http:// ijp.mums.ac.ir
Systematic Review (Pages: 1255-1271)

Exposure to Air Pollution and Pregnancy Outcomes in the East Mediterranean Region: a Systematic Review

*Yousef Khader[1], Mostafa Abdelrahman[2], Nour Abdo[1], Samah Awad[3], Munjed Al-Sharif [4], Ahmed Elbetieha[5], Mazen Malkawi[6]

[1]Department of Community Medicine, Public Health and Family Medicine, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan.
[2]Department of Allied Medical Sciences, Faculty of Applied Medical Sciences, Jordan University of Science and Technology, Irbid, Jordan.
[3]Department of Pediatrics and Neonatology, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan.
[4]School of Natural Resources Engineering and Management, German Jordanian University, Amman, Jordan.
[5]Department of Applied Biological Sciences, Faculty of Science and Arts, Jordan University of Science and Technology, Irbid, Jordan.
[6]Centre for Environmental Health Activities, Regional Office for the Eastern Mediterranean, WHO, Genève, Schweizer.

Abstract

The East Mediterranean region (EMR) suffers from high levels of air pollution which has a negative impact on pregnancy outcomes. This work systematically reviews the epidemiological evidence on maternal exposure to air pollution and adverse pregnancy outcomes in the region. Relevant papers and reports published between 2000 and 2014 were searched. Combinations of search terms including countries, exposures, and pregnancy outcomes were used to search for the relevant literature. Twelve articles from 6 countries met the inclusion criteria. There was a pattern of an association between outdoor air pollution and preterm birth and spontaneous abortion; indoor wood fuel smoke and birth weight; and second-hand smoke and birth weight, preterm birth, and spontaneous abortion.

The quality of evidence on the impact of air pollution on pregnancy outcomes in the EMR is inadequate to form a base for future adaptation strategies and action plans. Therefore, more quality research is needed to portrait the actual situation in the region

***Key Words*:** Air pollution; East Mediterranean region; Pregnancy outcomes.

*Please cite this article as: Khader Y, Abdelrahman M, Abdo N, Awad S, Al-Sharif M, Elbetieha A, et al. Exposure to Air Pollution and Pregnancy Outcomes in the East Mediterranean Region: a Systematic Review. Int J Pediatr 2016; 4(1): 1255-71.

Corresponding Author:

Prof. Yousef Khader, Department of Community Medicine, Public Health and Family Medicine, Faculty of Medicine, Jordan University of Science and Technology, Ibrid, Jordan. Fax: +962 (0) 2 720 1064.

Email: yskhader@just.edu.jo

Received date Dec 3, 2015 ; Accepted date: Dec 28, 2015

1-INTRODUCTION

It is well established now that air pollution has significant association with human mortality and morbidity. Exposure to particulate matter (PM) of sizes less than 10 µm (PM_{10}) and 2.5 µm ($PM_{2.5}$) and gaseous pollutants including nitrogen dioxide (NO_2), sulfur dioxide (SO_2), monoxide (CO), and ozone (O_3), have been associated with increased risk of morbidity and mortality (1). Despite the recognition of the serious health hazards of air pollution, most of the countries in the East Mediterranean Region (EMR) still do not have adequate regulations and/or systems for monitoring air pollution. Data from the WHO 2014 database on air pollution shows that out of the 1 524 cities that are reporting PM_{10} data from 91 countries globally, only 26 cities from 10 countries are in the EMR, all of which exceed the WHO Air Quality Guidelines (AQG) for annual concentration of 20 µg/m^3 (2).

Computer models and satellite-derived maps also provide strong evidence that almost all countries of the EMR exceed the WHO guidelines for annual mean of $PM_{2.5}$ (10 µg/m^3). In fact, the highest PM readings come from the EMR. In addition, indoor air pollution from coal and biomass fuel burning for cooking and heating present a serious issue in some low to middle income countries in the EMR such as Somalia, Afghanistan, Sudan, and Pakistan, where about 100%, 80%, 70%, and 58% of the population use solid fuel for energy compared to 40% globally (3). Solid fuel combustion smoke along with the household passive exposure to cigarettes and hookah smoke comprise a major biohazard, especially for women in some EMR countries who often spend hours cooking in insufficiently ventilated kitchens and exposed to Secondhand Smoke (SHS) from the husband and/or children (2). A dramatic example is Pakistani mothers who, in addition to the very high ambient air pollution, are very likely to suffer excessive exposure to solid fuel smoke and SHS. In utero exposure to outdoor air pollution has been studied extensively and was associated with lower neonatal mean birth weight (MBW) (4-6), low birth weight (LBW) (7, 8), small for gestational age (SGA) (9), shorter fetal femur length and head circumference (10), preterm birth (PTB) (6, 7, 11), spontaneous abortion (12), late fetal mortality (13), and congenital disorders such as coarctation of the aorta (14-16), congenital heart defects (4, 16, 17), genital defects (18), and digestive system and abdominal wall defects (15). Some effects have been found to be modified by the fetal gender, maternal body mass index (BMI), and time of exposure. In utero exposure to solid fuel smoke has been associated with lower MBW, LBW, and stillbirth (19, 20). Maternal exposure to SHS has been linked with lower MBW (12), which has been found to be modified by genetic susceptibility; stillbirth; and spontaneous abortion (21).

Health implications of air pollution are poorly studied in the EMR, despite it is one of the most polluted regions in the world. We therefore conducted a systematic review for all studies examining the association between outdoor air pollution, indoor air pollution, and SHS, and pregnancy outcomes in the EMR to synthesize the available work, to identify gaps in knowledge, and to propose future research priorities.

2-MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, PsychINFO, Cochrane Collection, Google scholar, Pubmed and ISI Web of Knowledge. Key references from extracted papers were also hand-searched. These searches focused upon papers published between 2000 and 2014.

2-2. Search Terms

Combinations of search terms from three categories (“country” keywords AND ‘air pollution” keywords AND “pregnancy related health outcomes” keywords) were used to search for the relevant literature.

2-2-1. “Country” Keywords

Bahrain OR Cyprus OR Iran OR Jordan OR Kuwait OR Lebanon OR Libya* OR Oman OR Qatar OR Saudi OR Syria* OR Tunisia OR Emirates OR Afghanistan OR Djibouti OR Egypt OR Iraq OR Morocco OR Pakistan OR Somalia OR Sudan OR Yemen OR Gaza OR Palestine OR "West Bank".

