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Pre-eclampsia and future cardiovascular risk factors: a systematic review

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DESIGNAÇÃO DA ÁREA DO PROJECTO

CIÊNCIAS MÉDICAS E DA SAÚDE, MEDICINA CLÍNICA

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Pre-eclampsia and future cardiovascular risk factors: a systematic review

ORIENTADOR

Professora Doutora Carla Maria de Almeida Carvalho

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 14/02/2023

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DEDICATÓRIA

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Pre-eclampsia and future cardiovascular risk factors: a systematic review

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Abstract

Introduction: Pre-eclampsia is one of the hypertensive disorders of pregnancy and it is associated with maternal complications that seem to remain after pregnancy. This systematic review aimed to evaluate the association between pre-eclampsia and future cardiovascular risk factors.

Methods: We performed a systematic review guided by the Systematic Reviews and Meta-Analyses guidelines (PRISMA). The search was performed on PubMed, Web of Science and Scopus. During the research, we selected articles that had pre-eclampsia as exposure. The cardiovascular risk factors considered as outcomes were hypertension, dyslipidemia, metabolic syndrome, and diabetes mellitus. From the selected articles, information regarding the year of publication, country/region, type of study, time of follow-up, inclusion criteria, results and conclusions were extracted and summarized. From these studies, the risk of bias was measured using the NIH Study Quality Assessment Tool, NIH quality assessment tool for case-control studies and NIH quality assessment tool for observational cohort and cross-sectional studies.

Results: In this systematic review with 13 articles, we obtained a total of 2,201 women with pre-eclampsia and 8,559 controls. The studies published from 2005 to 2020 covered several geographical regions including Europe, Asia, Oceania, South America, and North America. The follow-up time ranges from six months to 25 years postpartum. Four were case-control studies, seven cohort studies and two cross sectional studies. All the studies that evaluated hypertension as an outcome demonstrated a statistically significant relationship between pre-eclampsia and a higher risk of hypertension in the future. From the five studies evaluating metabolic syndrome, four of them established a statistically significant association between pre-eclampsia and metabolic syndrome. Five studies evaluated the relationship between pre-eclampsia and a higher prevalence of diabetes mellitus in the future and in none of the studies were found this relationship. Four articles presented dyslipidemia as an outcome and only one demonstrated a statistically significant relationship between pre-eclampsia and future risk of dyslipidemia.

Discussion: In this systematic review, including 10,769 women we demonstrated that there is an association between pre-eclampsia and future cardiovascular risk factors. There were some limitations in this study such as restriction of the studies to those in Portuguese and English. Also, there were differences in some criteria established by each study when defining outcomes and only seven of the 13 studies adjusted for potential confounding variables.

Keywords: Pre-eclampsia; Cardiovascular risk factors; Hypertension; Dyslipidemia; Metabolic syndrome; Diabetes mellitus.

Introduction

Around 15% of pregnant women develop at least one hypertensive disorder of pregnancy (1). These hypertensive disorders of pregnancy are associated not only with fetal but also maternal complications (2).

Pre-eclampsia is one of the hypertensive disorders of pregnancy, occurs in 2% to 8% of pregnancies and it is an important cause of maternal morbidity and mortality world-wide (3). It is defined as systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg occurring after 20 weeks of gestation in a woman who was previously normotensive with proteinuria and/or other maternal organ dysfunction or uteroplacental dysfunction evidenced by fetal growth restriction (4).

Cardiovascular diseases are one of the leading causes of death in women in the Western World (5). Women who have had pre-eclampsia have increased risk of cardiovascular diseases and premature death compared with women who have had normotensive pregnancies (6). Although this association has been recognized for many years, pre-eclampsia has only been listed as an independent risk factor for cardiac disease recently (7).

The aim of this study is to evaluate the association of pre-eclampsia with future cardiovascular risk factors.

Methods

We performed a systematic review guided by the Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8).

The search was performed on PubMed, Web of Science and Scopus in April 2022. The search terms used were “Heart Disease Risk Factors”, “Cardiovascular Risk Factors”, “Cardiovascular Risk Scores”, “Pre-eclampsia”, “Pre-eclampsia”, “Preeclampsia”, “Edema Proteinuria Hypertension Gestosis” and “EPH Gestosis”. Observational and experimental studies that sought to establish a relationship between preeclampsia and future cardiovascular risk factors were selected. Articles in Portuguese and English were included, with no date restriction.

During the research, we selected articles that had pre-eclampsia as exposure. The cardiovascular risk factors considered as outcome were hypertension, dyslipidemia, metabolic syndrome, and diabetes mellitus. For each of these outcomes, we evaluated its prevalence in women with and without a history of pre-eclampsia.

After the initial search the duplicates were removed. Afterwards, the titles and abstracts were evaluated by two authors independently and a meeting was held to discuss the articles in which there was no consensus in the choice. Lastly, there was a full reading of the articles by an author who evaluated the eligibility of the studies.

From the selected articles, information regarding the year of publication, country/region, type of study, time of follow-up, inclusion criteria, results and conclusions were extracted by one author independently.

The risk of bias was measured using the NIH Study Quality Assessment Tool, NIH quality assessment tool for case-control studies and NIH quality assessment tool for observational cohort and cross-sectional studies. The quality of the articles was rated as "Low" symbolized by "0", "Moderate" designated by "1", and "High" indicated by "2". Related to NIH quality assessment tool for case-control studies, we consider as low quality those who met less than ten criteria and high quality when they met ten or more criteria. Regarding the NIH quality assessment tool for observational cohort and cross studies sectional we considered as low quality when they met less than five criteria, moderate quality when they met less than ten criteria and high quality when they met ten or more criteria.

Due to associative nature of the variabilities in most of the studies, we will only perform a qualitative analysis of the results.

Results

The study selection process is presented in *Figure 1*. Database searching obtained 620 articles. After the duplicates removed, 327 articles were selected for reading of the title and abstract. Two hundred and ninety-three articles were excluded because didn't meet the eligibility criteria. A total of 59 articles were read in full and 28 were excluded because didn't have cardiovascular risk factors as outcome, 13 didn't evaluate pre-eclampsia as exposure, two didn't had pregnant women without pre-eclampsia as control group and three were systematic reviews. At the end of the selection process 13 studies were included.

The relevant data of the 13 included studies are presented in *Table 1*.

From the 13 articles, four were case-control studies (9-12), seven cohort studies (6, 13-18) and two cross sectional studies (19, 20).

The articles included in this review were published between 2005 and 2020. The studies covered several geographical regions including Europe, Asia, Oceania, South America, and North America.

