REVIEW

OPEN

What contributes to disparities in the preterm birth rate in European countries?

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Purpose of review
In countries with comparable levels of development and healthcare systems, preterm birth rates vary markedly – a range from 5 to 10% among live births in Europe. This review seeks to identify the most likely sources of heterogeneity in preterm birth rates, which could explain differences between European countries.

Recent findings
Multiple risk factors impact on preterm birth. Recent studies reported on measurement issues, population characteristics, reproductive health policies as well as medical practices, including those related to subfertility treatments and indicated deliveries, which affect preterm birth rates and trends in high-income countries. We showed wide variation in population characteristics, including multiple pregnancies, maternal age, BMI, smoking, and percentage of migrants in European countries.

Summary
Many potentially modifiable population factors (BMI, smoking, and environmental exposures) as well as health system factors (practices related to indicated preterm deliveries) play a role in determining preterm birth risk. More knowledge about how these factors contribute to low and stable preterm birth rates in some countries is needed for shaping future policy. It is also important to clarify the potential contribution of artifactual differences owing to measurement.

Keywords
cross-national comparisons, Euro-Peristat, preterm births, trends

INTRODUCTION

Preterm birth, defined as birth before 37 weeks of gestation, is a major cause of neonatal and infant mortality [1■■,2]. In Europe, about 75% of all neonatal deaths and 60% of all infant deaths occur to infants born preterm [1■■]. Although survival of preterm infants has increased significantly in the past decade, these infants remain at higher risks of long-term motor and cognitive impairments as well as of chronic disease and mortality later in life than infants born at term [3,4]. Initiatives to prevent preterm births have had limited success [5,6].

In countries with comparable levels of development and healthcare systems, preterm birth rates vary markedly – a range from 5 to 10% among live births in Europe [7■■,8,9■■]. Why these disparities exist is poorly understood, yet this knowledge is invaluable for orienting health policy and prevention initiatives. This review thus seeks to identify the most likely sources of heterogeneity in preterm birth rates, which could explain differences between European countries. Drawing on the most recent literature and in the light of data from the 2013 European Perinatal Health Report [1■■], our review focuses on population characteristics, reproductive policies as well as medical practices, which may affect preterm birth rates.

SEARCH STRATEGY AND SOURCES

We searched PubMed for publications between 2011 and 2014, which focused on explaining differences in preterm birth rates between countries in Europe.

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KEY POINTS

- Medical practices and policies related to subfertility treatments and indicated preterm deliveries have a clear impact on country-level preterm birth rates and trends.
- Recent studies confirmed the role of many potentially modifiable population factors – BMI, smoking, and environmental exposures – in determining preterm birth risk.
- It is important to rule out gestational age measurement artifacts.

Because we could not identify recent studies looking at this issue, we enlarged our search to studies from other high-income countries, including Australia, Canada, Japan, and the United States. Our assumption is that results from these contexts are relevant to European populations. We also extended our review to include studies that have evaluated the impact of specific risk factors on population-level preterm birth rates or trends in preterm birth rates within countries. Last, we used data from the Euro-Peristat project, which aims to monitor perinatal health using a recommended set of national-level indicators derived from routine systems [1■■]. These data illustrate the variability in specific risk factors for preterm birth across Europe and the extent to which preterm birth rate variations across countries may reflect differences in their prevalence. The 2013 Euro-Peristat report presented 2010 data from 29 countries on the preterm birth rate and factors affecting preterm birth risk such as: multiple births, maternal age, prepregnancy BMI, smoking during pregnancy, and migration status, which we compiled for this review (Table 1).

