Population Attributable Fractions of Caffeine and Water Pipe on low birth weight: The Bandar-Abbas Population-based Cohort in suburban areas

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Abstract

Background: Low Birth Weight (LBW) poses a major health challenge in low-resource suburban communities. Despite relatively commonality, there is little evidence on the effects of water pipe and dietary caffeine on reproductive outcomes in the Middle-East region. The Bandar Abbas Pregnancy Cohort (BAPC), as a population-based prospective study, has been investigating the effects of lifestyle and environmental factors on maternal wellbeing and child growth and development in suburban communities in the south of Iran. This study used the BAPC data to estimate the attribution of LBW incidence to fully or partially removal of dietary caffeine intake and water pipe smoking during pregnancy.

Methods: The present study used data on 861 live singleton pregnancies in the first two BAPC visits (response rate= 95.42%). Water pipe smoking (yes/no) was measured during pregnancy using a structured checklist recommended by the World Health Organization (WHO). Dietary caffeine intake was measured during pregnancy using a structured checklist and categorized into low for 0-99 mg/day, and high for≥100 mg/day. LBW (yes/no) was determined using recorded birth weight in infant`s vaccination card. Exposure relative risks were calculated using Modified Poisson regression models. Population Attributable Fractions (PAFs) and Generalized Impact Fractions (GIFs) were calculated on relative risk scale. The prevalence of counter fact was set as 3% for water pipe smokers and 14.9% for intake of ≥100 mg/day caffeine.

Results: The cumulative incidence of LBW was 16.1%. An estimated 19% (95%CI: 6, 30%) and 11% (95%CI: 8, 14%) of LBW were attributed to high intake of dietary caffeine and water pipe smoking, respectively. Reducing the intake of caffeine to less than 100 mg/day or prevalence of water pipe to 3% would prevent 10.7% (95%CI: 6.6, 25.3%) and 5.7% (95%CI: 5.0, 6.8%) of LBW incidence, respectively.

Conclusions: Our findings have provided evidence on quantitative contributions of caffeine and water pipe on LBW using real-world data. Integration of this information into practical action plans to prevent LBW is the next step in our cohort project. Furthermore, to get an overarching picture and in-depth understanding of reproductive effects of caffeine and water pipe, exercising this study`s analytic approach in other contexts is encouraged.

Background:

Low Birth Weight (LBW), defined as the birthweight below 2500 grams, is associated with increased morbidity and mortality in neonates (1). Previous studies have shown that annually, 5.0–8.0% of Iranian neonates are born with LBW while LBW incidence increases to nearly 12% in South of Iran (2). LBW is typically a consequence of inadequate fetal weight gain in utero and is linked to many interrelated risk factors, amongst them water pipe smoking (2–4). Water pipe is a prevailed mode of tobacco smoking in the south of Iran, where women use it more frequently compared to the rest of the country (5). Moreover, dietary indulgence in caffeine intake is also linked to LBW (6, 7). Over the recent decade, suburban and informal settlements have shaped in many Iranian cities with an estimated population of approximately 10.3 million (8). Suburban dwellers are among the most vulnerable sub-populations with inappropriate environmental conditions, specifically in lifestyle (9). They usually suffer from unhealthy lifestyle with no food diversity, malnutrition, and abundant smoking behaviour (10), which prompt context-specific epidemiologic evidence. Population Attributable Fraction (PAF), defined as the fraction of all cases of a particular health condition that is attributable to a specific exposure, is an epidemiologic measure widely in use to assess public health impact of various exposures. However, interpretation of PAF relies heavily on interventions that can perfectly remove exposure of interest. In other words, PAF interprets poorly for interventions for which success rate is below 100% (11). To overcome this conceptual pitfall, Generalized Impact Fraction (GIF), which calculates the change in disease burden when a risk factor is altered, is proposed. While PAF addresses complete elimination of a risk factor, GIF estimates the proportional reduction in disease incidence given a graded reduction in the prevalence of a risk factor (12).

Little is known about the likely impact of preventive interventions to control LBW by addressing water pipe or caffeine, especially in suburban communities. The present study aimed to predict the incidence of LBW following interventions to completely eliminate or partially decease the level of caffeine intake and water pipe during pregnancy using data from a population-based prospective cohort study.