Applying the NIH quality assessment tool for case-control studies (*Table 2*), we classified four articles with high quality (9-12). As for the NIH quality assessment tool for observational cohort and cross sectional studies (*Table 3*), we classified five articles with moderate quality (14, 16, 18-20) and four articles with high quality (6, 13, 15, 17).

The 13 articles included in this systematic review have a total of 2,201 women with pre-eclampsia and 8,559 controls.

The follow-up time of the studies ranges from six months postpartum to 25 years postpartum.

Seven studies (11-15, 17, 20) adjusted or matched for age, smoking or other potential confounders when estimating cardiovascular risk with pre-eclampsia.

Eight of the 13 studies evaluated hypertension as one of the outcomes (9-12, 14, 15, 17, 19) , five metabolic syndrome (10, 11, 14, 15, 18), six evaluated diabetes mellitus (9, 11, 12, 15, 17, 19) and four evaluated dyslipidemia (11, 12, 15, 17).

From the total of the 13 articles, nine demonstrated an increase in long-term cardiovascular risk factors in women with pre-eclampsia (9-12, 14, 15, 17-19) .

Hypertension

Eight studies evaluated hypertension as an outcome (9-12, 14, 15, 17, 19), defining hypertension as systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg or use of antihypertensive medication. All of them demonstrated a statistically significant relationship between pre-eclampsia and a higher risk of hypertension in the future (9-12, 14, 15, 17, 19).

In addition to these studies, four other studies (13, 16, 18, 20) evaluated systolic blood pressure and diastolic blood pressure values in an isolated measurement. Two studies (13, 18) demonstrated that women with a history of pre-eclampsia have significantly higher systolic and diastolic blood pressure. One study established this relationship only with systolic blood pressure (16) and another only with diastolic blood pressure (20).

Metabolic Syndrome

From the five studies evaluating metabolic syndrome, three of them (10, 11, 18) used the Adult Treatment Panel III Criteria for defining metabolic syndrome. All of them established a statistically significant association between pre-eclampsia and metabolic syndrome (10, 11, 18). One study (14) defines metabolic syndrome by two criteria, the Adult Treatment Panel III Criteria and Modified WHO criteria, and there were discrepant results. When evaluated according to Modified WHO criteria, it was established that there was a significant association between pre-eclampsia and metabolic syndrome (14). However, when they evaluated metabolic syndrome by NCEP III criteria, the authors

didn’t found an association with pre-eclampsia (14). The study performed by Garrido-Gimenez et al. (15) did not clarify the criteria that was used, and the results were not statistically significant.

Diabetes Mellitus

Five studies evaluated the relationship between pre-eclampsia and a higher prevalence of diabetes mellitus in the future (9, 11, 12, 15, 17, 19). In these studies, the authors defined diabetes mellitus as self-reported diabetes mellitus, diagnostic record of diabetes mellitus or use of medication (insulin or oral antidiabetics). It was not found a relationship between pre-eclampsia and a higher prevalence of diabetes mellitus in the future in none of the studies (9, 11, 12, 15, 17, 19).

Other studies showed results of isolated values in clinical analyses such as glycated hemoglobin (HbA1c) (6, 10, 11, 19), oral glucose tolerance test (OGTT) (16, 17, 20) or fasting glucose (10, 11, 14-18, 20). Of these all, only the study of Bokslag et al. (10) demonstrated that women with a history of pre-eclampsia have HbA1c values higher than women in the control group.

Dyslipidemia

Four articles presented dyslipidemia as an outcome (11, 12, 15, 17), defining it as self-reported dyslipidemia or use of lipid-lowering medicine. From these studies, only one demonstrated a statistically significant relationship between pre-eclampsia and future risk of dyslipidemia (15).

Other studies, although they did not present dyslipidemia as an outcome, they presented blood teste results of isolated measurements of total cholesterol (6, 10, 11, 13-15, 18-20), high-density lipoprotein (HDL) (6, 10, 11, 13-15, 17-20), low-density lipoprotein (LDL) (6, 10, 11, 13-15, 17, 18, 20) and triglycerides (6, 10, 11, 13-15, 17-20). Total cholesterol results were statistically higher in women with a history of pre-eclampsia in two studies (18, 19) from the nine studies that evaluated this (6, 10, 11, 13-15, 18-20). HDL cholesterol results were statistically higher in women with a history of pre-eclampsia in five studies (6, 10, 15, 18, 19) from the ten studies that evaluated this (6, 10, 11, 13-15, 17-20). Regarding LDL cholesterol values, only one study demonstrated higher LDL values in women with pre-eclampsia when comparing with control group (18) from the nine studies that evaluated this (6, 10, 11, 13-15, 17, 18, 20). Three studies demonstrated that pre-eclampsia women have higher levels of triglycerides than control group (6, 10, 19) from the ten studies that evaluated this (6, 10, 11, 13-15, 17-20).

Discussion

In this systematic review, including 13 studies with 10,769 women, we demonstrated that there is an association between pre-eclampsia and future cardiovascular risk factors.

Blood pressure has an independent and continuous relationship with the incidence of cardiovascular events (21). All studies included in this review that considered hypertension as outcome demonstrated relationship between pre-eclampsia and hypertension, which strengthens pre-eclampsia as a risk factor. Our results are consistent with the findings from other studies. A cohort study in Denmark, which included 1.5 million pregnant women, found association between hypertensive disorders of pregnancy and chronic hypertension in 1-20 years of follow-up (22). Also, Heida et al (23) stated that women with a history of hypertensive disorders of pregnancy were diagnosed with hypertension twice more often.

Additionally, we also demonstrated results of isolated measurements of systolic and diastolic blood pressure being higher in women with pre-eclampsia. However, blood pressure can be very variable and the diagnosis of hypertension should not be based on a single isolated measurement (21) and, for these same reason, these results are not included in the outcome hypertension.

Metabolic syndrome is associated with an increased risk of cardiovascular disease (24). In the same way, we demonstrated that women with a history of pre-eclampsia have a higher prevalence of metabolic syndrome. There were other studies that concluded that the prevalence of the metabolic syndrome was two-fold higher in women with a history of pre-eclampsia compared with women with a history of small-for-gestational-age, which is also a risk factor for metabolic syndrome (25). Other articles have highlighted that the presence of hypertensive disorders of pregnancy increases the risk of developing metabolic syndrome in the future and its development showed a shorter time period in these women (26).