2-2-2. “Air Pollution” Keywords

"Indoor air pollution" OR "household air pollution" OR biofuels OR "household fuel" OR biomass OR "domestic fuel" OR coal OR "cooking fuel" OR wood OR "cooking smoke" OR charcoal OR "solid fuel" OR "cooking firewood" OR "crop residue" OR "biomass fuel" OR "biomass smoke" OR "wood fuel" OR "wood smoke" OR "charcoal smoke" OR "Air pollution" OR "Particulate matter" OR "PM10" OR "PM2.5" OR ozone OR "nitrogen dioxide" OR "sulphur dioxide" OR "carbon monoxide" OR "Polycyclic Hydrocarbons" OR "Passive smoking" OR "second hand smoke" OR "second hand smoking" OR "secondhand smoke" OR "secondhand smoking" OR tobacco.

2-2-3. “Health Outcomes” Keywords

"Pregnancy outcome" OR "birth weight" OR "premature birth" OR “low birth weight” OR “low birthweight” OR "premature infant" OR "fetal growth retardation" OR "fetal development" OR "gestational age" OR "small for gestational age" OR "fetal mortality" OR "fetal death" OR "perinatal mortality" OR stillbirth OR "embryo loss" OR "spontaneous abortion" OR "congenital abnormalities" OR "neural tube defects" OR "low birth weight" OR "low birthweight".

2-3. Filtering and Study Selection

Literature search using the combinations of keywords and hand search resulted in 115 articles. Two researchers assessed the eligibility of all citations by reviewing the abstract. Where citations could not be excluded based on title or abstract or when there were discrepancies, the full-text paper was retrieved and assessed. Full papers of potentially eligible citations were identified following screening of all titles and abstracts by two study authors. These were further reviewed for eligibility and inclusion in the review by a single author, Master of Arts (MA).

2-4. Inclusion and Exclusion Criteria

Literature search was limited to papers and reports published since 2000. Papers and reports that met inclusion criteria were included in this review and were summarized in review tables and discussed in the text. Papers which examined the link between air pollution and human health without explicitly quantifying or qualifying the impact or the link were included in supporting text but not in the tables. Data from unpublished reports and websites were not systematically extracted into review tables, but sources including WHO and CDC were discussed in the accompanying text. Similarly, papers not fulfilling inclusion criteria were sometimes used to give a better contextual outline and are discussed in the relevant sections.

2-4-1. Inclusion Criteria

- Papers presented original data from cohort, case-control, or cross-sectional studies, ecologic studies, case-crossover or time-series studies;
- Studies examining the relations between gaseous air pollutants

(carbon monoxide, sulphur dioxide, nitrogen dioxide, ozone) or particulate ($PM_{2.5}$ or PM_{10}) or second-hand smoking and clearly defined pregnancy health outcomes;
- Conducted in a human population;
- Papers published in any country of the region between 1/1/2000 to 31/12/2014;
- Papers published in English.

2-4-2. Exclusion Criteria

- Editorials and letters;
- News articles;
- Non English language papers;
- Papers published before 2000.

2-5. Data Collection and Analysis

Data from scientific papers that met inclusion criteria were extracted systematically using a specially designed data extraction form. Column headings of summary tables included the followings: Study outcome, authors, year of publication, country, study design, population, study years, main results. For some health outcomes, a special column defining exposure was added. Because of the heterogeneity in study designs, exposure and outcomes, meaningful quantitative summary statistics were not possible.

3-RESULTS

3.1. Studies' characteristics

The flow chart in (Figure.1) shows the number of studies at each stage of the search and selection process. By applying the search criteria 115 papers were identified. Of these, 71 were found irrelevant after screening titles and abstracts, hence excluded. Further, 32 articles were excluded for reasons mentioned in (Figure.1).

Thus, 12 studies were selected to be included in the systematic review (22-33). Three studies were from each of Iran, Jordan and Saudi Arabia, and one from each of Palestine, Iraq, and Pakistan. The most studied outcomes were LBW (N = 10) and MBW (N = 9). Crown-heal length, head circumference, spontaneous abortion (SA), and PTB were investigated in 3 studies each. Only one study reported on the effect of air pollution on neonatal congenital malformation. Some studies had examined multiple outcomes. The most studied exposure was SHS (N = 7), followed by PM_{10} (N = 3) and gaseous air pollutants (N = 3), indoor wood fuel smoke (N = 2), and polycyclic aromatic hydrocarbons (PAH, N = 1).

The characteristics of the included studies and the results on the effects of exposure to air pollution on pregnancy outcomes are summarized in (Table.1).

Ten studies (22-31) from 6 countries in the EMR (Palestine, Iran, Iraq, Jordan, Pakistan, and Saudi Arabia) examined the effect of air pollution on neonatal anthropometric measurements. Studied anthropometric measurements included MBW (N = 8), crown-heel length (N = 3), and head circumference (N = 3). We also included LBW (N = 9) with this group. Most of studies (N = 6) employed a retrospective cohort design using birth record data, 4 were cross-sectional, and 2 were case-control studies. Individual studies were based on as few as 223 and as many as 8,490 births. Studies were based on data from the years 2004–2007 and 2011–2012.

The majority of studies examined the effect of SHS (N = 6). Two studies examined the effect of indoor wood fuel smoke, and 3 studies reported on the effect of outdoor air pollution. Exposure to SHS and wood fuel smoke was assigned based on subjects self-reporting in the format of personal interview-based questionnaire, while exposure to outdoor air pollutants including particulate matter (PM_{10} and

$PM_{2.5}$) and gaseous pollutants (NO_2, SO_2, CO, and O_3) was assigned based on data from the nearest central site monitoring station. The only study that reported on the effect of outdoor PAH assigned exposure based on maternal blood testing. Studies on the effect of SHS and wood fuel smoke employed only categorical measures of exposures, whereas studies on the effect of outdoor air pollution employed either continuous measures (N = 2) or ordinal measures (N = 1).

3-2. Birth Weight

3-2-1. Outdoor Air Pollution

The only study that has reported on the effect of PAH (24) showed no significant association between the placental blood levels of PAH and MBW. Two studies in the regions of Tehran (25) and Isfahan (26) in Iran investigated the association between outdoor gaseous air pollutants and LBW.

In Tehran, monitoring station data were used to estimate the average daily exposure of pregnant women for PM_{10}, CO, SO_2, NO_2, and O_3 during the entire pregnancy period and during each trimester. The study found CO exposure to be the only significant risk factor for LBW during the whole pregnancy [OR for the interquartile range (IQR) increase in CO concentration: 2.08; 95% CI: 1.7, 4.6], especially during the second trimester (OR: 3.96; 95% CI: 1.83, 12.5). On the other hand, in Isfahan, categorical pollutant standards index (PSI) was used to estimate exposure during the entire pregnancy period and during each trimester. The authors reported no association between PSI and LBW in all exposure periods, before and after adjustment for confounders. However, the latter study did not adjust for gestational age and the level of air pollution during the study period was generally low.