PRETERM BIRTH RATES IN EUROPE

In Europe, preterm birth rates for live births varied in 2010 between 5.2–5.9% in Iceland, Finland, Lithuania, Estonia, Latvia, Sweden, and Ireland and 8.2–10.4% in Belgium, Austria, Germany, Romania, Hungary, and Cyprus as illustrated in Fig. 1 and Table 1. This corresponds to a 50% excess in countries with higher vs. lower rates and corresponds to a 3 percentage-point absolute difference (Fig. 1). Although overall rates have increased in general, as reported by a World Health Organization (WHO) study of preterm birth in 64 countries [8], trends are heterogeneous and, in particular, rates of singleton preterm birth have been stable or declined in about half of European countries over the past 15 years [9■■].

MEASUREMENT

Measurement of gestational age is a potential source of variation between countries [10]. Timing of the first day of the mother's last menstrual period (LMP) or biometric measures from ultrasound (US) can be used to establish the first day of the pregnancy. The method of determining gestational age influences estimates of the preterm birth rate [5]. US dating tends to shift all pregnancies toward earlier gestational ages [10,11■] mainly because LMP dating assumes that all women have a 28-day cycle, whereas in reality, average cycle length is slightly longer [12]. However, US removes errors in gestational age estimation and these corrections reduce the preterm birth rate because errors have more influence at the extremes of the distribution. The algorithms used to derive gestational age when LMP and US are both available will also affect the preterm birth rate [10]. Another potential source of variation between countries may be the references for US dating, as these are not standardized [13]. Finally, population characteristics influence gestational age measurement and vary across healthcare systems; socially disadvantaged women have less accurate dates [10,14,15■], which may reflect difficulties in accessing prenatal care

In Europe, prenatal care starting in the first trimester is the norm and the 'best obstetric estimate' is the standard for pregnancy dating, although information on how this estimate is derived is not available in international databases [1■■,11■,16■■]. Some routine data systems, such as in Norway and Sweden, record both LMP and the US estimate. In the United States, official preterm estimates are mainly based on LMP, but the clinical/obstetrical estimate is also recorded [11■,17,18]. The use of LMP vs. clinical estimates explains half of the difference between United States and Canadian rates (12.3 vs. 7.6%, respectively in 2002) [19]. We could not find recent European studies about how gestational age measurement affects the preterm birth rate.

Differences in the registration of births and deaths at 22 and 23 weeks of gestation are highly problematic for international comparisons of perinatal and infant mortality [20,21■], but their effect on overall preterm birth rates is probably small: in 2010, only 0.1% of live births in the countries included in Table 1 were born at 22–23 weeks [1■■]. These differences will, however, have a larger impact on comparisons of very preterm birth rates.

MULTIPLE PREGNANCIES

Increasing multiple birth rates, starting in the 1980s, have contributed to overall rises in preterm birth rates [22,23]. In 2010, preterm birth rates for

Table 1. Preterm birth rates and prevalence of maternal risk factors in European countries in 2010