Diabetes mellitus is a major cardiovascular risk factor, increasing a two-fold excess risk of vascular outcomes (27). However, our results did not show a relationship between pre-eclampsia and risk of diabetes mellitus in the future. These results go against the results of other studies such as Leonie K. et al (28) that found a two-fold increase in diabetes mellitus 21 years after hypertensive pregnancy disorders. This discrepancy must be analyzed with caution since these studies present as exposure hypertensive disorders of pregnancy, which is not the exact outcome of our study.

However, one study included in our revision (10) demonstrated that women with a history of pre-eclampsia have higher HbA1c values. Although we know that the reduction of these values has some relationship with reduced risk of non-fatal myocardial infarction, we also know that it does not reduce the risk of many other cardiovascular events (27).

Also, for the diagnosis of diabetes, an isolated measurement of HbA1c is not enough (27) and, for this reason, this study was not included in the outcome of diabetes mellitus.

From the results of our study, it does not seem to exist a relationship between pre-eclampsia and subsequent dyslipidemia. Our results are in line with the results from the study of Heida et al. who, despite concluding that women with hypertensive disorders of pregnancy develop hypertension twice as much, was unable to conclude the same with dyslipidemia (23). Contrarily, Kuo et al. suggests that women with a history of pre-eclampsia/eclampsia have a higher risk of developing dyslipidemia (29).

In addition, we found that history of pre-eclampsia is related to lower values of HDL cholesterol and in some cases higher values of LDL, triglycerides, and total cholesterol. These results are consistent with other studies such as Hermes et al. (30). Ideally, to establish a diagnosis of dyslipidemia we would have at least one more measurement to confirm these results (31) and, therefore, we do not include this finding in the results with the outcome of dyslipidemia. However, we know that the increase in the absolute value of LDL cholesterol is associated with a higher risk of cardiovascular disease (31). In relation to triglycerides, it is known that the causal effect on cardiovascular diseases is more related to the concentration of ApoB particles than to the values of triglycerides by itself but, even so, this relationship is established (31). Total cholesterol and HDL cholesterol are also important for calculating cardiovascular risk scores and, although with some discrepancies, it is known that lower HDL values are related to higher cardiovascular risk (31).

There are some strengths and limitations in our study that should be considered. As strengths we can highlight that there was no restriction on date of publication and the research of the studies was made in three databases. In addition, the evaluation of the quality of the articles based on NIH quality assessment tool allowed to classify most articles with moderate and high quality. About our limitations, we limited the studies to those in Portuguese and in English and may have missed data from publications in other languages. In addition, there were differences in some criteria established by each study when defining outcomes. Furthermore, only seven of the 13 studies adjusted for potential confounding variables and so, some potential confounders may have contributed to the association between history of pre-eclampsia and cardiovascular risk factors in the future.

Conclusion

In summary, we found that women with history of pre-eclampsia have a higher prevalence of cardiovascular risk factors in the future. With our study we were able to demonstrate this relationship with risk factors such as hypertension and metabolic syndrome. This reinforces that further efforts should be made to understand when we should start

cardiovascular screening in these postpartum women and the establishment of guidelines that allow better and more uniform monitoring of these women and their cardiovascular risk factors after pregnancy complicated with pre-eclampsia.

Statements and declarations

Declaration of interest: None.

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Author contributions: AD and CR conceived and designed the study. AD proceeded to the initial search of articles in the databases. Both authors, AD and CR, participated in the reading of the title and abstract of the articles and in the selection of articles to be read in full. There was a full reading of the articles by AD who evaluated the eligibility of the studies. AD drafted the first version of the manuscript and CR proceeded to its the reading and correction. CR provided its clinical knowledge and practice to correct and make suggestions throughout the elaboration of the manuscript. All contributed to critically analyze the article and approve the final version of the manuscript.

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Figures and Tables

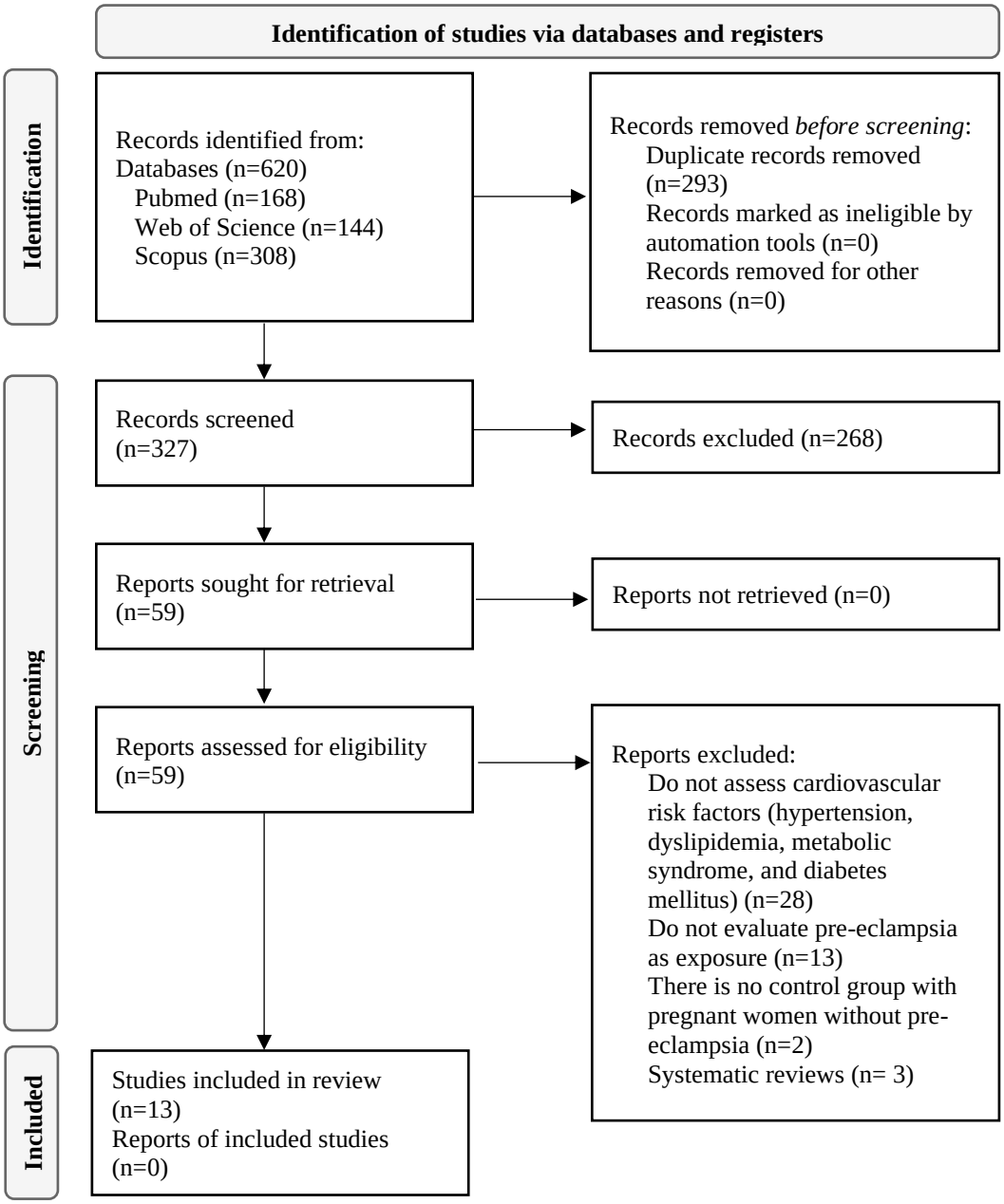

Figure 1. Flow diagram of study inclusion.