3-2-2. Indoor Biomass Fuel Smoke

The effect of maternal exposure to wood fuel smoke on MBW was reported in two studies. In Pakistan (28), infants born to wood users averaged 82 g lighter than infants born to natural gas users when weight was adjusted for confounders. However, the difference was only marginally significant ($P < 0.07$). In Palestine (23), the MBW was significantly lower by 309 g in infants born to women who were exposed to wood fuel smoke than in the unexposed group. Both studies reported similar odds of approximately 2 folds of delivering an infant with LBW in women who were exposed to wood fuel smoke after adjustment for confounders.

3-2-3. Second-hand Smoke

Six studies (22, 23, 27, 29, 30, 31) showed significantly lower MBW in children of exposed women compared to unexposed women. The difference ranged from as little as 35 g to up to 391 g. These 10 folds variation can be explained by the differences in study design, sample size, smoke source (cigarettes or *shisha*) and potential confounders accounted for. For example, 3 studies (27-29) did not adjust for gestational age and/or preterm birth (PTB). A dose–response relationship between SHS and MBW was reported in 3 studies. Abu-Baker et al. (22) from Jordan and Wadi and Al-Sharabatti (29) from Iraq demonstrated a negative relationship during the second trimester and for chronic exposure, respectively, using multiple linear regression models. Whereas, Abusalah et al. (23) from Palestine compared the MBW in 2 groups of women who were exposed to two different levels of SHS and found that maternal exposure to cigarette smoke during pregnancy was associated with a significantly lower MBW by 237 g (95% CI: 58, 415) and 391 g (95% CI: 140, 642) in infants of women exposed to smoke from 1 to 20, and from ≥ 21 cigarettes per day, respectively, after adjustment for confounders. The association between SHS and LBW was investigated in 6 studies (22, 23, 27, 29, 30, 31). Multivariate logistic regression was used to calculate the odds ratio after adjustment for potential confounders. In Jordan, exposed women at home and at work were found to be approximately 1.5 times (OR: 1.56; 95% CI: 1.31, 1.89) more likely to deliver a LBW baby compared to unexposed women (27).

Also, women who reported higher average number of SHS exposure hours per week from occupational exposure in the second trimester (OR for 1 hour increase in exposure time: 1.33; 95% CI: 1.05, 1.68) and from home (OR: 1.08; 95% CI: 1.03, 1.12) and outside (OR: 1.15; 95% CI: 1.06, 1.26) in the third trimester were at significantly greater risk for having a LBW neonate (22). In addition, a study from Iraq (29) showed that women exposed to ≥ 5 cigarettes a day were 3 times (OR 3.07 95%CI: 1.17, 8.01) more likely to have a LBW child compared to unexposed women and women exposed to < 5 cigarettes a day. Two studies from Saudi Arabia (30, 31) reported higher prevalence of LBW among infants of exposed mothers than unexposed mothers, although the difference did not reach statistical significance.

In Palestine, Abusalah (23) found maternal exposure to SHS to be a strong dose-dependent risk factor for LBW. Women who were SHS exposed from 1 to 20 cigarettes and from ≥ 21 cigarettes per day were 2.5 (95% CI: 1.4, 4.3) and 4.6 times (95% CI: 1.9, 10.7), respectively, more likely to give birth to a LBW infants than those who were not exposed.

Another study investigated the synergistic effect of SHS exposure and BMI on the risk of LBW in Saudi Arabia (31). Women who were unexposed to SHS and underweight (BMI < 18) were found to be 2.15 time (95% CI: 1.00, 4.57) more likely to deliver an infant with LBW than unexposed non-obese women (BMI of 20-29). This likelihood raised to approximately 3-fold (OR: 2.71; 95% CI: 1.82, 4.045) after exposure to SHS in both groups. Similarly, the odds of delivering an infant with LBW in obese women (BMI ≥ 30) compared to non-obese women increased from 1.18 (95% CI: 0.26, 15.9) to 2.15 (95% CI: 1.01, 4.73) after exposure to SHS.

3-3. Crown-Heel Length and Head Circumference

3-3-1. Outdoor Air Pollution

The only study that has reported on the effect of PAH (24) showed no significant association between the placental blood levels of PAH and crown-heel length or head circumference.

3-3-2. Second-hand Smoke

Two Saudi retrospective cohort studies by the same group investigated the effect of maternal SHS on crown-heel length or head circumference. The mean length of infants of mothers exposed to SHS was found to be 2.0 mm and 2.6 mm shorter than unexposed before and after adjustment to confounders, respectively (30, 31). In terms of infant’s head circumference, the results were controversial. Only one study (31) showed a significant difference (1.3 mm; $P < 0.05$) in mean head circumference between infants of exposed and unexposed mothers, whereas in the other study (30) the difference did not reach statistical significance (0.9 mm; $P = 0.17$) before and after adjustment for confounders.

3-4. Preterm Birth

3-4-1. Outdoor Air Pollution

Only 1 retrospective cohort study from Iran (26) reported on the effect of outdoor exposure to particulate matter and gaseous pollutants on PTB. Pollutant Standards

Index (PSI) was used to estimate exposure during the entire pregnancy period and during each trimester. A multiple regression analysis showed that the only significant association between PSI levels and PTB was during the entire pregnancy (OR for IQR increase in PSI: 1.26; 95% CI: 1.20, 1.33).

3-4-2. Second-hand Smoke

Two cross-sectional studies from Jordan reported on the effect of SHS exposure on PTB. One study found that exposure to SHS during the entire pregnancy was significantly associated with PTB (OR: 1.61; 95% CI: 1.30, 1.99) after controlling for confounders (27). Without adjusting for any covariates, the other study (32) reported significantly higher prevalence of PTB in women exposed for SHS (22.3%) than unexposed (10.7%)

3-5. Spontaneous Abortion (SA)

3-5-1. Outdoor Air Pollution

In Tehran, a case-control study (33) used data on outdoor air pollutants including PM_{10}, CO, SO_2, NO_2, and O_3 from fixed-site air-monitoring stations to estimate exposure during the entire pregnancy. Among the 5 pollutants, exposure to ambient CO showed the strongest association with SA (OR for 1 ppm increase in concentration: 1.95, 95% CI: 1.49– 2.54). Exposure to NO_2, PM_{10} and O_3 showed weak, but statistically significant, effect on SA (OR for 1 µg/m^3 increase in PM_{10}: 1.00, 95% CI: 1.00–1.01; OR for 1 ppb increase in NO_2: 1.03, 95% CI: 1.01–1.05; and OR for 1 ppb increase in O_3: 1.09; 95% CI: 1.05–1.13). No association was found between SO_2 and SA.