Country	Live births (*N*)	PTB[a] (%)	Multiple births (%)	Stand PTB[b] (%)	<20 years of age (%)	>35 years of age (%)	Foreign born[c] (%)	Smoking during pregnancy (%)	BMI <18.5 (%)	BMI ≥30 (%)
Austria	78698	8.4	3.5	8.3	3.2	19.7	29.3			
BE: Brussels	24860	8.4	4.5	7.8	2.0	23.2	66.2		5.7	10.4
BE: Flanders	69637	7.9	3.8	7.7	1.8	14.3	22.4		5.3	12.4
BE: Wallonia	38228	8.3	3.3	8.3	3.8	16.0	25.2		7.1	13.6
Cyprus (2007)	8575	10.4	5.4	9.2	1.9	15.5	32.7			
Czech Republic	116399	8.1	4.1	7.7	2.9	15.4	2.6	6.2		
Denmark	63273	6.4	4.1	6.1	1.4	20.9	15.2	12.8	6.8	12.6
Estonia	15816	5.6	2.9	5.8	2.3	20.7	24.9	7.8		
Finland	61191	5.7	3.1	5.7	2.3	18.0	6.2	1.0	3.6	12.1
France	14761	6.5	3.0	6.7	2.5	19.2	18.3	17.1	8.3	9.9
Germany	635561	8.4	3.7	8.1	2.1	23.6	16.9	8.5	3.6	13.7
Hungary	90322	8.9	NA	NA	5.9	17.5	NA			
Iceland	4886	5.2	2.8	5.4	3.1	19.1	12.1			
Ireland	75243	5.7	3.4	5.7	2.7	27.9	24.6			
Italy	544991	7.3	3.2	7.4	1.4	34.7	19.0			
Latvia	19139	5.8	2.5	6.1	5.9	14.7	30.2			
Lithuania	30831	5.4	2.6	5.7	3.8	14.9	12.8	4.5		
Luxembourg	6519	8.1	3.6	8.0	1.8	23.3	66.0	12.5		
Malta	4018	7.2	4.0	6.9	6.5	15.5	9.2		5.2	12.7
Netherlands	177817	7.5	3.4	7.4	1.4	21.6	21.1	6.2		
Norway	62678	6.2	3.3	6.2	2.2	19.5	24.8	7.6	4.1	12.2
Poland	413295	6.6	2.7	6.8	4.5	11.8	0.04	12.3	8.7	7.1
Portugal	101463	7.7	3.0	7.8	4.0	21.7	19.0			
Romania	212199	8.2	1.8	8.7	10.6	10.9	NA			
Slovakia	55645	7.1	2.9	7.3	7.3	12.6	NA			
Slovenia	22298	7.2	3.7	7.1	1.2	15.4	NA		4.7	9.0
Spain	398914	8.0	4.2	7.5	2.5	29.5	23.6	14.4[d]		
Sweden	114706	5.9	2.8	6.1	1.6	22.5	24.4	4.9	2.5	12.6
Switzerland	79931	7.1	3.7	6.9	1.1	25.8	41.1			
UK: England & Wales	718266	7.0	3.1	7.1	5.7	19.7	25.2	14.0[e]		
UK: Northern Ireland	25586	7.1	3.1	7.2	5.1	19.9	13.5	15.0		
UK: Scotland	57151	7.0	3.1	7.1	6.4	19.9	13.9	19.0	2.6	20.7
United Kingdom	799 082				5.7	19.7	24.0	12.0		
Total	4252575									

Source: European Perinatal Health Report. The health and care of pregnant women and babies in Europe in 2010 [1■■].
[a]PTB: preterm birth rate, defined as birth before 37 completed weeks of gestation.
[b]Stand. PTB: standardized preterm birth rate – adjusted on the prevalence of multiple births.
[c]Mothers born outside of the host country or of foreign nationality at birth (in Italy, Latvia, Lithuania, Malta, Poland) or ethnicity (in Denmark, Germany, Estonia) if data were unavailable.
[d]Data are from Catalonia.
[e]Average rate for UK: England (12.0%) and UK: Wales (16.0%).

multiples in Europe ranged between 39.6 and 66.0%, in contrast with between 4.1 and 7.6% for singletons [1■■]. Multiple birth rates vary from about 2 to 4% of all births, as shown in Table 1.

Variation in multiple birth rates is related to the proportion of older mothers who have more spontaneous multiple pregnancies and a greater demand for fertility treatments. It is also related