Table 1. Study design and characteristics.

Author, year, country	Type of study	Follow-up time	Inclusion criteria	Results	Conclusions
Andersgaard (19), 2012, Norway	Cross-sectional study.	Mean of 25 years.	Women in the Tromso study that answer questionnaires on parity and hypertensive complications in pregnancies.	The prevalence of BP equal to or greater than 140/90 mm Hg or use of antihypertensive medication was significantly higher in PE than in the control group. PE group had a significantly higher triglycerides and total cholesterol. HDL cholesterol was significantly lower in PE group. Prevalence of diabetes mellitus was not significantly higher in pre-eclampsia group. HbA1c did not present statistically significant higher values between the two groups.	Women with a history of PE have an unfavorable cardiovascular risk profile and a higher frequency of hypertension.
Aykas (9), 2015, Turkey	Observational case-control study.	In the PE group was 6.12 ± 3.59 years. In the control group was 6.05 ± 4.06 years.	Patients with pre-eclampsia and control subjects were recruited from the Department of Obstetrics and Gynecology of Kayseri Education and Research Hospital, Turkey.	The prevalence of hypertension was significantly higher in PE than in the control group Prevalence of diabetes mellitus was not significantly higher in pre-eclampsia group.	Cardiovascular disease risk factors are significantly more prevalent in patients with previous PE when compared with women without PE.
Bokslag (10), 2017, Netherlands	Retrospective case-control study.	Nine to 16 years.	All women giving birth between 1998 and 2005 were recruited from obstetrical databases of two tertiary medical centers in the Netherlands.	The prevalence of hypertension was significantly higher in PE than in the control group. The prevalence of metabolic syndrome was significantly higher in PE than in the control group. PE group have lower levels of HDL and higher levels of triglyceride compared to controls. HbA1c values are statistically higher in the PE group. Both fasting glucose, CT, and LDL cholesterol did not present statistically significant values.	Women with a history of pre-eclampsia have high rates of cardiovascular risk factor.
Brown (6), 2020, Australia	Prospective cohort study.	Six months.	Women from the P4 study who had delivered following a normotensive pregnancy and women who had a pre-eclamptic pregnancy were invited to participate.	HDL was lower and triglycerides higher in the PE group. Both HbA1c, CT, and LDL cholesterol did not present higher statistically significant values.	Six months after pregnancy women who have had pre-eclampsia have higher BP and more features of metabolic syndrome than women who had normotensive pregnancies.
Canti (20), 2010, Brazil	Cross-sectional study.	In the PE group was 15.9 ± 3.6 years. In the control group was 14.6 ± 3.1 years.	Patients who delivered at the Gynecology and Obstetrics service of the Hospital de Clínicas de Porto Alegre (HCPA) 10 or more years before the time of the	The women in the pre-eclampsia group had significantly higher diastolic blood pressure than presented by the control group and more frequency of abnormal values. Fasting glycose, OGGT, triglycerides, LDL, HDL and total cholesterol did not present higher statistically significant values.	Patients who had had pre-eclampsia ten or more years earlier presented significantly higher diastolic blood pressure and prevalence of hypertension than

			present study were selected.		did those in the control group.
Drost (11), 2012, Netherlands	Prospective case-control study.	Ten years.	At the Department of Obstetrics at the Isala Klinieken in Netherlands, all women registered on the pre-eclampsia database were invited as well as an equal number of age-matched females without pre-eclampsia from the regular obstetric database at the same time.	The prevalence of hypertension was significantly higher in PE than in the control group. The prevalence of metabolic syndrome was significantly higher in PE than in the control group. The prevalence of diabetes mellitus and hypercholesterolemia was not statistically significant. Fasting glycose, HbA1c, triglycerides, LDL, HDL, and total cholesterol did not present higher statistically significant values.	Women with pre-eclampsia have a higher risk of hypertension and a higher risk for development of the metabolic syndrome in women post pre-eclampsia at ten years post index pregnancy.
Edlow (12), 2009, Pennsylvania	Prospective case-control study.	Six to 13 months.	Pre- eclampsia: Mechanisms and Consequences (PMC) study was performed at the Hospital of the University of Pennsylvania between 2005 and 2007. Cases were prospectively identified based on maternal criteria for pre-eclampsia.	The prevalence of hypertension was significantly higher in PE than in the control group. The prevalence of dyslipidemia, diabetes mellitus did not present higher statistically significant values.	Pre-eclampsia is associated with an increase in hypertension six to 13 months after delivery.
Escouto (13), 2018, United Kingdom	Prospective longitudinal cohort study.	Mean of 7.1 weeks.	All women with a history of hypertension in pregnancy and healthy controls were invited to a six-week postpartum follow-up visit at the Maternity Unit, Nottingham City Hospital, United Kingdom.	The women in the pre-eclampsia group had significantly higher systolic and diastolic blood pressure than control group and both values are above the normal values. Both triglycerides, LDL, HDL, and total cholesterol did not present higher statistically significant values.	Women with a history of pre-eclampsia have high rates of cardiovascular risk factor. Six weeks after delivery is an opportunistic time to assess cardiovascular risk for women these women.
Forest (14), 2005, Canada	Prospective cohort study.	Mean of 7.8 years (range 5.1–13.0 years).	From a cohort of 3,799 nulliparous women prospectively recruited between 1989 and 1997, resulting in a observational study on 168 case-control pairs 7.8 years after delivery.	The prevalence of hypertension was significantly higher in PE than in the control group. The prevalence of metabolic syndrome was significantly higher in PE than in the control group when using the WHO criteria. When using NCEP III criteria the prevalence of metabolic syndrome was higher in PE group, but it was not statistically significant. Both triglycerides, LDL, HDL and total cholesterol and fasting glycose did not present higher statistically significant values.	This study shows that many cardiovascular risk factors are more prevalent in women in their mid-30s with a history of PE than in controls. The prevalence of metabolic syndrome is 3 to 5-fold increase in these women compared with those with uneventful pregnancy.
Garrido-Gimenez (15), 2020, Spain	Prospective cohort study.	Mean of 12.7 years (range 12.3–13.0 years).	Pregnant women, who participated in a previous study performed between	The prevalence of hypertension was significantly higher in PE than in the control group.	Women with previous pre-eclampsia had more cardiovascular risk