Methods:

The present study used data from the first two visits of a population-based prospective cohort study in Bandar Abbas city entitled Bandar Abbas Pregnancy Cohort (BAPC). Since 2014, BAPC is investigating the effects of lifestyle and environmental factors on maternal wellbeing and child growth and development in Bandar Abbas city, the capital of Hormozgan Province in the south of Iran. Through door-by-door inquiry in the suburban neighborhoods, BAPC has recruited over 1,500 pregnant women. Any pregnant woman aged above 16 years who is residing in the suburban areas was eligible to participate in the study. Those who were unable to communicate in Farsi or unwilling to participate were excluded. Following providing the informed consent, data from subjects and their babies are gathering through four visits in pregnancy, 1, 6, and 12 months after birth. The details of the cohort methodology have been published elsewhere (13).

The present paper used the data of 897 subjects who completed the second visit of BAPC (participation rate: 92%, response rate: 95.42%) during September 2016 to May 2019. For this study, the following subjects were further excluded: miscarriage (n = 24, 2.55%), stillbirth or multiple pregnancies (n = 8, 0.85%), and self-report cigarette smoking during pregnancy (n = 4, 0.44%). Therefore, data of 861 live singleton pregnancies (mean ± SD gestational age at recruitment: 22.62 ± 9.66 weeks) was included in the analysis (Fig. 1). Data of the first visit of BAPC is collected during pregnancy and the second visit is performed during post-partum period (0–42 days post-delivery) by in-person or telephone visit. The main study`s outcome was set as LBW and was defined as birth weight below 2,500 grams (yes/no) (1). The main exposures were water pipe and caffeine intake during pregnancy, which both were measured during the first visit of BAPC. Water pipe during pregnancy (regular/only for leisure/never) was measured by a checklist recommended by the World Health Organization (WHO) (14), and was merged into yes/no categories. The checklist was validated by a group of healthcare professionals and epidemiologists while the reliability was checked on a subset of BAPC subjects (n = 25, Cronbach`s alpha = 0.78). The checklist also contained additional information on age at water pipe initiation, duration of water pipe smoking, number of water pipe sessions per day, and Environmental Tobacco Smoking (ETS). Caffeine was measured by a structured checklist using Bunker categorization as a guideline (15). The checklist was validated by a team of nutritionist, epidemiologist and gynecologist to measure dietary intake of caffeine during pregnancy. The checklist contained questions on daily intake of any type of caffeinated beverages available in the local market (including black coffee, instant coffee, black tea, green tea, hot chocolate, soft drinks) and caffeinated medications (e.g., painkillers). The reliability was further checked on a subset of BAPC subjects (n = 15, Cronbach`s alpha = 0.64). The cumulative daily dose of caffeine was then dichotomized to normal (0–99 mg/day) and high (≥ 100 mg/day) (16). Number of prenatal care visits to healthcare centers and/or gynecologist office was dichotomized into regular (i.e., at least nine visits recommended by the national guideline,) and irregular (i.e., less than nine visits). Monthly expenditure as a proxy of socio-economic status was defined as monthly average of usual household expenses during the last six months on housing, food, clothing, and healthcare.

Confounders were selected using the Change-In-Estimate (CIE) strategy. The CIE selects covariates on the basis of how much their control changes exposure effect estimates, i.e. amount of confounding by the covariate. Suppose RR_a and RR_u denote the estimated risk ratio with and without adjustment for the covariate; then RR_a/RR_u is traditionally used to judge change importance. By this strategy, an "important covariate" was determined as whether the change in the exposure effect estimate from adjusting for the covariate falls outside an interval of practical equivalence; e.g., $0.91 < RR_a/RR_u < 1.1$ (which is the 10%-change rule for the risk ratio modified to be proportionally symmetric) (17). Based on the CIE strategy, duration of water pipe smoking, maternal education, intake of iron supplement during pregnancy, infant sex, preterm birth, history of LBW infant, and monthly expenditure were included in the final regression model. Adjusted Relative Risks (ARRs) for the effects of the main exposures on LBW were calculated using Modified Poisson regression models (18). The *Miettinen* formula was applied to calculate PAFs for caffeine intake and water pipe (11). Accordingly, we estimated the PAFs from the estimated ARRs for the exposures of interest (water pipe and caffeine intake, both as dichotomous variables). The prevalence of exposure among cases (p_c) was estimated as 22.3% for water pipe smoking and 67.63% for high caffeine intake. The PAF finally estimated as: PAF = $p_c(1 - 1/RR)$(12).

