



Epidemiology of uterine fibroids: a systematic review

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Background Uterine fibroids (UFs) are the most common neoplasm affecting women that can cause significant morbidity and may adversely impact fertility.

Objectives To examine UF epidemiology and to evaluate the relative strengths of putative risk factors.

Search strategy MEDLINE and Embase were searched for studies published in English between January 1995 and April 2015.

Selection criteria Publications reporting relevant data from registries and other observational studies with over 1000 patients and single-centre studies with over 100 patients were selected.

Data collection and analysis Data on UF incidence, prevalence and associated risk factors were extracted from 60 publications.

Main results Wide ranges were reported in both UF incidence (217–3745 cases per 100 000 women-years) and prevalence (4.5–68.6%), depending on study populations and diagnostic methods. Black race was the only factor that was recurrently reported to increase UF risk, by two–threefold compared with white race. Eleven other factors affected UF risk to a magnitude similar to or greater than race. Age,

premenopausal state, hypertension, family history, time since last birth, and food additive and soybean milk consumption increased UF risk; use of oral contraceptives or the injectable contraceptive depot medroxyprogesterone acetate, smoking in women with low body mass index and parity reduced UF risk.

Conclusions We identified 12 risk factors that play an important role in UF epidemiology. The UF risk factor with the strongest evidence is black race. High-quality prospective observational data are needed to improve our understanding of UF epidemiology, and thus its aetiology and optimal management.

Keywords Epidemiology, incidence, leiomyoma, prevalence, race, risk factors, uterine fibroids.

Tweetable abstract Uterine fibroids occur in about 70% of women. Black race and 11 other factors affect uterine fibroid risk.

Linked article This article is commented on by P Vercellini and MP Frattaruolo, p. 1513 in this issue. To view this mini commentary visit <https://doi.org/10.1111/1471-0528.14730>.

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Introduction

Uterine fibroids (UFs), also known as uterine leiomyomas, are benign smooth muscle neoplasms of the uterus that affect women of reproductive age.^{1–3} They may be asymptomatic or cause a range of severe and chronic symptoms. The most common presenting symptom is heavy menstrual bleeding, which can lead to anaemia, and fatigue and painful periods.^{4–9} Other UF symptoms include non-cyclic pain, abdominal protuberance, painful intercourse or pelvic pressure, and bladder or bowel dysfunction resulting in urinary incontinence or retention, pain or constipation.^{4–10} UFs

may also be associated with reproductive problems, including impaired fertility, pregnancy complications and loss, and adverse obstetric outcomes.^{11–18} UFs are one of the leading causes of hospitalisations for gynaecological disorders, and are the most frequent reason for hysterectomy in the USA.^{19–24}

Uterine fibroids are the most common neoplasm affecting women, and it has been postulated that they occur in over 70% of women by the onset of menopause.^{25–27} They are estimated to be clinically apparent in 25% of women of reproductive age and cause symptoms severe enough in approximately 25% of women with UFs to require treatment.^{4,28,29} The frequency of the condition is, however, likely to be underestimated because in many women it is asymptomatic, or symptoms develop insidiously, and

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therefore remains undiagnosed.^{30,31} The unknown extent and impact of undetected UFs bias the epidemiological data and evidence on associated factors to reflect severe disease.³²

Although many studies on the epidemiology of UFs have been published, reports of the incidence and prevalence of UFs vary widely depending on the method of diagnosis and the population studied; for example, estimates of the incidence of UFs range from 5.4% to 77% of women of reproductive age.^{2,33–38} Furthermore, many different risk factors have been associated with the development of UFs, including biological, demographic, reproductive and lifestyle factors.^{26,39–41} The true incidence and prevalence of UFs, and thus their global impact on women's health, and the role of putative risk factors, are therefore currently unknown.

This study is the first systematic review of the epidemiology of UFs. The objectives of this review are to comprehensively survey the epidemiological data on UFs to describe their incidence and prevalence, and to examine trends in the epidemiology of UFs according to region. In addition, we have assessed the importance of the numerous risk factors that have been associated with the condition to identify the key factors that influence its occurrence.