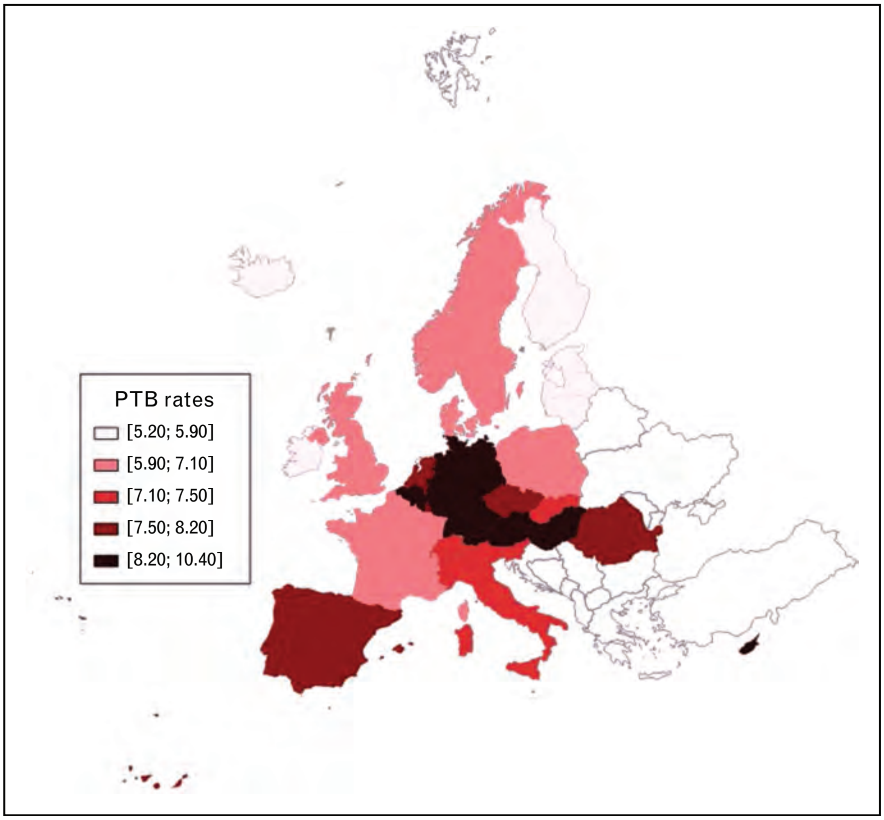

FIGURE 1. Rates of preterm birth (PTB) among live births in Europe in 2010.

to subfertility treatment policies and practices (in-vitro fertilization, ovulation induction and inseminations), which differ across high-income countries [24,25▪,26▪▪]. For instance, elective single embryo transfer (eSET) has been extensively promoted by several countries including Belgium, Sweden, Finland, and Australia [24,25▪,27]. In contrast, in Italy, the law requires transfer of all fertilized embryos in each cycle, although it limits the number of fertilized embryos to three [28]. Recent studies comparing use of eSET across countries showed a clear impact on multiple births [25▪,26▪▪]. eSET policies in Slovenia were credited with the stabilization of the proportion of assisted reproductive technology (ART) very preterm twins in past years after a 27-fold increase from 1987 to 2010 [29].

One source of heterogeneity between countries could thus be multiple births. To assess their contribution, we recomputed preterm birth rates assuming that all countries had the same multiple birth rate (set at the European average of 3.2%), as shown in Table 1. Substantial variability persists after this adjustment, although standardized rates are over half a percentage point lower in some countries. Larger declines occur more often in countries with high rates.

CHARACTERISTICS OF THE POPULATION OF CHILDBEARING WOMEN

Maternal characteristics associated with preterm delivery risk include age, socioeconomic status, migration status, BMI, smoking, drug use and alcohol consumption, occupational exposure, short interpregnancy intervals, previous preterm birth, preexisting medical conditions, ART use, and previous induced abortions [30,31▪▪,32▪▪,33–36]. It is hard to obtain European-level data on the prevalence of many of these risk factors, but as shown in Table 1, those available in the Euro-Peristat project clearly differ between countries, including maternal age, migrant status, smoking, and BMI. Articles included in our review addressed maternal age, social status, migration, smoking, obesity, diet, and previous induced abortion.

In 2010, the proportion of mothers 35 years of age and older in European countries ranged between 11 and 35% (Table 1); given that older women face higher risks of preterm birth, this could be one explanation for country-level differences. Auger *et al.* [37▪▪] tested the hypothesis that advancing maternal age may be a cause of rising preterm birth rates. In a study comparing singleton births in Denmark and Quebec, where preterm birth rates rose over the past 15 years, they found that rates had increased the most among women aged 20–29 years and stayed stable or decreased for women 35 and older. Paradoxically, the increase in the proportions of older mothers appeared to favor more stable rates over time in these countries.