3-6. Congenital Malformations

3-6-1. Second-hand Smoke

Only 1 cross-sectional study from Jordan (32) reported a significantly higher prevalence of congenital malformations in women exposed to SHS (6.4%) than unexposed (3.6%). The study was merely descriptive and no association analysis or adjustment for confounders was performed.

4- Discussion

This work is the first to review the literature on the link between air pollution and pregnancy outcomes in the EMR. It serves to screen the quality of available research and to identify informational gaps in the region. Because of the heterogeneity of the exposure, outcome and confounders measures; and the small number of studies per outcome the calculation of summary effects estimates was not meaningful.

4-1. Outdoor Air Pollution and Pregnancy Outcomes

The available evidence on the association between outdoor air pollution and pregnancy outcomes showed no association with reduced anthropometric measurements (MBW, crown-heel length, and head circumference); conflicting association with LBW; and significantly positive association with PTB and SA. Nine previous reviews on the association between outdoor air pollution and pregnancy outcomes were identified; 6 systematic reviews (34-39) and 3 meta-analysis studies (6, 14, 16). The systematic reviews reported significant association between outdoor air pollution and MBW (39); and weak or conflicting evidence on the association with LBW (34, 38), intra-uterine growth restriction (IUGR) (35-37; 39), SGA (34, 37, 38), PTB (34-39), and congenital malformations (35). On the other hand, the meta-analysis studies reported significant association between NO_2 and SO_2 and coarctation of aorta (14, 16); between PM_{10} and atrial septal defect (16); and between outdoor air pollutants and MBW and LBW (6); Whereas the evidence of the association with PTB was inconclusive.

4-2. Indoor Air Pollution and Pregnancy Outcomes

The evidence on the effect of indoor air pollution on pregnancy outcomes in the EMR is very limited. This review showed that exposure to wood fuel smoke may have an association with LBW. On the other hand, results on the association with reduced MBW were inconclusive. No other outcomes were tested against exposure to indoor air pollution. Three reviews on the association between indoor air pollution and pregnancy outcomes were identified; 1 systematic review (40) and 2 meta-analysis studies (19, 20). The systematic review reported a significant inverse association between prenatal exposure to $PM_{2.5}$ and MBW and crown-heel length; and significant positive association between PAH (from indoor sources) and LBW, SGA and PTB. Both meta-analysis studies reported increased risk of reduced MBW, LBW, and stillbirth as a result of exposure to solid fuel smoke.

4-3. Second-hand Smoke and Pregnancy Outcomes

This review found compelling evidence on the association between SHS and lower MBW, LBW, PTB, and SA. No conclusive evidence was reached on the relationship between SHS and reduced crown-heel length and head circumference, as well as congenital malformations. This is comparable with results from 2 previous meta-analysis studies (41, 42) which reported significant association between SHS and reduced anthropometric measurements, including LBW.

4-4. Quality of Evidence and Gaps in Knowledge

The available evidence on the association between air pollution and pregnancy outcomes from the EMR has the following drawbacks:

1. Limited number of studies: A limited number of studies for a limited number of outcomes in a limited number of regions have assessed the association between various exposures and pregnancy outcomes. Therefore, research on air pollution and pregnancy outcomes is sporadic and insufficient to render a robust evidence for the situation in the EMR. More research is needed to sufficiently represent the different geographic locations and topography of the countries (38), to further investigate the currently studied outcomes, to identify susceptible subpopulation, and to study other pregnancy outcomes such as SGA, IUGR, congenital abnormalities, and late fetal mortality.

2. Lack of precise estimation of exposure: Except for one study (24), outdoor air pollution measurements were based on stationary air pollution monitoring, instead of personal exposure. This method does not account for potential sources other than ambient air such as the personal macro- (*e.g.*, living next to a busy road) and microenvironment (*e.g.*, SHS exposure at home (26, 43). Also, relying on residential address to estimate exposure based on the distance from a monitoring station critically ignores the subject mobility (38). In addition, exposure to SHS and indoor wood fuel smoke was based on women's retrospective self–reporting, instead of the use of biomarker to verify exposure, which may result in imprecision and recall bias (22, 23, 42). The association between self-reported exposure status to SHS and urinary cotinine in nonsmokers has been reported to be poor (44, 45). It is recommended that a combination of different methods of assessing SHS exposure is often the best approach (46).

3. Inconsistent exposure metrics: Different metrics have been used to quantify outdoor air pollution exposure in the EMR (*e.g.*, continuous daily average concentrations of individual air pollutants *vs.* ordinal PSI). Heterogeneity in SHS exposure metrics also exists between studies. SHS exposure has been reported on a dichotomous scale (*e.g.*, exposed *vs.* unexposed), continuous exposure hours, or continuous number of cigarettes. Heterogeneity in exposure metrics adds more challenges for the task of constructing conclusions on the effect of air pollution on pregnancy outcomes and should be standardized for future research.

4. Insufficient and inconsistent control for potential confounders: Most of studies did not adjust for critical potential confounders. For example, many studies on the effect of air pollution on anthropometric measurements did not control for gestational age (N = 4) or congenital malformations (N = 7), which are known risk factors for reduced measurements (47, 48). Not to mention, gestational age was mainly estimated based on women's self–reporting to her last menstrual period, which may introduce imprecision and recall bias. Also, the only study on the effect of air pollution on SA did not consider that some women may have had illegally induced abortion and were admitted as SA (33).

5. Methods for determining sample size are unclear or absent: In most studies (N = 7) sample size calculation was not performed; instead all available eligible patients were included. The results of these studies should be considered carefully as they may only represent the local population. Finding enough participants to satisfy the required calculated sample size for this type of studies can be very challenging in countries with small population such as Palestine, Bahrain, and Qatar. The effect of air pollution on pregnancy outcomes is generally small and the there is a wide spectrum of covariates and subpopulations to study. Therefore, sample sizes that are required to produce reliable results will naturally be large. Also, it may be useful to cluster countries with small population to improve the power of air pollution and health studies.

4-5. Strengths and Limitations

This review has several strengths. This is the first work to systematically review the available literation on the association between air pollution and pregnancy outcomes in the EMR. It presents evidence on the shortcoming research in the region and provides insights on what has to be done for future research. However, the review also has limitations. No pooled evaluations were made due to the low number of studies for each exposure-outcome relation and the heterogeneity between studies. Also, the search was restricted to English language publication, primarily due to the scope of information that may or may not be available in other languages. Another limitation is that all studies that met the inclusion criteria were included in this review, regardless to their quality. However, it was the authors' intention to highlight the presence of low-quality research in the EMR.