			2003 and 2005, were reinvited to participate for a cardiovascular risk assessment from January 2017 to June 2018.	The prevalence of dyslipidemia was significantly higher in PE than in the control group. PE group have lower levels of HDL compared to controls. The prevalence of diabetes mellitus, metabolic syndrome and did not present higher statistically significant values. Fasting glycose, triglycerides, LDL, and total cholesterol did not present higher statistically significant values.	factors and comorbidities compared with uncomplicated pregnancies.
Kvehaugen (16), 2010, Norway	Cohort study.	Five to eight years.	Women recruited to a pregnancy biobank at Oslo University Hospital, in 2001–2004, due to a pregnancy complicated by PE, as well as uncomplicated pregnancies, were invited to a clinical follow-up study, 'CHASE' in 2008–2009.	Women in the PE group had higher systolic BP compared to the control group but within normal values. There were no statistically significant differences between PE and control group in relation to diastolic BP. There were no statistically significant differences between PE and control group in relation to values of fasting glycose and OGGT.	Due to the objectively observed differences in risk factors for cardiovascular and associated diseases, there may be a potential for lifestyle intervention among mothers following pregnancies complicated by PE.
McDonald (17), 2013, Canada	Retrospective cohort study.	Twenty years.	Women who had pre-eclampsia diagnosed at delivery between January 1986 and December 1995 that were previously assembled as a cohort in the McMaster Outcome Study of Hypertension in Pregnancy. They were recruited prior to delivery.	The prevalence of hypertension was significantly higher in PE than in the control group. There were no statistically significant differences between PE and control group in relation to prevalence of diabetes mellitus, hyperlipidemia, hypertriglyceridemia. There were no statistically significant differences between PE and control group in relation to values of fasting glycose, OGGT, triglycerides, LDL, HDL, and total cholesterol.	Women with previously PE have increased risks of cardiovascular risk factors, relative to women with uncomplicated pregnancies.
Smith (18), 2009, Canada	Prospective cohort.	One year.	All women diagnosed with PE at the time of presentation to clinic or admission/transfer to either the Kingston or Ottawa General Hospitals were approached to participate.	The prevalence of hypertension was significantly higher in PE than in the control group. The prevalence of metabolic syndrome was significantly higher in PE than in the control group. PE group have more women with abnormal HDL levels. PE group have higher levels of total cholesterol and LDL cholesterol. There were no statistically significant differences between PE and control group in relation to values of fasting glycose and triglycerides.	Pre-eclampsia is associated with underlying cardiovascular risk factors. Incorporating all data and the markers of obesity it was identified a higher significant number of PE women with metabolic syndrome.

PE, Pre-eclampsia; HDL cholesterol, High-density lipoprotein cholesterol; LDL Cholesterol, Low density lipoprotein cholesterol; NCEP III, Adult Treatment Panel III Criteria; BP, Blood pressure; OGTT, Oral glucose tolerance test; HbA1c, Glycated hemoglobin.

Table 2.NIH quality assessment tool for case-control studies.

	Aykas et al.(9)	**Bokslag et al. (10)**	**Drost et al. (11)**	**Edlow et al.(12)**
Was the research question or objective in this paper clearly stated and appropriate?	*	*	*	*
Was the study population clearly specified and defined?	*	*	*	*
Did the authors include a sample size justification?	X	*	X	X
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	*	*	*	*
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	*	*	*	*
Were the cases clearly defined and differentiated from controls?	*	*	*	*
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	*	*	*	*
Was there use of concurrent controls?	*	*	*	*
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	*	*	*	*
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time) across all study participants?	*	*	*	*
Were the assessors of exposure/risk blinded to the case or control status of participants?	*	NR	NR	NR
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	X	X	*	*
Quality	2	2	2	2

Yes, *; No, X; CD, cannot determine; NR, not reported; NA, not applicable.

Table 3. NIH quality assessment tool for observational cohort and cross studies sectional.

	Andersgaard et al. (19)	**Brown et al. (6)**	**Canti et al. (20)**	**Escouto et al. (13)**	**Forest et al. (14)**	**Garrido-Gimenez et al.(15)**	**Kvehaugen et al.(16)**	**McDonald et al. (17)**	**Smith et al. (18)**
Was the research question or objective in this paper clearly stated?	*	*	*	*	*	*	*	*	*
Was the study population clearly specified and defined?	*	*	*	*	*	*	*	*	*
Was the participation rate of eligible persons at least 50%?	X	*	NR	NR	X	X	X	X	X
Were all the subjects selected or recruited from the same or similar populations (including the same time)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	*	*	*	*	*	*	*	*	*
Was a sample size justification, power description, or variance and effect estimates provided?	*	*	*	*	NR	NR	*	*	*
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	*	*	*	*	*	*	*	*	*
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	*	*	*	*	*	*	*	*	*
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	*	*	*	*	*	*	*	*	*
Was the exposure(s) assessed more than once over time?	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	*	*	*	*	*	*	*	*	*
Were the outcome assessors blinded to the exposure status of participants?	NR	*	NR	NR	NR	*	NR	*	NR
Was loss to follow-up after baseline 20% or less?	*	*	NR	*	*	*	X	NR	NR

Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NR	NR	*	*	*	*	NR	*	NR
Quality	1	2	1	2	1	2	1	2	1

Yes, *; No, X; CD, cannot determine; NR, not reported; NA, not applicable.