Recent studies explored the relationship between preterm birth and disadvantaged socioeconomic circumstances [38–41]. Two studies found that social disadvantage was more strongly associated with very preterm than moderate preterm birth [42▪,43▪]. The 2010 WHO Multicountry study also found that less educated mothers had fewer provider-initiated preterm deliveries [44▪▪]. In northern England, although overall preterm birth rates stayed the same between 1960 and 2000, rates increased in the most deprived areas and decreased in less deprived areas resulting in widened social inequalities [45▪]. In Iceland, the 2008 economic crisis was associated with increases in the risk of low birth weight, but no change in preterm birth [46]. These studies illustrate the complexity of assessing the importance of social conditions in cross-national studies, both because of the variation across population sub-groups and the dependence on other contextual factors.

Migrant flows between European member states and from non-European countries have been increasing and migrant status has been identified as a risk factor for preterm birth [47▪,48,49▪]. In 2010, foreign born mothers represented between 0.0 (Poland) and 66.0% (Luxembourg) of childbearing women (Table 1). However, associations with preterm birth depend on preterm birth subtype (spontaneous vs. nonspontaneous), region of origin, reference groups used for comparison, reasons for migration (refugee, economic migrants), and length of residence [50,51▪▪,52]. A review by Urquia *et al.* [53] showed that adverse pregnancy outcomes in Europe were different depending on maternal country of origin. In another study, eastern European migrants had better perinatal health outcomes than United States born women even with later entry into prenatal care or less education, which may be explained by the healthy migrant effect [54]. However, in Sorbye *et al.*'s study of migrant women in Norway between 1999 and 2009, both spontaneous and nonspontaneous preterm birth rates were higher among immigrants than among Norwegian-born women. For migrants, provider-initiated preterm deliveries increased with increased length of residence, whereas spontaneous preterm deliveries remained unchanged [51▪▪].

Behavioral risk factors mediate the relationship between sociodemographic characteristics and preterm birth. A systematic review published in 2010 summarized the epidemiologic evidence on behavioral factors, including tobacco, alcohol, and illicit drug use, and physical, sexual, and occupational activity. The authors concluded that with the exception of tobacco, which was consistently but weakly associated with preterm birth, evidence for a causal role for other factors was slight [30]. A recent national French study added new results by showing that cannabis consumption increased spontaneous preterm birth risks; however, only 1.2% of women reported smoking during pregnancy [55].

Prenatal smoking rates vary across Europe, from 5 to 19% of women in the countries that could provide these data (Table 1). Smoking was found to explain differences in preterm birth rates between socioeconomic groups, about one-third of the variation in Finland from 1987 to 2010 [56▪]. However, in another international study, the effect was not as large across Europe [57]. A study from Belgium reported reductions in the risk of preterm birth subsequent to the introduction of smoking bans in 2007 and 2010 [58], raising the question of exposure to second-hand smoke [59,60▪]; however, other factors may have contributed to these observed effects.

Recent studies advanced our knowledge of the impact of maternal BMI on preterm birth, another maternal characteristic that varies in Europe (Table 1). Cnattingius *et al.* [31▪▪] found a dose–response relationship between maternal overweight and indicated preterm birth in a large population-based study from Sweden and also showed that obese women were at increased risk for extremely preterm delivery following premature rupture of membranes and spontaneous labor. This latter finding has been confirmed in other populations [61▪▪,62]. In a study that looked at more refined BMI categories including severe ($<16\,kg/m^2$), moderate ($16–16.99\,kg/m^2$), and mild thinness ($17–18.49\,kg/m^2$), Lynch *et al.* [61▪▪] showed that women at the lower extremes of BMI were at increased risk for both spontaneous preterm labor and medically indicated delivery.