GIFs were calculated using the following formula:

$$GIF = \frac{\sum_{i=1}^{n} PiRRi - \sum_{i=1}^{n} P_i'RR_i}{\sum_{i=1}^{n} P_iRR_i}$$

Where, P_i denoted the proportion of the population in exposure category *i* (fact) (8.59% for water pipe smoking, 56.98% for high caffeine intake). $P_i^{`}$ denoted the proportion of the population in exposure category after an intervention or other change is implemented (counter fact) (3% as hypothesized prevalence of water pipe). Using the WHO recommended safety threshold of 100 mg/day caffeine in pregnancy, we hypothesized that an effective intervention would successfully decrease the proportion of women with high intake of caffeine to 14.9%. Adjusted relative risks were derived from the modified Poisson regression model (12). GIFs were calculated based on a series of proposed action plans to: A) Decrease caffeine intake to less than 100 mg/day only among subjects with high intake of caffeine; and B) Decrease the prevalence of water pipe to national report of the prevalence of water pipe among Iranian women in reproductive age (i.e. 3%) (5). All the analyses were performed using Stata version 13 (Stata Corp., College Station, TX, USA). P-values less than 0.05 were considered statistically significant for the final model.

Results:

Out of 861 newborns, one hundred and thirty-nine (16.14%) were LBW, while the incidence of LBW was higher in illiterate/ elementary education mothers (21.1%), mothers with no gestational intake of iron supplementation (19.3%), and mothers with a history of LBW newborn (24.5%). Overall, 482 (56%) pregnant women reported high intake of caffeine, among whom the three most frequently reported sources of caffeine were black tea (43.3%), soft drinks (33.8%), and instant coffee (19%). Compared to normal caffeine intake, the proportion of LBW neonates was significantly higher in mothers with high caffeine intake (13.2% vs. 18.4%, $p = 0.038$). Sixty-nine (8.59%) pregnant women reported water pipe smoking, with an average of 1.87 sessions per day. Compared to the non-smokers, the proportion of LBW neonates was significantly higher in the water pipe smokers (14.27% vs. 37.68%, $p \leq 0.001$). The mean (SD) of duration of water pipe smoking was 6.7 (30.8) months. The duration of water pipe smoking was significantly higher in LBW neonates (11.8 (43) months vs. 5.8 (27) months in normal-weight neonates, P = 0.01) (Table-1). After adjusting on duration of water pipe smoking, maternal education, prenatal iron supplementation, infant sex, preterm birth, history of LBW infant, and monthly expenditure; intake of more than 100 mg/day caffeine during pregnancy increased the risk of LBW by 36% (ARR = 1.36, 95%CI:1.00,1.88). The risk of LBW was more than two times higher in women who smoked water pipe during pregnancy (ARR = 2.12, 95%CI: 1.32, 3.40) (Table-2). The results of PAFs showed that 19% (95%CI: 6.2, 30.3%) of LBW neonates would not have occurred if we could prevent caffeine intake entirely during pregnancy. Moreover, 11% (95%CI: 8.3, 14.0%) of LBW neonates would not have occurred if we could successfully eliminate water pipe smoking from the population of pregnant women.

By implementing community-based action plans to reduce the proportion of high caffeine intake, 10.7% of LBW neonates would not have occurred (GIF = 10.7, 95%CI: 6.6, 25.3%). Similarly, implementation of action plans to reduce the prevalence of water pipe to the average national level (i.e. 3%) would decrease the number of LBW neonates by 5.7% (GIF = 5.7, 95%CI: 5.0, 6.8%). (Table 3)

Table 1
General characteristics of BAPC subjects according to birth weight, 2016-19