5- CONCLUSION

Twelve studies from 6 countries in the EMR have examined the effect of air pollution on pregnancy outcomes. The most studied exposure in the region was SHS. Although the quantity and quality of the research from the region are inadequate to draw robust conclusions, it is possible to appreciate an association, although inconclusive, between outdoor air pollution and PTB and SA; indoor wood fuel smoke and LBW; and SHS and MBW, LBW, PTB, and SA. Although numbers show that air pollution levels are particularly high in the EMR, the quality of the evidence on its effect on pregnancy outcomes is poor. This is primarily due to the small number of studies and heterogeneity among studies. It is critical to first build a quality body of evidence in order to design effective adaptation strategies and action plans. This review identified the weaknesses in the current research and how to overcome them.

6-CONFLICT OF INTEREST: None.

7-ACKNOWELEDMENTS

This research was supported by WHO/CEHA, Amman, Jordan. The funder had no role in the study design, data collection and analysis, interpretation of data, decision to publish or preparation of the manuscript.

8- REFERENCES

1. World Health Organization. 2012. Burden of disease from ambient and household air pollution.Available: http://www.who.int/phe/health_topics/outdoorair/databases/en/. Accessed 8th Jun 2015.

2. World Health Organization. 2014. Ambient (outdoor) air pollution in cities database 2014. Available: http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/. Accessed 9 May 2015.

3. World Health Organization. 2013. Population using solid fuels (estimates) – data by country. Available: http://apps.who.int/gho/data/node.main.135?lang=en. Accessed 9 May 2015.

4. Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environmental health perspectives 2013;121(3):267-373.

5. Geer LA, Weedon J, Bell ML. Ambient air pollution and term birth weight in texas from 1998 to 2004. Journal of the Air & Waste Management Association 2012; 62:1285-95.

6. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. Environmental research 2012; 117:100-11.

7. Fleischer NL, Merialdi M, van Donkelaar A, Vadillo-Ortega F, Martin RV, Betran AP, et al. Outdoor air pollution, preterm birth, and low birth weight: Analysis of the world health organization global survey on maternal and perinatal health. Environmental health perspectives 2014; 122:425-430.

8. Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, Andersen AM, Ballester F, et al. Ambient air pollution and low birthweight: A european cohort study (escape). The Lancet Respiratory medicine 2013; 1:695-704.

9. Hannam K, McNamee R, Baker P, Sibley C, Agius R. Air pollution exposure and adverse pregnancy outcomes in a large uk birth cohort: Use of a novel spatio-temporal modelling technique. Scandinavian journal of work, environment & health 2014; 40:518-30

10. van den Hooven EH, Pierik FH, de Kluizenaar Y, Willemsen SP, Hofman A, van Ratingen SW, et al. Air pollution exposure during pregnancy, ultrasound measures of fetal growth, and adverse birth outcomes: A prospective cohort study. Environmental health perspectives 2012; 120:150-56.

11. Olsson D, Mogren I, Forsberg B. Air pollution exposure in early pregnancy and adverse pregnancy outcomes: A register-based cohort study. British Meical Journal 2013; 3:e001955.

12. Wu T, Hu Y, Chen C, Yang F, Li Z, Fang Z, et al. Passive smoking, metabolic gene polymorphisms, and infant birth weight in a prospective cohort study of chinese women. American journal of epidemiology 2007; 166:313-22.

13. Scheers H, Mwalili SM, Faes C, Fierens F, Nemery B, Nawrot TS. Does air pollution trigger infant mortality in western europe? A case-crossover study. Environmental health perspectives 2011; 119:1017-22.

14. Chen EK, Zmirou-Navier D, Padilla C, Deguen S. Effects of air pollution on the risk of congenital anomalies: A systematic review and meta-analysis. International journal of environmental research and public health 2014; 11:7642-68.

15. Schembari A, Nieuwenhuijsen MJ, Salvador J, de Nazelle A, Cirach M, Dadvand P, et al. Traffic-related air pollution and congenital anomalies in barcelona.

Environmental health perspectives 2014;122(3):317-23.

16. Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, et al. Ambient air pollution and risk of congenital anomalies: A systematic review and meta-analysis. Environmental health perspectives 2011; 119:598-606.

17. Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C. Air pollution and congenital heart defects. Environmental research 2013; 124:28-34.

18. Farhi A, Boyko V, Almagor J, Benenson I, Segre E, Rudich Y, et al. The possible association between exposure to air pollution and the risk for congenital malformations. Environmental research 2014; 135:173-180.

19. Amegah AK, Quansah R, Jaakkola JJ. Household air pollution from solid fuel use and risk of adverse pregnancy outcomes: A systematic review and meta-analysis of the empirical evidence. PloS one 2014; 9:e113920.

20. Pope DP, Mishra V, Thompson L, Siddiqui AR, Rehfuess EA, Weber M, et al. Risk of low birth weight and stillbirth associated with indoor air pollution from solid fuel use in developing countries. Epidemiologic reviews 2010; 32:70-81.

21. Hyland A, Piazza KM, Hovey KM, Ockene JK, Andrews CA, Rivard C, et al. Associations of lifetime active and passive smoking with spontaneous abortion, stillbirth and tubal ectopic pregnancy: A cross-sectional analysis of historical data from the women's health initiative. Tobacco control 2014; 24:328-35.

22. Abu-Baker NN, Haddad L, Savage C. The influence of secondhand smoke exposure on birth outcomes in jordan. International journal of environmental research and public health 2010; 7:616-34.

23. Abusalah A, Gavana M, Haidich AB, Smyrnakis E, Papadakis N, Papanikolaou A, et al. Low birth weight and prenatal exposure to indoor pollution from tobacco smoke and wood fuel smoke: A matched case-control study in gaza strip. Maternal and child health journal 2012; 16:1718-27.

24. Al-Saleh I, Alsabbahen A, Shinwari N, Billedo G, Mashhour A, Al-Sarraj Y, et al. Polycyclic aromatic hydrocarbons (pahs) as determinants of various anthropometric measures of birth outcome. The Science of the total environment 2013; 444:565-78.

25. Araban M, Kariman N, Tavafian SS, Motesaddi S, Alavimajd H, Shokravi FA. Air pollution and low birth weight: A historical cohort study from tehran. Eastern Mediterranean health journal 2012; 18:556-60.

26. Janghorbani M, Piraei E. Association between air pollution and preterm birth among neonates born in isfahan, iran. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2013; 18:875-81.

27. Khader YS, Al-Akour N, Alzubi IM, Lataifeh I. The association between second hand smoke and low birth weight and preterm delivery. Maternal and child health journal 2011; 15:453-59.