Bloomfield [63], based on a review of epidemiological and experimental studies, posited an important role for poor maternal nutrition in the association between extreme BMIs and prematurity. Other studies also explored dietary risk factors for preterm birth, such as artificially sweetened drinks, which were responsible for increased preterm birth risk in two large cohort studies [64,65]. Further, probiotics, vitamin D, and vitamin C supplementation may reduce preterm birth risk by preventing genital infections, but more research is needed [66▪].

Recent studies examined the contribution of previous induced abortion to preterm birth rate [35,67▪▪]. The EuroPOP study had shown that induced abortions were associated with preterm birth rates [68]. In Scotland, using data from the 1980s to 2000, this association was found to weaken over time and disappeared altogether by 2000, maybe because of changes in abortion methods [68]. However, a study from Finland showed no statistically significant difference in preterm birth by abortion method (4.0% in the medical group vs. 4.9% in the surgical group) [69]. In parts of Eastern Europe where there is a history of abortion being used as contraception, variations in the prevalence of induced abortion may impact on differences in preterm birth rates.

VARIATION OWING TO INDICATED PRETERM BIRTH

There is strong evidence that preterm birth rates in high-income countries are affected by obstetric practices related to indicated preterm births. Indicated singleton late preterm births have been identified as the main driver of North American preterm birth rates as opposed to changes in women's risk profiles [70–73]. Vanderweele *et al.* [74] showed that in the United States, although overall preterm births increased from 11.2 to 12.8% between 1989 and 2004, medically induced rates increased 94% from 3.4 to 6.6% and spontaneous rates declined by 21%, from 7.8 to 6.2%.

In Europe, Zeitlin *et al.* [9▪▪] showed that both spontaneous and induced preterm deliveries contributed to increasing preterm birth trends between 1996 and 2008; the contribution of each subgroup varied across countries, especially for singletons. In 2008, rates of nonspontaneous singleton preterm births ranged from 1.1 to 3.0%, whereas spontaneous onset preterm births ranged from 2.8 to 4.8%. For multiples, the rates of nonspontaneous preterm birth ranged from 12.0 to 34.4%, and spontaneous onset births from 15.1 to 38.2% [9▪▪]. In Scotland, for instance, between 1989 and 2004, nonspontaneous onset deliveries increased by almost 50% and spontaneous deliveries by 10% [75]. In other European countries, however, nonspontaneous onset preterm births have not increased over past decades.

Previous obstetric history and delivery mode are strong predictors of both spontaneous and indicated preterm delivery [32▪▪,76▪▪], but women's risk profiles can influence preterm birth subtypes in different ways. An Australian study, using population-based data from 1984 to 2006, showed that over time the population-attributable fraction associated with women's preexisting medical conditions and pregnancy complications increased, for both indicated and spontaneous preterm deliveries. The proportion of women with more than one medical condition increased from 4.9 to 19% in spontaneous preterm births and from 10.4 to 25.8% in medically indicated preterm deliveries [76▪▪].

Provider-initiated preterm births aim to improve the health of the child, and especially to reduce the risk of stillbirth; however, they are controversial, as evidence of the benefits to the child of early extraction are not always conclusive and countries have more or less interventionist policies. Variations in gestational age patterns of cesarean delivery rates in Europe were recently described; these suggest wide variations in clinical practice by gestational age and highlight areas where consensus on best practices is lacking [77▪]. Further research should analyze the extent to which increases in indicated preterm births have affected not only preterm birth rates but also perinatal mortality.

ENVIRONMENTAL FACTORS

Pregnant women are exposed to a myriad of environmental factors and this field of research is expanding [4]. Patel *et al.* [78] used United States national survey data from 2000 to 2006 and looked at 201 different environment factors (i.e., amount of chemical compound in tap water sources of participants) including the number one suspect in terms of adverse health outcomes, Bisphenol A (BPA), which proved to be associated with preterm birth. BPA may represent an important health threat because of its toxicity and high prevalence in everyday products.

