnett, A. G., & Tong, S. (2011). The influence of season and ambient temperature on birth outcomes: A review of the epidemiological literature. *Environmental Research*, *111*(3), 451–462. doi:10.1016/j.envres.2011.01.023

Vicedo-Cabrera, A. M., Iñíguez, C., Barona, C., & Ballester, F. (2014). Exposure to elevated temperatures and risk of preterm birth in Valencia, Spain. *Environmental Research*, *134*, 210–7. doi:10.1016/j.envres.2014.07.021

Wang, J., Williams, G., Guo, Y., Pan, X., & Tong, S. (2013). Maternal exposure to heatwave and preterm birth in Brisbane, Australia. *BJOG: An International Journal of Obstetrics and Gynaecology*, *120*(13), 1631–1641. doi:10.1111/1471-0528.12397

Weather Undeground. (2015). http://www.wunderground.com/about/data, Accessed June 2015. Retrieved from http://www.wunderground.com/about/data

Wells, J. C. K., & Cole, T. J. (2002). Birth Weight and Environmental Heat Load: A Between-Population Analysis. *American Journal of Physical Anthropology*, *119*(February), 276–282. doi:10.1002/ajpa.10137

Wilhelm, M., & Ritz, B. (2002). Residential Proximity to Traffic and Adverse Birth Outcomes in Los Angeles County, California, 1994-1996. *Environmental Health Perspectives*, *111*(2), 207–216. doi:10.1289/ehp.5688

Wu, Y. W., & Colford, J. M. (2000). Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. *JAMA : The Journal of the American Medical Association*.

doi:10.1097/00006254-200105000-00004

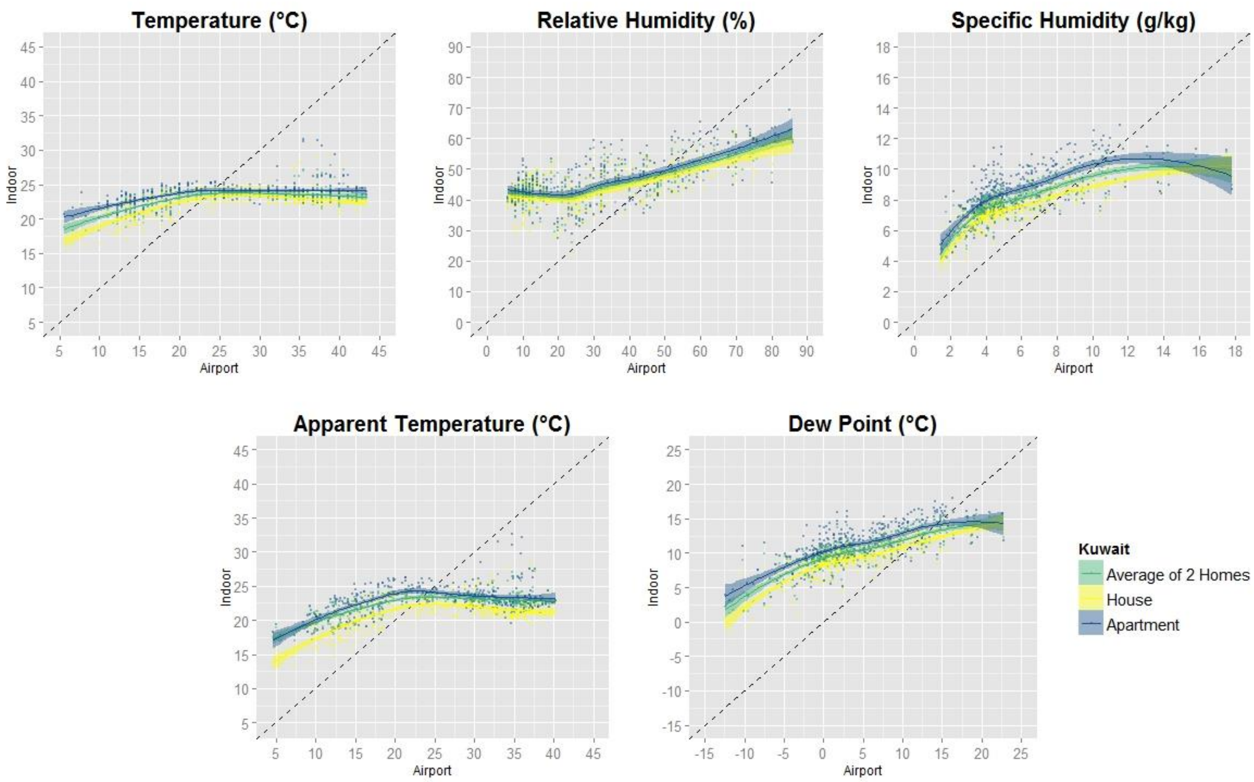
Yackerson, N., Piura, B., & Sheiner, E. (2008). The influence of meteorological factors on the emergence of preterm delivery and preterm premature rupture of membrane. *Journal of Perinatology : Official Journal of the California Perinatal Association*, *28*(10), 707–711. doi:10.1038/jp.2008.69