Variable	Category	Total (%)	Birth weight, N (%)		P
			≥ 2500 g	< 2500 g	
Caffeine consumption					
Caffeine intake (mg/day)	0–99	379 (44.02)	334 (86.75)	51 (13.25)	0.038
	≥ 100	482 (56.98)	388 (81.51)	88 (18.49)	
Pattern of water pipe smoking					
Water pipe smoking	No	792 (91.41)	679 (85.73)	113 (14.27)	< 0.001
	Yes	69 (8.59)	43 (62.32)	26 (37.68)	
Duration of water pipe smoking (months)		6.77 (30.87)	5.80 (27.57)	11.82 (43.98)	0.0175
Maternal characteristics					
Age	≤ 30	563 (65.39)	477 (84.7)	86 (15.3)	0.341
	> 30	298 (34.61)	245 (82.2)	53 (17.8)	
Occupation	Housekeeper	837 (97.21)	700 (83.6)	137 (16.4)	0.756
	Employed	24 (2.79)	22 (91.6)	2 (8.4)	
Education	Illiterate/elementary	241 (27.99)	190 (78.8)	51 (21.16)	0.038
	Middle/High school	494 (57.38)	426 (86.23)	68 (13.77)	
	Academic	126 (14.63)	106 (84.13)	20 (15.87)	
LBW history	No	739 (85.83)	630 (85.25)	109 (14.75)	0.006
	Yes	122 (14.17)	92 (75.41)	30 (24.59)	

Environmental Tobacco Smoking (among non-water pipe smokers, n = 792), £ In 1,000,000 Iranian Rials

Variable	Category	Total (%)	Birth weight, N (%)		P
			≥ 2500 g	< 2500 g	
Miscarriage history	No	837 (97.21)	702 (83.87)	135 (16.13)	0.944
	Yes	24 (2.79)	20 (83.33)	4 (16.67)	
Prenatal care visit	Regular	702 (81.53)	593 (84.47)	109 (15.53)	0.301
	Irregular	159 (18.47)	129 (81.13)	30 (18.87)	
ETS	No	637 (73.98)	543 (86.05)	88 (13.95)	0.733
	Yes	224 (26.01)	136 (85)	24 (15)	
Prenatal Iron supplementation	No	259 (30.08)	209 (80.69)	50 (19.31)	0.008
	Yes	602 (69.92)	513 (85.22)	89 (14.78)	
Prenatal vitamin supplementation	No	251 (29.15)	206 (82.07)	45 (17.93)	0.361
	Yes	610 (70.85)	516 (84.59)	94 (15.41)	
Monthly expenditure£ (Mean ± SD)		6.18 (5.94)	6.29 (6.02)	5.60 (5.52)	0.041
Infant characteristics					
Infant sex	Boy	441 (53.26)	380 (86.17)	61 (13.83)	0.062
	Girl	387 (46.74)	315 (81.40)	72 (18.60)	
Preterm birth	No	801 (93.03)	704 (87.89)	97 (12.11)	< 0.001
	Yes	60 (6.97)	18 (30.00)	42 (70.00)	
Birth order	1	351 (40.77)	290 (82.62)	61 (17.38)	0.414

Environmental Tobacco Smoking (among non-water pipe smokers, n = 792), £ In 1,000,000 Iranian Rials

Variable	Category	Total (%)	Birth weight, N (%)		P
			≥ 2500 g	< 2500 g	
	> 1	510 (59.23)	432 (84.71)	78 (15.29)	

Environmental Tobacco Smoking (among non-water pipe smokers, n = 792), £ In 1,000,000 Iranian Rials

Table 2

Univariate and multivariate Modified Poisson Regression Models on low birth weight in BAPC, 2016-18

Predictor	**Univariate Poisson model**			**Multivariate Poisson model**		
	β (Robust SE$_{(\beta)}$)	**Risk Ratio (95%CI)**	**P**	**β (Robust SE$_{(\beta)}$)**	**Risk Ratio (95%CI)**	**P**
Caffeine intake (mg/day)						
0–99	Reference			Reference		
≥ 100	0.49 (0.16)	1.64 (1.18,2.28)	0.003	0.31 (0.16)	1.36 (1.00,1.88)	0.055
Water-pipe smoking						
No	Reference			Reference		
Yes	1.11 (0.16)	3.05 (2.21,4.20)	< 0.001	0.75 (0.24)	2.12 (1.32,3.40)	0.002
Water pipe smoking* Caffeine > 100$_{mg/d}$	-	-	-	0.17 (0.35)	1.19 (0.59, 2.38)	0.201
Duration of water pipe smoking (months)	0.003 (0.001)	1.00 (1.000,1.007)	0.022	-0.003 (0.002)	0.99 (0.99,1.00)	0.261
Maternal education						
Illiterate	Reference			Reference		
Below diploma	-0.43 (0.16)	0.65 (0.46, 0.90)	0.010	-0.31 (0.15)	0.72 (0.53 ,0.99)	0.047
University degree	-0.28 (0.23)	0.75 (0.46,1.20)	0.231	-0.12 (0.24)	0.88 (0.55, 1.41)	0.608
Prenatal Iron supplementation						
No	Reference			Reference		
Yes	-0.13 (0.08)	0.87 (0.74,1.02)	0.096	-0.07 (0.07)	0.93 (0.79, 1.08)	0.349