Methods

A systematic search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.⁴² MEDLINE and Embase were searched to identify studies related to the epidemiology of UFs, without selecting for symptomatic or asymptomatic UFs, published in English between 1 January 1995 and 22 April 2015 (Figure S1). This time frame was chosen because developments in diagnostic techniques since the mid-1990s have affected the rate of UF diagnosis. Most studies on UF epidemiology published before the mid-1990s were based on diagnosis by pathological examination of surgical specimens.³⁰ These older data therefore represent a population of highly selected patients who required hysterectomy, who may constitute only 10–30% of women with ultrasound evidence of UFs.^{43,44} The development and widespread use of ultrasonography for UF detection since the mid-1990s has expanded the epidemiological data on UFs to represent a wider population.

After removal of duplicates, all references were manually screened and categorised. For consistency, one person made final decisions for screening the manuscripts and data extraction. A final data check was performed before data analysis. Study population size thresholds ($N > 1000$ for registries and 'other observational' studies, $N > 100$ for single-centre studies) were applied to ensure inclusion of larger studies only. Papers that presented no data on incidence or prevalence of UFs or risk factors for UFs, epidemiological studies focused on other diseases or specific patient populations,

randomised controlled trials, animal and *in vitro* studies, case studies, review, editorials and letters were excluded. Studies of genetics relating to risk of UFs were beyond the scope of the current review and were also excluded.

The publications retrieved were divided into five categories: registries; single-centre studies; 'other observational' studies (such as community-based investigations conducted in more than one centre); hysterectomy studies; and pregnancy studies. Hysterectomy studies and pregnancy studies were excluded from the analysis at this stage, because they are based on enriched populations that are subject to intensive clinical investigations (i.e. pathological examination and frequent ultrasounds, respectively), which would add bias in UF diagnosis as they are not representative of the general population. We assessed the study and reporting quality of each study using the STROBE checklist,⁴⁵ and also evaluated the risk of recall, selection and detection bias in each study.

For each study, we extracted data on: study period; study type (e.g. prospective or retrospective); patient group (e.g. hospitalised or community-based); age of overall population, age of UF population; race; how cases were confirmed; prevalence of UFs; incidence of UFs; risk factors for UFs reported as relative risks (RRs), odds ratios (ORs) or incidence rate ratios (IRRs) with 95% confidence intervals (CIs).

As a large number of individual risk factors were examined across all studies, we present data for risk factors only when at least one category was statistically significant (Table S1). For risk factors that were stratified by intervals (e.g. years of oral contraceptive use in Marshall et al., 1998⁴⁶), only the significant intervals with $P_{\text{trend}} < 0.05$ are included (Table S1). Owing to the heterogeneity of the data extracted (e.g. in risk measures reported and diagnostic methods used), it was not possible to perform a meta-analysis.

Results

After manual screening of titles and abstracts, 82 publications remained. Following screening of the full text, 60 publications were included [16 single-centre studies, 37 registry studies (including 16 reporting on the Black Women's Health Study and nine on the Nurses' Health Study II) and seven 'other observational' studies]. Information on the 60 publications from which data were extracted is presented in Table S1.

There was considerable diversity among the selected studies, including investigation type (e.g. prospective cohort studies, case-control studies), study design and the populations analysed (e.g. international or local populations with different racial compositions, women undergoing screening or treatment, or survey respondents), diagnostic methods used (e.g. self-report, pelvic examinations, ultrasound or surgery), comparator group definitions, risk measures (e.g. IRRs, ORs or RRs) and statistical methods used.

Although our search did not exclude studies on asymptomatic UFs, only one study focused on women with no UF symptoms or previous UF diagnosis.⁴⁷ In over half the studies (52%; 31/60), pre-existing UF diagnoses were recorded without diagnostic history, and presumably UFs were primarily symptomatic in these cases. In at least one third of the studies ($\geq 35\%$; $\geq 21/60$), the study population was mixed, consisting of both participants with symptomatic UFs and those with asymptomatic UFs.

Study quality and reporting quality were good in most (80%; 48/60) of the included publications, defined as fulfilling 19 or more of the 22 statements on the STROBE checklist (Table S3).⁴⁵ This included all the registry studies and six of the seven 'other observational' studies, but less than one third (31%; 5/16) of the single-centre studies. Over half the studies (60%; 36/60) relied on self-report and may therefore have been subject to recall bias. Selection bias was present in most of the included studies, with study populations being randomly selected in only five studies. In over half the studies (58%; 35/60), participants were self-selected (e.g. survey respondents), and were gynaecological patients in nearly one third of the studies (30%; 18/60). Detection bias may have been introduced by the use of different methods for UF diagnosis: the less specific method of pelvic examination was used in 20% (12/60) of studies, and more reliable methods including ultrasonography, surgical pathology or magnetic resonance imaging were used in 66% (40/60) of studies (Table S3).