Supplementary Table 4.1. Time series analysis over different time periods of exposure scaled to cohort standard deviation

	2 day average				4 day average				7 day average			
	OR	**95%**	**CI**	**p-value**	**OR**	**95%**	**CI**	**p-value**	**OR**	**95%**	**CI**	**p-value**
Mean temperature	SD= 9.41				SD= 9.31				SD= 9.25			
Overall	0.76	0.43	1.35	0.35	0.95	0.50	1.80	0.88	0.95	0.47	1.94	0.89
Average mean temp>22°C	0.72	0.40	1.28	0.26	0.96	0.50	1.84	0.91	0.88	0.42	1.81	0.72
Average mean temp<22°C	0.59	0.28	1.22	0.15	0.99	0.44	2.21	0.98	0.73	0.30	1.77	0.48
Heat Index	SD= 8.89				SD= 8.8				SD= 8.73			
Overall	0.87	0.52	1.47	0.61	1.07	0.60	1.92	0.80	1.14	0.60	2.16	0.69
Average mean temp>22°C	0.85	0.50	1.43	0.53	1.09	0.61	1.95	0.78	1.09	0.57	2.09	0.79
Average mean temp<22°C	0.71	0.37	1.36	0.30	1.14	0.56	2.34	0.72	0.95	0.43	2.10	0.91
Relative Humidity	SD= 21.91				SD= 21.38				SD= 20.83			
Overall	1.12	0.82	1.54	0.45	1.21	0.88	1.70	0.26	1.31	0.92	1.85	0.12
Average mean temp>22°C	1.28	0.90	1.81	0.16	1.27	0.86	1.89	0.23	1.51	1.00	2.26	0.05
Average mean temp<22°C	1.02	0.73	1.43	0.92	1.18	0.83	1.67	0.35	1.23	0.86	1.77	0.26
Dew Point	SD= 5.34				SD= 4.87				SD= 4.46			
Overall	1.04	0.87	1.26	0.65	1.14	0.94	1.38	0.19	1.16	0.95	1.41	0.16
Average mean temp>22°C	1.10	0.89	1.35	0.37	1.12	0.90	1.40	0.32	1.15	0.92	1.45	0.21
Average mean temp<22°C	0.93	0.69	1.24	0.62	1.18	0.89	1.56	0.25	1.15	0.88	1.52	0.31
Specific Humidity	SD= 2.5				SD= 2.27				SD= 2.07			
Overall	1.05	0.88	1.25	0.60	1.09	0.91	1.31	0.35	1.12	0.93	1.35	0.22
Average mean temp>22°C	1.08	0.90	1.29	0.40	1.09	0.90	1.32	0.38	1.14	0.94	1.38	0.17
Average mean temp<22°C	0.92	0.71	1.20	0.55	1.10	0.86	1.41	0.45	1.07	0.84	1.36	0.60

All models have been adjusted for month and year of conception, nationality, income, age, education, pre-pregnancy BMI, Ramadan (Muslim fasting month), holidays, active smoking, and second hand smoke exposure.