in 1,000,000 Iranian Rials; $^{\Omega}$ Environmental Tobacco Smoking

Predictor	Univariate Poisson model			Multivariate Poisson model		
	β (Robust $SE_{(\beta)}$)	Risk Ratio (95%CI)	P	β (Robust $SE_{(\beta)}$)	Risk Ratio (95%CI)	P
Infant sex						
Boy	Reference			Reference		
Girl	0.29 (0.15)	1.34 (0.98,1.83)	0.063	0.25 (0.14)	1.29 (0.96,1.73)	0.081
Preterm birth						
No	Reference			Reference		
Yes	1.75 (0.12)	5.78 (4.50,7.41)	< 0.001	1.56 (0.15)	4.78 (3.54, 6.44)	< 0.001
History of LBW infant						
No	Reference			Reference		
Yes	0.51 (0.18)	1.66 (1.16, 2.38)	0.005	0.17 (0.18)	1.19 (0.83, 1.70)	0.332
Monthly expenditure[□]	-0.01 (0.01)	0.98 (0.95, 1.00)	0.107	-0.02 (0.01)	0.98 (0.95, 1.00)	0.178
Maternal age						
< 30	Reference			Excluded		
> 30	0.15 (0.15)	1.16 (0.85,1.59)	0.340			
ETS[Ω]						
No	Reference			Excluded		
Yes	-0.08 (0.20)	0.91 (0.60,1.37)	0.079			

[□]in 1,000,000 Iranian Rials; [Ω] Environmental Tobacco Smoking

Predictor	Univariate Poisson model			Multivariate Poisson model		
	β (Robust $SE_{(β)}$)	Risk Ratio (95%CI)	P	β (Robust $SE_{(β)}$)	Risk Ratio (95%CI)	P
Birth order						
1	Reference			Excluded		
> 1	-0.12 (0.15)	0.88 (0.64, 1.19)	0.414			
Prenatal care visit						
Irregular	Reference			Excluded		
Regular	-0.19 (0.18)	0.82 (0.57, 1.18)	0.296			
in 1,000,000 Iranian Rials; $^{\Omega}$ Environmental Tobacco Smoking						

Table 3
Population Attributable Fractions and Generalized Impact Fractions of caffeine consumption and water-pipe on the incidence of low birth weight

Measure	Intervention	Estimate	95%CI
Population Attributable Fraction (PAF)	Caffeine	0.19	0.062, 0.303
	Water pipe smoking	0.11	0.083, 0.140
Generalized Impact Fraction (GIF)	Caffeine [A]	10.77	6.63,25.34
	Water pipe smoking [B]	5.72	5.02, 6.86
A:Intervention to reduce caffeine intake to 100 mg/d			
B:Intervention to reduce the prevalence of water pipe smoking to 3%			

Discussion:

The present study used data of 861 live singleton births from the BAPC study. Sixteen percent of neonates were born with LBW while one-third of them were preterm as well. The incidence of LBW in our sample of suburban residents was higher than both the United Nations Children's Fund (UNICEF) report for Iran (8%) and previous studies (19, 20). Totally, 73% of the pregnant women reported consumption of any dose of dietary caffeine during their current pregnancy while the average dose of caffeine was 104.7 mg/day. By defining the threshold for the safety dose of caffeine as 100 mg/day (16), we found that 56%

of our study subjects reported high caffeine intake. We also observed that women belonging to lower educational and socio-economic groups and those who used water pipe, reported higher doses of caffeine intake. The estimated dose of caffeine intake in our study was similar to those reported among pregnant women in the US and Poland (21, 22). The primary sources of dietary caffeine in our study; however, disagreed with the previous reports. While black tea (60%) and soft drinks (44%) were the predominant sources of caffeine intake in our study, black coffee was reported as the dominant source of caffeine intake in the developed world. This discrepancy can be attributed to social and cultural context. Differences in weather circumstances and availability and affordability of black tea and soft drinks advertise their consumption over other sources of caffeine (e.g. coffee or chocolate). Nevertheless, due to lack of national estimates on pattern of caffeine intake in Iran, we cannot provide a comprehensive discussion on caffeine consumption in our sample compared to the general population. Our study showed that consumption of more than 100 mg/day caffeine significantly increased the risk of LBW, which was consistent with the results of previous studies (7, 23, 24). We used one-week dietary recall to measure daily intake of caffeine during pregnancy. Due to many exogenous and endogenous factors, it is likely that the measured dose of caffeine did not necessarily reflect the actual concentration of caffeine metabolites in body (24). Moreover, we are aware that the amount of caffeine in beverages is heavily determined by methods of beverage preparation; therefore, non-differential misclassification bias for the measured dose of caffeine is likely (25).