28. Siddiqui AR, Gold EB, Yang X, Lee K, Brown KH, Bhutta ZA. Prenatal exposure to wood fuel smoke and low birth weight. Environmental health perspectives 2008; 116:543-49.

29. Wadi MA, Al-Sharbatti SS. Relationship between birth weight and domestic maternal passive smoking exposure. Eastern Mediterranean health journal 2011; 17:290-96.

30. Wahabi HA, Alzeidan RA, Fayed AA, Mandil A, Al-Shaikh G, Esmaeil SA. Effects of secondhand smoke on the birth weight of term infants and the demographic profile of saudi exposed women. BMC public health 2013; 13:341.

31. Wahabi HA, Mandil AA, Alzeidan RA, Bahnassy AA, Fayed AA. The independent effects of second hand smoke exposure and maternal body mass index on the anthropometric measurements of the newborn. BMC public health 2013b; 13:1058.

32. Amasha HA, Jaradeh MS. Effect of active and passive smoking during pregnancy on its outcomes. Health Science Journal 2012; 6:335-52.

33. Moridi M, Ziaei S, Kazemnejad A. Exposure to ambient air pollutants and spontaneous abortion. The journal of obstetrics and gynaecology research 2014; 40:743-48.

34. Bosetti C, Nieuwenhuijsen MJ, Gallus S, Cipriani S, La Vecchia C, Parazzini F. Ambient particulate matter and preterm birth or birth weight: A review of the literature. Archives of toxicology 2010; 84:447-60.

35. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Particulate air pollution and fetal health: A systematic review of the epidemiologic evidence. Epidemiology (Cambridge, Mass) 2004; 15:36-45.

36. Maisonet M, Correa A, Misra D, Jaakkola JJ. A review of the literature on the effects of ambient air pollution on fetal growth. Environmental research 2004; 95:106-15.

37. Polichetti G, Capone D, Grigoropoulos K, Tarantino G, Nunziata A, Gentile A. Effects of ambient air pollution on birth outcomes: An overview. Critical Reviews in Environmental Science and Technology 2012; 43:752-74.

38. Shah PS, Balkhair T, Knowledge Synthesis Group on Determinants of Preterm LBWb. Air pollution and birth outcomes: A systematic review. Environment international 2011; 37:498-516.

39. Sram RJ, Binkova B, Dejmek J, Bobak M. Ambient air pollution and pregnancy outcomes: A review of the literature. Environmental health perspectives 2005; 113:375-82.

40. Patelarou E, Kelly FJ. Indoor exposure and adverse birth outcomes related to fetal growth, miscarriage and prematurity-a systematic review. International journal of environmental research and public health 2014; 11:5904-33.

41. Leonardi-Bee J, Smyth A, Britton J, Coleman T. Environmental tobacco smoke and fetal health: Systematic review and meta-analysis. Archives of disease in childhood Fetal and neonatal edition 2008; 93:F351-61.

42. Salmasi G, Grady R, Jones J, McDonald SD, Knowledge Synthesis G. Environmental tobacco smoke exposure and perinatal outcomes: A systematic review and meta-analyses. Acta obstetricia et gynecologica Scandinavica 2010; 89:423-41.

43. Bell ML, Ebisu K, Belanger K. Ambient air pollution and low birth weight in connecticut and massachusetts. Environmental health perspectives 2007; 115:1118-24.

44. Matt GE, Wahlgren DR, Hovell MF, Zakarian JM, Bernert JT, Meltzer SB, et al. Measuring environmental tobacco smoke exposure in infants and young children through urine cotinine and memory-based parental reports: Empirical findings and discussion. Tobacco control 1999; 8:282-89.

45. Paek YJ, Kang JB, Myung SK, Lee DH, Seong MW, Seo HG, et al. Self-reported exposure to second-hand smoke and positive urinary cotinine in pregnant nonsmokers. Yonsei medical journal 2009;50::345-51.

46. Jaakkola MS, Jaakkola JJ. Assessment of exposure to environmental tobacco smoke. The European respiratory journal 1997; 10:2384-97.

47. Coutinho PR, Cecatti JG, Surita FG, Costa ML, Morais SS. Perinatal outcomes associated with low birth weight in a historical cohort. Reproductive health 2011; 8:18.

48. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: The newborn cross-sectional study of the intergrowth-21st project. Lancet 2014; 384:857-68.

49 P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. Maternal exposure to particulate air pollution and term birth weight: A multi-country evaluation of effect and heterogeneity. Environmental health perspectives 2013; 121:267-373.

Table 1: Summary of characteristics and main results of included studies

Authors (Year)	Country	Study Year	Exposure	Pregnancy Outcome	Study Design	Population	Exposure Assessment	Outcome Assessment	Confounders Adjusted
Abu-Baker NN et al. (2010)	Irbid, Jordan	---	SHS	BW	Cross-sectional study on 300 births in one hospital	Older than 18 years of age; Did not smoke tobacco for one year prior to conception; Singleton pregnancy	Personal interview-based questionnaire	Hospital records	Neonate's gender, gestational age, number of mother's previous pregnancies, weight gain during pregnancy, initiation of prenatal care, maternal age, maternal height, maternal weight before pregnancy, mother's years of education, mother's occupation during pregnancy, and total family income
Main results: Number of SHS exposure hours per week during the second semester from home and from work had a negative association with the neonatal BW (β: -0.38* and -0.25* respectively). Exposure to SHS from home and from outside during the third trimester, and from work during the second trimester increased the odds of having an LBW infant [OR (95% CI) for every hour/week increase in exposure time: 1.08* (1.03, 1.12), 1.15* (1.06, 1.26), and 1.33* (1.05, 1.68) respectively].									
Abusalah A et al. (2012)	Gaza strip, Palestine	2007	SHS, wood fuel smoke	BW	Case-control study on 223 matched pairs of exposed (case) and unexposed (control) births in 2 hospitals	Residents of Gaza Strip at least 1 year before delivery; Singleton pregnancy	Personal interview-based questionnaire	Clinician at delivery	Parents' education, occupation, and residence; BMI; income and consanguinity; preterm birth, and gestational age
Main results: Women chronically exposed to wood fuel smoke had lighter infants than unexposed women [adjusted mean difference (95%CI): -186 g* (-354, -19 g)]. They also were at higher risk of having an LBW infant [OR (95% CI): 2.3* (1.2, 4.7)]. There was a dose-response relationship between MBW and SHS. Chronic exposure to the smoke of 1–20 cigarettes/day had smaller effect on MBW than ≥ 21 cigarettes/day [adjusted mean difference (95%CI): -237 g* (-415, -58 g) and -391 g* (-548, -28 g) respectively). In addition, chronic exposure to the smoke of 1–20 cigarettes/day increased the odds of having an LBW infant by 2.5* times (95% CI: 1.4, 4.3), whereas the exposure ≥ 21 cigarettes/day raised the odds further to 4.6* times (95% CI: 1.9, 10.7).									
Al-Saleh et al. (2013)	Al-Kharj, Saudi Arabia	2005–2006	PAH	BW; CHL; HC	A cross-sectional study on 1,578 births in one hospital	Non-smoker; No history of occupational exposure	Blood PAH concentrations	Hospital records	Mother's age, parity, newborn gender, mother's educational level, geographical distribution of current residence, gestational age and preterm birth.
Main results: No significant association was found between the placental PAH ($\log_{10}$) level and any of the studied pregnancy outcomes.									
Amasha & Jaradeh (2012)	Amman & Zarqa, Jordan	2009	SHS	PTB; CM	A cross-sectional study on 223 births in 4 hospitals	Aged 20–35 years; Singleton pregnancy	Personal interview-based questionnaire	Hospital records	None
Main results: PTB had significantly higher prevalence among women chronically exposed to SHS (22.3%) than unexposed women (10.7%). There was no significant difference in the prevalence of CM among women chronically exposed to SHS compared to the unexposed women.									