Attachment 1

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 6: "Pre-eclampsia and future cardiovascular risk factors: a systematic review".
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	See PRISMA 2020 Abstracts checklist.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 8 (3rd paragraph): "Cardiovascular diseases are one of the leading causes of death in women in the Western world (5). Women who have had pre-eclampsia have increased risk of cardiovascular diseases and premature death compared with women who have had normotensive pregnancies (6). Although this association has been recognized for many years, pre-eclampsia has only been listed as an independent risk factor for cardiac disease recently. (7)"
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 8 (4th paragraph): "The aim of this study is to evaluate the association of pre-eclampsia with cardiovascular risk factors."
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 8 (6th paragraph): "Observational and experimental studies that sought to establish a relationship between preeclampsia and future cardiovascular risk factors were selected. Articles in Portuguese and English were included, with no date restriction." Page 8 (7th paragraph): "During the research, we selected articles that had PE as exposure. The cardiovascular risk factors considered as outcome were hypertension, dyslipidemia, metabolic syndrome, and diabetes mellitus. For each of these outcomes, we evaluated its prevalence in women with and without a history of pre-eclampsia."
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8 (6th paragraph): "The search was performed on PubMed, Web of Science and Scopus in April 2022."
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 8 (6th paragraph): "The search terms used were "Heart Disease Risk Factors", "Cardiovascular Risk Factors", "Cardiovascular Risk Scores", "Pre-eclampsia", "Pre-eclampsia", "Preeclampsia", "Edema Proteinuria Hypertension Gestosis" and "EPH Gestosis"."
Selection process	8	Specify the methods used to decide whether a study met the	Page 9 (1st paragraph): "After the initial search the duplicates were removed. Afterwards, the titles and abstracts were evaluated by two authors independently and a meeting was held to discuss the articles in which there was no consensus in the choice. Lastly, there was a full reading of the articles by an author who evaluated the eligibility of the studies."

Section and Topic	Item #	Checklist item	Location where item is reported
		inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 9 (2nd paragraph): "From the selected articles, information regarding the year of publication, country/region, type of study, time of follow-up, inclusion criteria, results and conclusions were extracted by one author independently."
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 8 (7th paragraph): "During the research, we selected articles that had PE as exposure. The cardiovascular risk factors considered as outcome were hypertension, dyslipidemia, metabolic syndrome, and diabetes mellitus. For each of these outcomes, we evaluated its prevalence in women with and without a history of pre-eclampsia."
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 9 (2nd paragraph): "From the selected articles, information regarding the year of publication, country/region, type of study, time of follow-up, inclusion criteria, results and conclusions were extracted by one author independently."

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9 (3rd paragraph): "The risk of bias was measured using the NIH Study Quality Assessment Tool, NIH quality assessment tool for case-control studies and NIH quality assessment tool for observational cohort and cross-sectional studies. The quality of the articles was rated as "Low" symbolized by "0", "Moderate" designated by "1", and "High" indicated by "2". Related to NIH quality assessment tool for case-control studies, we consider as low quality those who met less than ten criteria and high quality when they met ten or more criteria. Regarding the NIH quality assessment tool for observational cohort and cross studies sectional we considered as low quality when they met less than five criteria, moderate quality when they met less than ten criteria and high quality when they met ten or more criteria."
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable as this review does not include a meta-analysis.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable as this review does not include a meta-analysis.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable as this review does not include a meta-analysis.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applicable as this review does not include a meta-analysis.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s),	Not applicable as this review does not include a meta-analysis.

Section and Topic	Item #	Checklist item	Location where item is reported
		method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable as this review does not include a meta-analysis.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable as this review does not include a meta-analysis.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable as this review does not include a meta-analysis.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable as this review does not include a meta-analysis.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9 (5th paragraph): "The study selection process is presented in Figure 1. Database searching obtained 620 articles. After the duplicates removed, 327 articles were selected for reading of the title and abstract. Two hundred and ninety-three articles were excluded because didn't meet the eligibility criteria." Page 19 (Figure 1): "Flow diagram of study inclusion."
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9 (5th paragraph): "A total of 59 articles were read in full and 28 were excluded because didn't have cardiovascular risk factors as outcome, 13 didn't evaluate pre-eclampsia as exposure, two didn't had pregnant women without pre-eclampsia as control group and three were systematic reviews. At the end of the selection process 13 studies were included."
Study characteristics	17	Cite each included study and present its characteristics.	Page 9 (7th paragraph): "From the 13 articles included, four were case-control studies (9-12), seven cohort studies (6, 13-18) and two cross sectional studies (19, 20)."

Section and Topic	Item #	Checklist item	Location where item is reported
			Page 9 (8th paragraph): "The articles included in this review were published between 2005 and 2020. The studies covered several geographical regions including Europe, Asia, Oceania, South America, and North America." Page 20,21 and 22 (Table 1): "Study design and characteristics."
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 10 (1st paragraph): "Applying the NIH quality assessment tool for case-control studies (Table 2), we classified four articles with high quality (9-12). As for the NIH quality assessment tool for observational cohort and cross sectional studies (Table 3), we classified five articles with moderate quality (14, 16, 18-20) and four articles with high quality (6, 13, 15, 17)" Page 23 (Table 2): NIH quality assessment tool for case-control studies. Page 24 and 25 (Table 3): NIH quality assessment tool for observational cohort and cross studies sectional.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable as this review does not include a meta-analysis.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable as this review does not include a meta-analysis.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable as this review does not include a meta-analysis.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable as this review does not include a meta-analysis.

Section and Topic	Item #	Checklist item	Location where item is reported
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable as this review does not include a meta-analysis.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable as this review does not include a meta-analysis.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable as this review does not include a meta-analysis.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12 (2nd paragraph):"Blood pressure has an independent and continuous relationship with the incidence of cardiovascular events (21). All studies included in this review that considered hypertension as outcome demonstrated relationship between pre-eclampsia and hypertension, which strengthens pre-eclampsia as a risk factor. Our results are consistent with the findings of other studies. A cohort study in Denmark, which included 1.5 million pregnant women, found association between hypertensive disorders of pregnancy and chronic hypertension in 1-20 years of follow-up (22). Also, Heida et al (23) stated that women with a history of hypertensive disorders of pregnancy were diagnosed with hypertension twice more often. Lykke et al (32) mentioned on a 7.58-fold increased risk of subsequent hypertension in women with severe pre-eclampsia." Page 12 (4th paragraph): "Metabolic syndrome is associated with an increased risk of cardiovascular disease (24). In the same way, we demonstrated that women with a history of pre-eclampsia have a higher prevalence of metabolic syndrome. There were other studies that concluded that the prevalence of the metabolic syndrome was two-fold higher in women with a history of pre-eclampsia compared with women with a history of small-for-gestational-age, which is also a risk factor for metabolic syndrome (25). Other articles have highlighted that the presence of hypertensive disorders of pregnancy increases the risk of developing metabolic syndrome in the future and its development showed a shorter time period in these women (26). " Page 12 (5th paragraph): "Diabetes mellitus is a major cardiovascular risk factor, increasing a two-fold excess risk of vascular outcomes (27). However, our results did not show a relationship between pre-eclampsia and risk of diabetes mellitus in the future. These results go against the results of other studies such as Leonie K. et al (28) that found a two-fold increase in diabetes mellitus twenty-one years after hypertensive pregnancy disorders. This discrepancy must be analyzed with caution since these studies present as exposure hypertensive disorders of pregnancy, which is not the exact outcome of our study." Page 13 (1st paragraph): "From the results of our study, it does not seem to be a relationship between pre-eclampsia and subsequent dyslipidemia. Our results are in line with the results from the study of Heida et al. who, despite concluding that women with hypertensive disorders of pregnancy develop hypertension twice as much, they were