The self-reported prevalence of water pipe during pregnancy was 8% in our study, which was higher than previous estimates in Iran (5, 26); yet similar to the estimates from countries of Arabian Peninsula (27). Consistent with previous reports, we found that water pipe during pregnancy significantly increased the risk of LBW (2, 28).

The final hypothesis of our study was the extent to which partial or complete removal of either exposures of interest would reduce the risk of LBW. To answer that, we calculated PAF, which is defined as the fraction of all cases of an adverse condition in a population that is attributable to a specific exposure (29). We estimated that 11% and 19% of LBW cases would be prevented if interventions to eliminate water pipe or dietary caffeine intake were to be implemented, respectively. In order to interpret PAF using our observational data, we must assume that removal of the study exposures did not affect or alter the distribution of other risk factors for LBW (such as cigarette smoking replaces water pipe). We also must assume that there was no bias in the study design and data analysis, which means that the estimated effects were adjusted for all measured confounders (11). The estimate of PAF only applies to interventions that can completely remove the exposure of interest, while such interventions, especially in lifestyle factors, may not be pragmatic. To calculate the impact of partially successful interventions, we developed real-time scenarios and calculated GIFs, which measure the reduced fraction of cases that would result from changing the current level of the exposure to some modified level (12). The first intervention targeted decreased proportion of pregnant women with high caffeine intake. By implementing such program, 19% of LBW neonates would be prevented. The second scenario targeted decreases marginal prevalence of water pipe to the estimated national level of 3% among women. Implementation of such program would result in 11% reduction in LBW cases.

This study used data from a population-based sample to find the extent to which various preventive interventions on caffeine intake and water pipe during pregnancy would influence the risk of LBW. Despite the high generalizability of a population-based sample, our results should be translated carefully. We restricted our study subjects to women who had conception without medical assistance and had no history of infertility, hence our sample might be a healthier sample compared to the general population of women of reproductive age (30). Caution must be taken if the estimated effects of water pipe and high caffeine intake are to be generalized to women who had prior history of infertility or medically-assisted conception. Moreover, generalization of the estimated PAF to other setting requires similar distribution of LBW and valid estimates for the exposure effects in that setting (11). The possible mediation effect of preterm birth in causal pathways between the exposures of interest and LBW is another controversial point. Whether preterm birth lies in the causal pathways from water pipe or caffeine to LBW is not clear yet. Nonetheless, we acknowledged the likelihood of mediating association and we recommend that use of the results of our study to preterm infants should be done with caution.

The present study was one of the first prospective epidemiologic studies to investigate public health impacts of caffeine and water pipe on reproductive outcomes in Iran. It used data from a prospective cohort study, while suitability of prospective epidemiological studies to investigate pregnancy outcomes has been well-documented (30, 31).

Out study had some limitations. We calculated the risk of LBW based on a risk set of total live births, whereas, the true theoretical risk set is defined as the total of successful conceptions. Therefore, the estimated risk of LBW might be inflated due to exclusion of unsuccessful pregnancies from the denominator (30). We used a structured checklist to measure the prevalence of water pipe based on the WHO recommendations. Nevertheless, exact estimation of the amount of absorbed substances from water pipe smoking is impractical due to lack of a ubiquitous standard tool. Therefore, the estimated magnitude and effects of water pipe on pregnancy outcomes might be different from previous results partly because of using different data collection tool. Additionally, we did not measure the cumulative effects of water pipe smoking as an important predictor of fetal growth. This was because of the inconclusive evidence regarding such association at the time of the BAPC development. Therefore, our results only apply to the effects of water pipe during pregnancy rather than cumulative effects of water pipe during life span.