Incidence of UFs

Evaluation of the incidence or prevalence of UFs was not the primary objective of most of the included studies, but they were reported in 51 of them. Data on the incidence of UFs reported in four large US registry studies (N , 9910–1 795 473; median, 42 098) ranged widely, from 217 cases per 100 000 women-years in the California Teachers Study to 3745 cases per 100 000 women-years in the Black Women's Health Study (Figure 1A).^{44,48–70} The incidence reported from the Black Women's Health Study, in which all participants were black, was consistently higher than that in the California Teachers Study and the Nurses' Health Study II (845–1348 cases per 100 000 women-years), in which 3% and 1% of participants were black, respectively.^{44,48–70} In the Nurses' Health Study II, the incidence of UFs among Hispanic, Asian and white women was similar, but the incidence in black women was approximately three times higher than in the other populations (Figure 1B).⁴⁴ This pattern was unchanged by the method of diagnosis of UF. It should be noted, however, that 95% of the 95 061 women included in this study were white.

In the studies that reported the lowest incidences, UF diagnoses were based on self-report or were confirmed by surgery.^{48,71,72} Most studies, reporting a wide range of

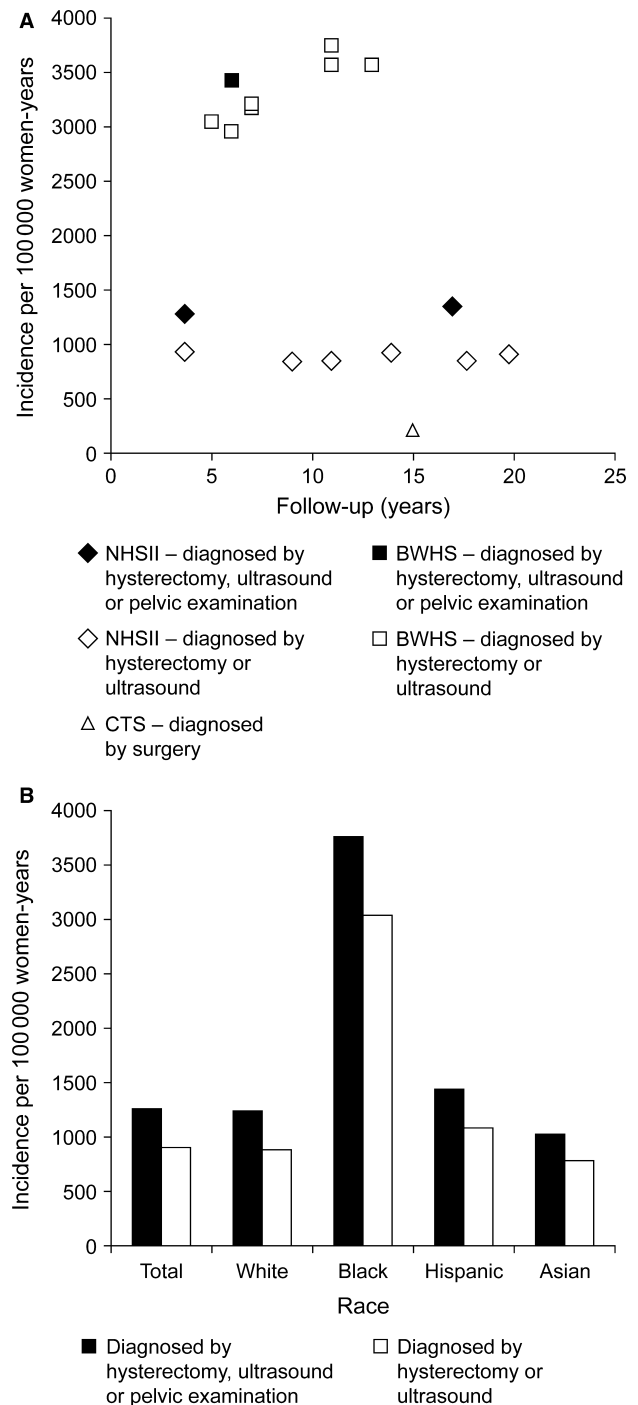


Figure 1. (A) Incidence of uterine fibroids (UFs) in US registry studies.^{44,46,48,50–56,58–68,96} (B) Incidence of UFs according to race in the Nurses' Health Study II.⁴⁴ BWHS, Black Women's Health Study; CTS, California Teachers Study; NHSII, Nurses' Health Study II.