Supplemental figure 4.1. Residential indoor temperature from two homes in Kuwait (Nguyen & Dockery, 2015).



Chapter 6: Synthesis and Conclusions

Dissertation synthesis

In this thesis we explored multiple maternal pregnancy exposures to socioeconomic, lifestyle, and environmental factors in association with gestational diabetes mellitus (GDM) and preterm delivery (PTD). Our results show suggestive patterns of a positive association of adverse maternal lifestyle factors such as pre-pregnancy obesity, excessive gestational weight gain, pregnancy active smoking, and lack of physical activity with GDM. We found patterns suggestive of an association between maternal home passive tobacco smoking (PTS) and GDM. Ambient humidity especially on hot days was associated with PTD in Kuwait.

The Kuwaiti environment is very challenging as it promotes the prevalence of the aforementioned factors associated with adverse pregnancy outcomes including those studied in this dissertation. For example, rates of pre-pregnancy obesity and excessive gestational weight gain are high due to the lack of physical activity and excessive nutrient intake promoted by Kuwait's social environment, built environment, and local climate. Being forced to spend more time indoors poses additional health problems that are associated with indoor air pollution exposure. This was reflected in our results when we examined the high prevalence (22%) of pregnancy exposure to passive tobacco smoke at home. When tackling public health problems in the country it is important consider the societal, cultural, and regional characteristics that promote the adverse risk factors rather than myopically focusing on the risk factors themselves without considering their root causes.

Our study focused on a specific subgroup of the Kuwaiti population which is pregnant women. While the prevalence of type 2 diabetes is at least 25% among those 45 years or older, we found the prevalence of GDM to be within a range similar to other countries. We expected a higher than average incidence of GDM in our study sample that corresponds to the very high prevalence of type-2-diabetes in the general population. This was not the case when we examined the data. This may have a few explanations. There could have been selection bias for healthier women among those able and willing to participate in our cohort such that their risk of GDM was lower than the rest of the country. This is possible especially because of the low response rate for study enrollment (23%). The participants within our study are reproductive age which is a young segment of the population. The risk of GDM may be lower among younger women with increases over time as the cumulative effects of years of risk factor exposure impacts health. Thus, it is important to focus on reducing these adverse risk factors early in life before long term exposure has resulted in development of adverse health. More importantly, it may be easier to establish and sustain positive health habits acquired at younger ages than to change long-standing adverse health habits in later life.

The findings from the analysis examining the association between ambient weather variables and preterm delivery are of particular importance. Climate change and global warming are of great concern and results from Kuwait may provide us with clues of what to expect with severe weather due to climate change. The significant disconnect between ambient temperature and indoor temperatures may be viewed as a limitation. However, it may also be very informative. For example, when we see a lack of association between health outcomes and extreme temperature this indicates that climate control interventions and public health advisories to avoid hot days may be successful in mitigating negative health outcomes due to severe weather.

While this thesis highlights important findings pertaining to the Kuwaiti population, there were some challenging limitations. In our gestational diabetes analyses the main limitation was the small sample size. This decreases the power and precision of our results. However, the associations between the negative risk factors and GDM were in concordance with our expectations from *a priori* knowledge of biological mechanisms and epidemiological results from the published literature. Nevertheless, it is important for our results to be corroborated using larger studies. Examining first time GDM as opposed to recurrent GDM was challenging. Past pregnancy experiences, and past GDM specifically, may confound associations or even cause self-selection bias. This may affect the validity of our findings among multiparous women. Even in absence of confounding and selection bias it is important to keep in mind that incident GDM risk and recurrent GDM risk may be fundamentally different, and therefore may have different interpretations. These were factors in our decision to restrict many of our analyses to primiparous women which resulted in our small sample size.

In conclusion, this dissertation examines many important health outcomes in the Kuwaiti population. We gained unique insight into the health problems and risk factors pertinent to Kuwait and the Arab region. Kuwait faces many social and environmental challenges that need to be addressed to reduce health risk. If results from our studies e are corroborated in larger samples, such information could play an important role in informing health risk reduction strategies in Kuwait.