Table 1: Continued...

Authors (Year)	Country	Study Year	Exposure	Pregnancy Outcome	Study Design	Population	Exposure Assessment	Outcome Assessment	Confounders Adjusted
Araban et al. (2012)	Tehran, Iran	2007	CO, O_3, NO_2, SO_2, PM_{10}	BW	Cohort study on 225 births in 6 hospitals	Aged 18–35 years; Singleton pregnancy; Living within 5 km of a unique air pollution monitoring station; Had at least 2 prenatal care visits during their pregnancy	Average concentration of pollutants obtained from the nearest monitoring station (within a 5 km radius)	Hospital records	Maternal age, maternal education, maternal job, socioeconomic factor, stress status, number of prenatal care visits, weight gain during pregnancy, gestational age, sex of the baby and planned pregnancy
Main results: Women exposed to CO during the entire pregnancy and during the second trimester were at higher risk of having an LBW infant [OR for every For IQR increase in concentration (95% CI): 2.08* (1.70, 4.60) and 3.96* (1.83, 12.5) respectively]. There was no evidence on the association between the exposure to the other pollutants during the entire pregnancy or the different trimesters and LBW.									
Janghorbani & Piraei (2013)	Isfahan, Iran	2010–2012	CO, O_3, NO_2, SO_2, PM_{10}	BW; PTB	Cohort study on 4,758 births in one hospital	Aged 18–35 years; Healthy; Living in urban areas of Isfahan city with air pollution monitoring stations; Singleton pregnancy	PSI calculated from average concentration of pollutants obtained from the nearest monitoring station	Clinician at delivery	Maternal age, neonatal gender, and birth order
Main results: There was no evidence on the association between the exposure to outdoor air pollution during the entire pregnancy or the different trimesters and LBW. Exposure to outdoor air pollution during the entire pregnancy was associated with PTB [OR for IQR increase in PSI (95% CI): 1.26* (1.20–1.33)].									
Khader et al. (2011)	Northern Jordan	2007	SHS	BW; PTB	A cross-sectional study on 8,490 births in 4 hospitals	Women attended for delivery	Personal interview-based questionnaire	Clinician at delivery	Age, level of education, employment, family income, height, blood type, parity, history of preterm delivery
Main results: Women exposed to SHS at home and at work during the entire pregnancy gave birth to lighter infants (mean difference: 140 g*) and were at higher risk of having an LBW infant than unexposed women [OR (95% CI): 1.56* (1.31, 1.89)]. They were also at higher risk of having a PTB [OR (95% CI): 1.61* (1.30–1.99)].									

Table 1: Continued...

Authors (Year)	Country	Study Year	Exposure	Pregnancy Outcome	Study Design	Population	Exposure Assessment	Outcome Assessment	Confounders Adjusted
Moridi et al. (2014)	Tehran, Iran	2010–2011	CO, O_3, NO_2, SO_2, PM_{10}	SA	Retrospective case–control study on 148 matched pairs of women who experienced SA before 14 weeks of gestation (case) and pregnant women after 14 weeks of gestation (control) in 10 hospitals	Aged 18–35 years; Singleton pregnancy; Healthy; Did not smoke during pregnancy; No previous history of PTB, LBW and occupational exposure to environmental toxins	Average concentration of pollutants obtained from the nearest monitoring station	Hospital records	Maternal age, husband age, gravidity, duration from last delivery in multiparous women, history of previous abortion, pre-pregnancy BMI, occupation, educational status, SHS exposure, socioeconomic status, consanguinity with the spouse and duration of residence in Tehran.
Main results: There was a significant association between the exposure to CO during the entire pregnancy and SA [OR for every 1 ppm increase in CO (95% CI): 1.95 (1.50, 2.55)] There was a weak, but significant, association between the exposure to NO_2, O_3, and PM_{10} during the entire pregnancy and SA [OR for every 1 ppb increase in NO_2 and O_3 concentration (95% CI): 1.04* (1.02, 1.05) and 1.09* (1.06, 1.13) respectively; OR for every 1 μg/m^3 increase in PM_{10} concentration (95% CI): 1.01* (1.00, 1.02)] There was no evidence on the association between the exposure to SO_2 during the entire pregnancy and SA.									
Siddiqui et al. (2008)	Rehri Goth, Pakistan	2004–2005	Wood fuel smoke	BW	Cohort study on 634 women	Singleton pregnancy	Personal interview-based questionnaire	Hospital records	Maternal age, marital status, number of family members, house type, number of rooms, source of water, type of sanitation, monthly income, occupation and education of spouse and participant, maternal daytime work and rest duration, smoking habits of all household members for number, frequency and duration of use of tobacco inside and outside the house, frequency, location, and provider of prenatal care, immunizations and illnesses during the index pregnancy, reproductive and neonatal outcomes, fuel type, propensity scores
Main results: Wood fuel women users had lighter infants than gas fuel women users (adjusted mean difference: -82 g). They also were at higher risk of having a LBW baby [OR (95% CI): 1.86* (1.11, 3.14)]									
Wadi and Al-Sharbatti (2011)	Baghdad, Iraq	2004	SHS	BW	Retrospective cohort study on 300 births in one hospital; 150 housewife mothers not exposed to passive smoking at home and 150 exposed	Healthy; Singleton pregnancy; Non-smoker	Personal interview-based questionnaire	Hospital records	Residence, sex of newborn, maternal iron/folic acid supplementation, antenatal care, weight gain during pregnancy, education level of both parents, and parity
Main results: Number of cigarettes/day had a negative association with the neonatal BW (β: -281.7*) Women chronically exposed to the smoke of ≥ 5 cigarettes per day had lighter infants than unexposed or exposed to < 5 cigarettes per day (mean difference: 198 g*). They were also more likely to have an LBW infants [OR (95% CI): 3.07* (1.17, 8.01)].									