incidences from 845 to 3745 cases per 100 000 women-years, were based on self-reports of a physician-made diagnosis after ultrasound or hysterectomy.^{50,66} UF incidence was reported to be higher when pelvic examination was included

as a diagnostic method than when only ultrasound or hysterectomy was used (Figure 1A, B). This higher incidence is, however, likely to be an overestimate reflecting the lack of diagnostic specificity of pelvic examination.

Prevalence of UFs

The prevalence of UFs varied widely across the studies, from 4.5% to 68.6% (Figure 2).^{9,73} Study population characteristics such as country/region and health status (healthy women or those requiring gynaecological care), factors relating to study methodology, including the type of investigation (registry, single-centre or 'other observational' study), and follow-up time did not consistently influence the prevalence data recorded.

The source of clinical data (e.g. medical record review, screening or self-report) and the diagnostic method used (e.g. ultrasound or histology) also showed no clear impact on prevalence. Analyses of the Nurses' Health Study II and the Black Women's Health Study showed that inclusion of pelvic examination as a diagnostic method in addition to ultrasound or hysterectomy can increase the reporting of UFs compared with ultrasound or hysterectomy alone (Figure 1A).^{44,62}

Risk factors for developing UFs

In total, over 30 broad categories of risk factor for UFs were examined across the studies (Table S2). Black race was the only factor that was shown to be consistently associated with an increased risk of UFs in prospective cohort registry studies. The multivariate-adjusted RR or OR of UFs associated with black race compared with white race was reported in four registry studies. In all four studies, black women were found to have a two–threefold greater risk of developing UFs than white women (Figure 3A; Table 1);^{27,44,48,54} the lower boundary of the 95% CI of the risk (black versus white) was 1.69 or higher in all four studies.

Owing to the large number of risk factors discussed in the selected studies, here we focus on those risk factors for which the magnitude of the effect was approximately the same as or greater than the effect of race (Table 1; i.e. 95% CI ≥ 1.5 for a risk factor or ≤ 0.67 for a protective factor). Using this criterion, 11 other factors were identified.

Demographic factors

Three other demographic factors were found to affect UF risk to a similar or greater magnitude as black race. The risk factor with the greatest magnitude was age, which was found to increase the risk of UFs by up to approximately tenfold. In a retrospective, single-centre study of the ultrasound records of women in Israel experiencing UF symptoms, those aged 41–50 or 51–60 years were 10 times more likely to have UFs than those aged 21–30 years (Table 1).⁷⁴ However, in a postmenopausal age group, i.e. over 60 years

old, UF risk declined.^{48,75} A similar retrospective review of ultrasound records in the UK found that women aged over 40 years were four times more likely to have UFs than those under the age of 40 years (Table 1).⁷⁶

A family history of fibroids was also shown to increase UF risk in a multicentre case–control study of hospitalised women in Thailand. Women with a positive family history of UFs were over three times more likely to have UFs than those without such a history (Table 1).⁷⁷

In contrast, smoking, especially in women with low body mass index (BMI), was negatively associated with UF risk. In the Cancer and Steroid Hormone Study, smoking was associated with one third the risk of UFs in women with a BMI ≤ 22.2 kg/m² compared with women with similar BMI who had never smoked (Figure 3B; Table 1).⁷⁵ Smoking did not alter UF risk in women with a BMI greater than the median in this study (>22.2 kg/m²; Figure 3B). There was no significant difference in the risk of developing UFs between women of all BMIs who had ever smoked and those who had never smoked (OR 0.8, 95% CI 0.5–1.1).⁷⁵ In three other studies (the California Teachers Study, an Italian single-centre study and a Thai multicentre study), smoking was found to have a smaller but still statistically significant protective effect in women who currently smoked or had ever smoked compared with those who had never smoked.^{48,77,78} In the Black Women's Health Study, however, smoking status was not found to have a significant effect on UF occurrence.⁶¹