Conclusions:

Our findings have provided evidence on quantitative contributions of caffeine and water pipe on LBW using real-world data. Integration of this information into practical action plans to prevent LBW is the next step in our cohort project. Furthermore, to get an overarching picture and in-depth understanding of reproductive effects of caffeine and water pipe, exercising this study`s analytic approach in other contexts is encouraged.

Declarations

Ethics approval and consent to participation

All the study`s methods were performed in accordance with the declaration of Helsinki. The ethical approval for the BAPC cohort study was granted by the National Institute for Medical Research Development (Code:N. IR.NIMAD.REC.1396.205) and the Institutional Review Board of the Tehran University of Medical Sciences (Code: 42933244/3246). Written informed consent was sought from the study subjects prior to study`s interviews.

Consent for Publication

All the data were analyzed de-coded and in aggregated form. The participants agreed to use the data for publication without reporting any personal identifiers.

Availability of data and materials

The dataset generated and analysed during the current study is not publicly available due to the restrictions applied by the National Institute for Medical Research Development as the sponsored agency. The de-identified data; however, is available from the authors upon reasonable request and with permission of the sponsor.

Competing interests

The authors declare no competing interests.

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Authors' contributions

SN contributed in study design, data analysis and manuscript preparation, MM and KH supervised the study conduction, data analysis and manuscript finalization, AR contributed in data analysis and manuscript preparation, AM and HS supervised the field-data collection and manuscript writing. All the authors have read and approved the manuscript.

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Figures

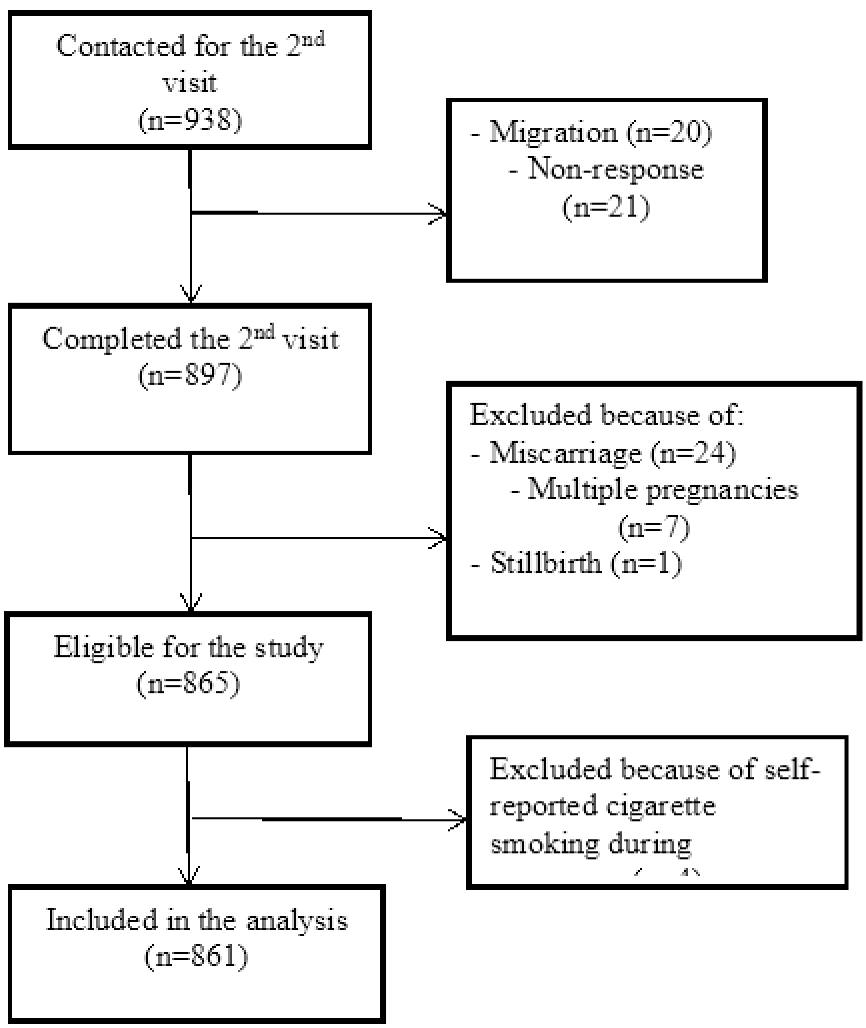

Figure 1

Flowchart of the BAPC subjects participated in the resent study