Section and Topic	Item #	Checklist item	Location where item is reported
			unable to conclude the same with dyslipidemia (23). Contrarily, Kuo et al. suggests that women with a history of pre-eclampsia/eclampsia have a higher risk of developing dyslipidemia (29)."
	23b	Discuss any limitations of the evidence included in the review.	Page 13 (3rd paragraph): "About our limitations (…) there were differences in some criteria established by each study when defining outcomes. Furthermore, only seven of the 13 studies adjusted for potential confounding variables and so, some potential confounders may have contributed to the association between history of pre-eclampsia and cardiovascular risk factors in the future."
	23c	Discuss any limitations of the review processes used.	Page 13 (3rd paragraph): "About our limitations, we limited the studies to those in Portuguese and in English and may have missed data from publications in other languages."
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13 (4th paragraph): "In summary, we found that women with history of pre-eclampsia have a higher prevalence of cardiovascular risk factors in the future. With our study we were able to demonstrate this relationship with risk factors such as hypertension and metabolic syndrome. This reinforces that further efforts should be made to understand when we should start cardiovascular screening in these postpartum women and the establishment of guidelines that allow better and more uniform monitoring of these women and their cardiovascular risk factors after pregnancy complicated with pre-eclampsia."
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not applicable as registration was not done.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not applicable as registration was not done.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable as registration was not done.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Not applicable.
Competing interests	26	Declare any competing interests of review authors.	Not applicable.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found; template data collection forms; data	Not applicable.

Section and Topic	Item #	Checklist item	Location where item is reported
		extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Not applicable
Registration	12	Provide the register name and registration number.	Not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Attachment 2

EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY: X

AUTHOR INFORMATION PACK

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DESCRIPTION

***European Journal of Obstetrics & Gynecology and Reproductive Biology: X* is the open access companion journal of European Journal of Obstetrics & Gynecology and Reproductive Biology and has the same aims and scope, editorial board and peer-review process.**

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Web submission, including a new Fast track review and publication route is now available.

ABSTRACTING AND INDEXING

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GUIDE FOR AUTHORS

introduction

The *European Journal of Obstetrics & Gynecology and Reproductive Biology X* is the open access companion journal of The *European Journal of Obstetrics & Gynecology and Reproductive Biology*.

The *European Journal of Obstetrics & Gynecology and Reproductive Biology* is the leading general clinical journal covering all European countries. It publishes peer reviewed original research articles, expert opinions and reviews, and also news, book reviews and biographical, historical and educational articles. Fields covered include obstetrics, prenatal diagnosis, materno-fetal medicine, perinatology, general gynecology, gynecologic oncology, uro-gynecology, reproductive medicine, infertility, reproductive endocrinology, sexual medicine and reproductive ethics. It provides a forum for scientific and clinical professional communication in obstetrics and gynecology throughout Europe and the world.

Editorial policies

The following articles will be considered for publication: original research articles, review articles, expert opinions and letters to the Editor - brief communications (formerly case reports).

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis), that it is not under consideration for publication elsewhere, that its publication is approved by all Authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, without written consent of the Publisher.

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You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

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- E-mail address
- Full postal address

All necessary files have been uploaded:
Manuscript:
- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print

Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)

Further considerations
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• A competing interests statement is provided, even if the authors have no competing interests to declare
• Journal policies detailed in this guide have been reviewed
• Referee suggestions and contact details provided, based on journal requirements

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BEFORE YOU BEGIN

Ethics in publishing

Please see our information on Ethics in publishing.

Studies in humans and animals

If the work involves the use of human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript should be in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. The terms sex and gender should be used correctly.

Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Research Council's Guide for the Care and Use of Laboratory Animals and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

Declaration of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential competing interests include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Authors must disclose any interests in two places: 1. A summary declaration of interest statement in the title page file (if double anonymized) or the manuscript file (if single anonymized). If there are no interests to declare then please state this: 'Declarations of interest: none'. 2. Detailed disclosures as part of a separate Declaration of Interest form, which forms part of the journal's official records. It is important for potential interests to be declared in both places and that the information matches. More information.

Author agreement

An agreement by all authors (maximum 6 to 7) is required for submission. A statement to this effect is requested at submission stage.

Submission declaration

Submission of an article implies that the work described has not been published previously (except in the form of an abstract, a published lecture or academic thesis, see 'Multiple, redundant or concurrent publication' for more information), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. When coding terminology is used, we recommend to avoid offensive or exclusionary terms such as "master", "slave", "blacklist" and "whitelist". We suggest using alternatives that are more appropriate and (self-) explanatory such as "primary", "secondary", "blocklist" and "allowlist". These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

Reporting sex- and gender-based analyses

Reporting guidance

For research involving or pertaining to humans, animals or eukaryotic cells, investigators should integrate sex and gender-based analyses (SGBA) into their research design according to funder/sponsor requirements and best practices within a field. Authors should address the sex and/or gender dimensions of their research in their article. In cases where they cannot, they should discuss this as a limitation to their research's generalizability. Importantly, authors should explicitly state what definitions of sex and/or gender they are applying to enhance the precision, rigor and reproducibility of their research and to avoid ambiguity or conflation of terms and the constructs to which they refer (see Definitions section below). Authors can refer to the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER guidelines checklist. These offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting and research interpretation - however, please note there is no single, universally agreed-upon set of guidelines for defining sex and gender.

Definitions

Sex generally refers to a set of biological attributes that are associated with physical and physiological features (e.g., chromosomal genotype, hormonal levels, internal and external anatomy). A binary sex categorization (male/female) is usually designated at birth ("sex assigned at birth"), most often based solely on the visible external anatomy of a newborn. Gender generally refers to socially constructed roles, behaviors, and identities of women, men and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man) and unchanging whereas these constructs actually exist along a spectrum and include additional sex categorizations and gender identities such as people who are intersex/have differences of sex development (DSD) or identify as non-binary. Moreover, the terms "sex" and "gender" can be ambiguous—thus it is important for authors to define the manner in which they are used. In addition to this definition guidance and the SAGER guidelines, the resources on this page offer further insight around sex and gender in research studies.

Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Changes to authorship

Authors are expected to consider carefully the list and order of authors **before** submitting their manuscript and provide the definitive list of authors at the time of the original submission. Any addition, deletion or rearrangement of author names in the authorship list should be made only **before** the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the **corresponding author**: (a) the reason

for the change in author list and (b) written confirmation (e-mail, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed.
Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of authors **after** the manuscript has been accepted. While the Editor considers the request, publication of the manuscript will be suspended. If the manuscript has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Manuscript categories

During submission the author must select a category from the following list: Review Article, Research Article, Book Review, Letter to the Editor. In preparing submissions, authors should check the general requirements for the preparation of manuscripts (see below)

Review articles
As well as invited articles we welcome submitted reviews on topics of current interest in obstetrics and gynecology. Reviews are allowed a maximum of 3500 words (excluding title page, abstract and references), 10 figures and 10 tables. The reference list should not exceed 3 pages.

Expert Opinions
These are generally ”invited” by the Editor-in-Chief but submission may be considered, with a maximum of 2000 words, 20 citations and 2 figures or 2 tables.

Research articles
For details, see below: ”General Requirements for the preparation of manuscripts”. There is a limit of 2500 words (excluding title page, abstract and references), 10 figures and 10 tables. The reference list should not exceed 3 pages.

Letters to the Editor are limited to a maximum of 600 words (excluding references, names and addresses of the signers, and the phrase "to the Editor"). Only one type of letter will be considered for publication:
Letter to the Editor - Brief Communication giving a brief case presentation or short report of a pertinent clinical observation. Please use the correct format following the criteria: max 600 words, max 5 references, max 1 table or 1 figure, no abstract, no keywords, no headings. The information must be presented as a true Letter, e.g. starting with ”Dear Editor, we found that... etc.” Brief communications that do not meet this criteria will be returned to the author.

Announcements of major meetings and other significant activities should be sent to the Editor-in-Chief.

Editorial review process

Authors are responsible for following the criteria for the manuscript categories listed above before submitting the article to the Editorial Office. Articles not meeting these criteria will be rejected immediately without going through to peer review.

At submission authors will be asked to assign their article to a specialty subject area covered by the journal: obstetrics, maternal-fetal medicine, reproductive medicine and endocrinology, gynecology, gynecology oncology and urogynecology. All articles will undergo an initial review by an Advisory Board Editor expert in a particular specialty area. Articles will be assessed for:
- having sound methodological structure
- reporting novel results
- driving the field forward
- being within the scope of the journal
- being written clearly and understandably for a reviewer to do his/her job properly, and
- a potential for FastTrack review and publication

Articles not meeting these criteria will be rejected immediately without going through to full peer review.

Articles that have passed the initial review process are assigned by the Editorial Office to a Specialty Editor on the basis of the corresponding author's address. At least 2 independent reviewers are assigned per article for a systematic review of the article's aims, methodology, results and conclusions.

Following peer review, articles may be accepted without revision, accepted pending minor revision, not accepted but eligible for re-submission following major revision, or rejected. No more than two revision cycles are permitted per article - articles that after two revisions have still not adequately addressed the reviewers and Specialty Editors concerns will be rejected.

Authors are advised that during the review process the reviewers and/or the Specialty Editor may request additional statistical and language review. These articles will be reviewed by respectively an independent Statistical Advisor and Language Editor to the journal, either of whom may subsequently request additional changes prior to final acceptance of the manuscript.

Author's suggested reviewers
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For questions about the editorial process (including the status of manuscripts under review) or for technical support on submissions, please visit our Support Center.

Peer review
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Use of word processing software
It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure
Subdivision - numbered sections
Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Theory/calculation
A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Vitae
Submit a short (maximum 100 words) biography of each author, along with a passport-type photograph accompanying the other figures. Please provide the biography in an editable format (e.g. Word), not in PDF format.

Essential title page information

• ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
• ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
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Highlights

Highlights are optional yet highly encouraged for this journal, as they increase the discoverability of your article via search engines. They consist of a short collection of bullet points that capture the novel results of your research as well as new methods that were used during the study (if any). Please have a look at the examples here: example Highlights.

Highlights should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations

Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Math formulae

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

Artwork

Electronic artwork

General points

- Make sure you use uniform lettering and sizing of your original artwork.
- Embed the used fonts if the application provides that option.
- Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the published version.
- Submit each illustration as a separate file.
- Ensure that color images are accessible to all, including those with impaired color vision.

A detailed guide on electronic artwork is available.

You are urged to visit this site; some excerpts from the detailed information are given here.

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Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.

TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.

TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.

TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.

Please do not:

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- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

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Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article**. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

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Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References

Citation in text
Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references
This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

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Where a preprint has subsequently become available as a peer-reviewed publication, the formal publication should be used as the reference. If there are preprints that are central to your work or that cover crucial developments in the topic, but are not yet formally published, these may be referenced. Preprints should be clearly marked as such, for example by including the word preprint, or the name of the preprint server, as part of the reference. The preprint DOI should also be provided.

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Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

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Reference style

Adhere to the maximum number of references for each category of article (see above). Number references consecutively in the order in which they are mentioned in the text. Use the format of the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (Vancouver style) (N Engl J Med 1991: 324: 424-8). Journal titles should conform to the abbreviations used in Cumulated Index Medicus. If six or fewer authors, list all; if seven or more authors, list three then "et al".

Examples:
Journals
(1) Paterok EM, Roenthal H, Sabel M. Nipple discharge and abnormal galactogram. Results of a long-term study (1964-1999). Eur J Obstet Gynecol Reprod Biol 1993; 50: 227-34.
Books
(2) Brown SS, ed. Prenatal Care. Reaching Mothers, reaching infants. Washington: National Academy Press, 1998.
(3)[dataset] [3] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.

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Journal abbreviations source
Only standard abbreviations may be used. Consult the Council of Biology Editors Style Manual or the AMA's Manual of Style: http://healthlinks.washington.edu/hsl/styleguides/ama.html.

Abbreviations in the title are not acceptable. They should be avoided, if possible, in the abstract and keywords. In the text they should be kept to practical minimum. The full term for which an abbreviation stands should not precede its first use in the text unless it is a standard unit of measurement.

The generic, chemical or proprietary names of pharmaceuticals may be used. If the generic or chemical names are used, authors may, if they desire, insert the proprietary name in parentheses after the first mention in the text, with the name of the manufacturer and city and state.

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