Reproductive status

Two reproductive factors were found to increase the risk of UFs and three were found to exert a protective effect. Time since last birth increased the risk of developing UFs approximately two–threefold in women who last gave birth 5 or more years ago compared with those who gave birth more recently, in both black [the Black Women's Health Study (100% black women)] and white populations [the Nurses' Health Study II (1% black women); Figure 3D; Table 1].^{51,60} Premenopausal women were at an approximately three–five-times higher risk of symptomatic UFs than postmenopausal women in two registry studies (Figure 3C; Table 1).^{48,75} Furthermore, in an Italian single-centre case–control study, premenopausal women showed a tenfold increase in UF risk compared with postmenopausal women (Table 1).⁷⁸

Parity was associated with a reduced risk of developing UFs. In a single-centre study in Japan, the risk of UFs in women who had given birth three or more times was less than one-fifth that of nulliparous women (Table 1).⁷⁹

Use of both oral and injectable contraceptives has also been found to be associated with a reduced risk of developing UFs. In an Italian single-centre study, women who currently used oral contraceptives were less than one-third as likely to have UFs as those who had never used them

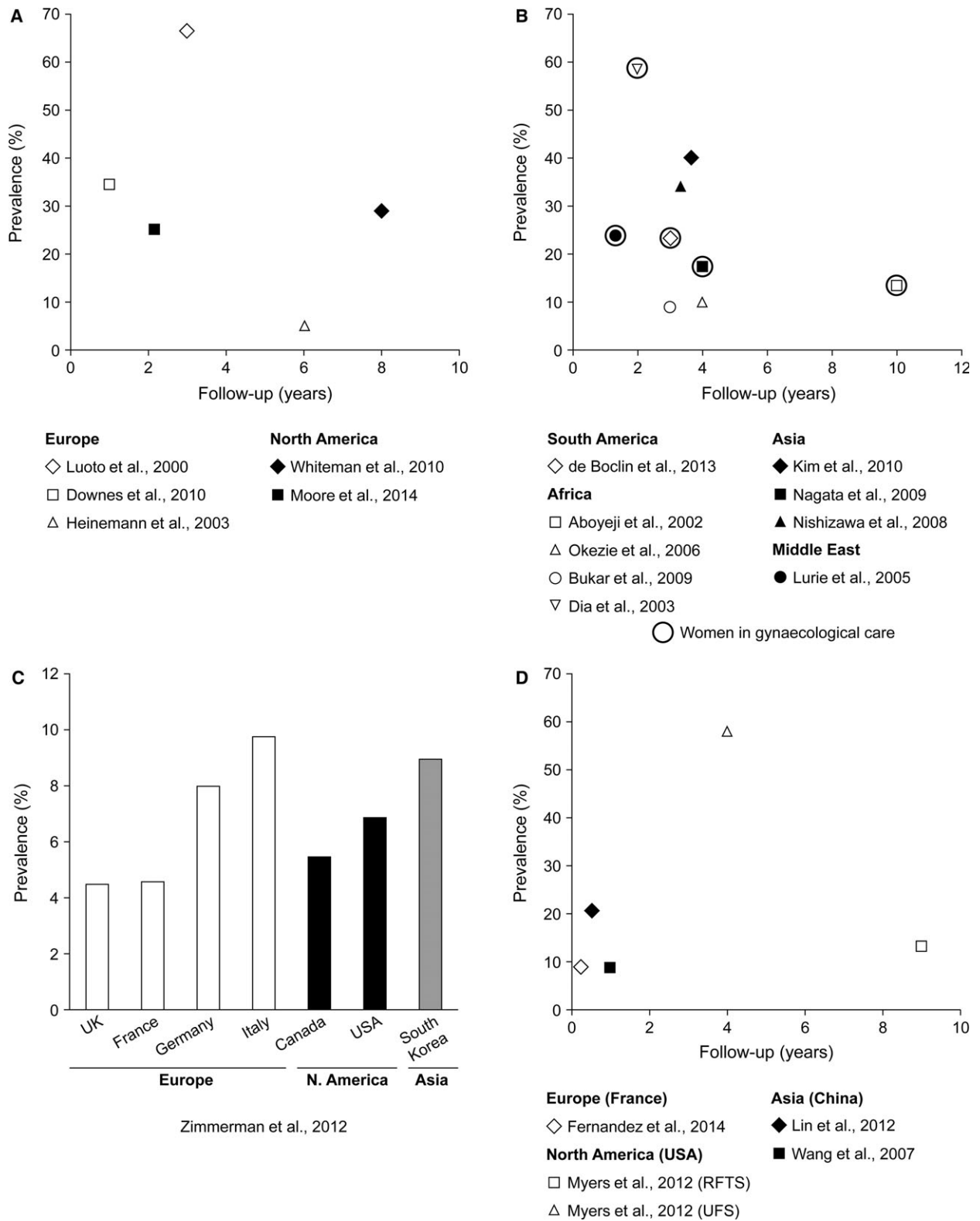


Figure 2. (A) Prevalence of uterine fibroids (UFs) in registry studies by follow-up time.^{24,71,97-99} (B) Prevalence of UF in single-centre studies by follow-up time.^{74,100-108} (C) Prevalence of self-reported UF in unselected, premenopausal women according to country in an online survey (follow-up time, 0.17 years).⁹ (D) Prevalence of UF in unselected, premenopausal women by follow-up time in four community-based studies.^{107,109-111}