Air pollution has also been linked in several recent studies to preterm birth. Air pollution exposures differ across Europe and vary over time [79▪▪]. For instance, urban population exposure to fine particulate matter has decreased between 2002 and 2011 in most countries except in central and eastern European countries where it increased dramatically [79▪▪]. Fine particulate matter may induce systemic inflammation, which could influence the duration of pregnancy [80▪]. Dadvand *et al.*'s [81▪] is the first study to report on the association between PPROM and PM2.5 and to report an increased risk of up to 50% in premature rupture of membranes associated with air pollution exposure. The negative impact of air pollution on gestational age was confirmed in Stieb *et al.*'s [82] 2012 meta-analysis, although there was a wide heterogeneity in study design and measures of exposure. More research on the physiological mechanisms through which air pollution influences gestational length is needed and clinical data are lacking from many observational studies.

Other environmental factors such as temperature [83,84■■,85,86] and UV light-induced vitamin D deficiency [87] have been explored, but it is unknown whether these could contribute to variations in preterm birth across countries.

INTEGRATED APPROACHES

Several recent studies tackled the larger question of how multiple population risk factors and medical practices explained preterm rate variations across countries or time. Zeitlin *et al.* [88■■] compared singleton preterm birth rates, based on obstetric estimates of gestational age, in France and the United States in 1995, 1998, and 2003; although many risk factors were different – in the United States, there were more teen pregnancies and women with insufficient prenatal care, but fewer smokers – adjustment for these factors did not reduce the constant excess risk of 70% in the United States (8.4% in the United States vs. 4.9% in France in 2003). Differences in rates could not be explained by obstetric interventions either: although preterm births associated with cesarean and induction were higher in absolute terms in the United States, spontaneous preterm birth rates were also elevated and the proportion of preterm births linked to these obstetrical interventions was the same. Garn *et al.* [89■■] compared maternal social and lifestyle characteristics, including stressful life events in Canada and the United States in 2005–2006 (preterm birth rates: 4.9 vs. 7.6%, respectively). Risk factors for preterm birth differed across countries and after adjustment, women in the United States still had a higher risk [89■■]. These results reinforce conclusions from a study which found that half of the increase in preterm birth rates from 1989 to 2004 (10.6–12.5%) in the United States remained unexplained after taking into account the contribution of maternal age, maternal race, maternal education, ART, multiple births, stillbirths averted, marital status, pregnancy intention, barriers to prenatal care initiation, as well as nonmedically indicated cesarean delivery and labor induction [7■■].

These studies illustrate the complexity of understanding the drivers of a country's preterm birth rate and pinpointing those that 'explain' the difference between countries. Multiple risk factors impact on preterm birth and studies in this review underscored the interdependence between them. Data on the whole range of key exposures are unlikely to be included in any one database and studies that combine databases face issues related to the comparability of data definitions [89■■]. Further, many risk factors interact with the type of preterm birth, that is spontaneous vs. indicated and differing approaches to indicated preterm births by country mean that common relationships may be obscured.

CONCLUSION

Among the multiple factors that emerged from this review of recent studies on preterm birth variations and trends within and between high-income countries, medical practices and policies related to subfertility treatments and indicated preterm deliveries had a clear impact on country-level preterm birth rates and trends. Understanding how some countries have maintained stable indicated preterm birth rates, whereas others have not – as well as the impact of these variations on child health – is an important research area. United States and Canadian studies showed that measurement of gestational age can have a large impact on the preterm birth rate estimate. Although this is unlikely to be a large contributor to European differences, we do not know whether gestational age determination differs across countries and it is important to rule out measurement artifacts. Finally, studies confirmed the role of many potentially modifiable population factors – BMI, smoking, and environmental exposures – in determining preterm birth risk. These factors likely interact and are associated with more general health and social policies that promote healthy childbearing. More knowledge about how these contribute to low and stable preterm birth risk would be enormously useful for shaping future policy.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
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■■ of outstanding interest

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