Table 1: Continued...

Authors (Year)	Country	Study Year	Exposure	Pregnancy Outcome	Study Design	Population	Exposure Assessment	Outcome Assessment	Confounders Adjusted
Wahabi et al. (2013)	Riyadh, Saudi Arabia	2011–2012	SHS	BW; CHL; HC	Retrospective cohort study on 3,231 women in one hospital	Singleton pregnancy; Did not smoke during pregnancy	Personal interview-based questionnaire	Hospital records	Maternal age, parity, BMI, GDM and gestational age
Main results: Women chronically exposed to SHS had lighter infants than unexposed women (mean difference: 50 g*) Exposure to SHS was associated with increased rate of LBW infants, irrespective of maternal BMI. The odds of delivering an LBW infant was 2.71* times (95% CI: 1.82, 4.05) higher in underweight women (BMI < 18 kg/m^2) chronically exposed to SHS compared to non-obese (18–29.9 kg/m^2) exposed women The odds of delivering an LBW infant was 2.15* times (95% CI: 1.01, 4.73) higher in obese women (BMI ≥ 30 kg/m^2) chronically exposed to SHS compared to non-obese exposed women Women chronically exposed to SHS gave birth to infants with significantly shorter crown-heel length (mean difference: 2.0 mm*) and head circumference (mean difference: 1.3 mm*) than unexposed women.									
Wahabi et al. (2013)	Riyadh, Saudi Arabia	2011–2012	SHS	BW; CHL; HC	Retrospective cohort study on 3,426 women in one hospital	Singleton pregnancy; Did not smoke during pregnancy	Personal interview-based questionnaire	Hospital records	Maternal age, parity, BMI, GDM and gestational age
Main results: Women chronically exposed to SHS had lighter infants and infants with shorter crown-heel lengths [adjusted mean difference (95% CI): 2.61 mm (0.58, 4.64)] than unexposed women [adjusted mean difference (95% CI): 35 g* (2, 68)]. Head circumference was also shorter in infants of exposed women (mean difference: 0.9 mm); however, the difference was not statistically significant.									

BMI: body-mass index; BW: birth weight; CHL: crown-heel length; CI: confidence interval; CM: congenital malformation; HC: head circumference; LBW: low mean birth weight; MBW: mean birth weight; OR: odds ratio; PM_{10}: particulate matter of sizes < 10 µm; PTB: preterm birth; SA: spontaneous abortion; SHS: second-hand smoke.
* $P < 0.05$

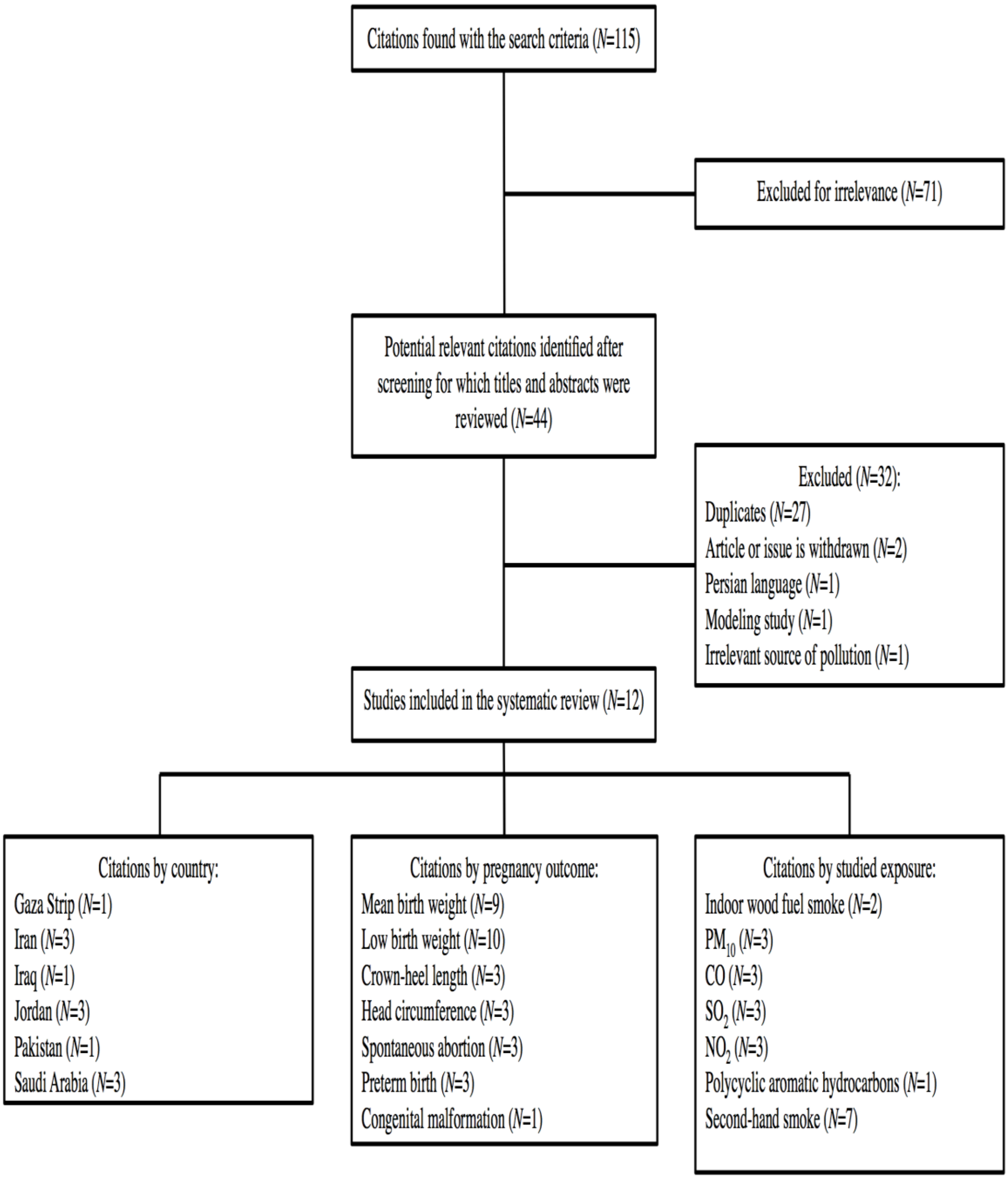

Fig. 1: Flow chart of study selection