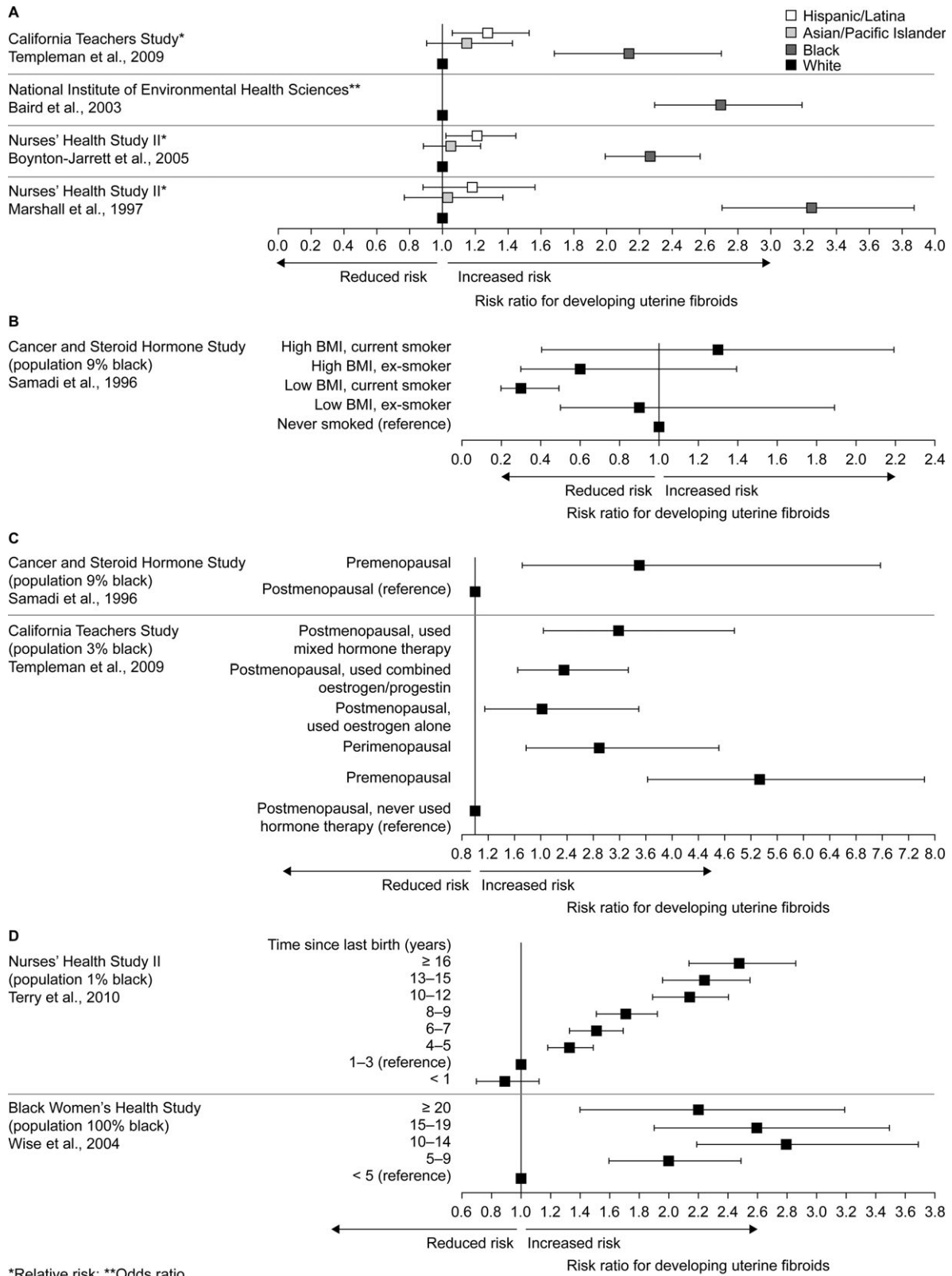


Figure 3. Risk ratios for developing uterine fibroids (UFs) by: (A) race and ethnicity in four registry studies;^{27,44,48,54} (B) smoking status and BMI;⁷⁵ (C) menopausal state;^{48,75} and (D) time since last birth.^{51,60} BMI, body mass index.

Table 1. Risk and protective factors for developing UFs with the same or greater magnitude as race

Factor	Comparison	Magnitude (95% CI)	Study type	References
Demographic risk factors				
Black race	Black vs white	RR, 3.25 (2.71–3.88)	Registry study	Marshall et al. ⁴⁴
	Black vs white	RR, 2.27 (2.00–2.58)	Registry study	Boynton-Jarrett et al. ⁵⁴
	Black vs white	RR, 2.14 (1.69–2.71)	Registry study	Templeman et al. ⁴⁸
	Black vs white	OR, 2.7 (2.3–3.2)	Registry study	Baird et al. ⁹³
Age	41–50 vs 21–30 years	RR, 10.4 (3.8–30.2)	Single-centre study	Lurie et al. ⁷⁴
	51–60 vs 21–30 years	RR, 10.6 (3.9–31.5)		
	>40 years vs <40 years	OR, 4.14 (3.5–6.7)	Single-centre study	Selo-Ojeme et al. ⁷⁶
Family history of UFs	Positive vs negative	OR, 3.47 (2.55–4.71)	'Other observational' study	Lumbiganon et al. ⁷⁷
Demographic protective factors				
Smoking	In women with low BMI, current smoker vs never	OR, 0.3 (0.2–0.5)	Registry study	Samadi et al. ⁷⁵
Reproductive risk factors				
Time since last birth	8–9 years vs 1–3 years	RR, 1.71 (1.51–1.93)	Registry study	Terry et al. ⁵¹
	10–12 years vs 1–3 years	RR, 2.14 (1.89–2.41)		
	13–15 years vs 1–3 years	RR, 2.24 (1.96–2.56)		
	≥16 years vs 1–3 years	RR, 2.48 (2.13–2.87)		
Premenopausal state	5–9 vs <5 years	IRR, 2.0 (1.6–2.5)	Registry study	Wise et al. ⁶⁰
	10–14 vs <5 years	IRR, 2.8 (2.2–3.7)		
	15–19 vs <5 years	IRR, 2.6 (1.9–3.5)		
	Pre- vs postmenopausal	RR, 5.33 (3.62–7.85)	Registry study	Templeman et al. ⁴⁸
Premenopausal state	Pre- vs postmenopausal	OR, 3.5 (1.7–7.2)	Registry study	Samadi et al. ⁷⁵
	Post- vs premenopausal	OR, 0.1 (0.04–0.1)	Single-centre study	Chiapparino et al. ⁷⁸
Reproductive protective factors				
Parity	≥3 vs 0 births	OR, 0.17 (0.08–0.36)	Single-centre study	Sato et al. ⁷⁹
Oral contraceptive use	Current use vs never used	OR, 0.3 (0.2–0.6)	Single-centre study	Chiapparino et al. ⁷⁸
DMPA use	Ever vs never used	OR, 0.42 (0.34–0.53)	'Other observational' study	Lumbiganon et al. ⁷⁶
Disease risk factors				
Hypertension	High vs normal blood pressure	OR, 4.90 (2.31–10.38)	Single-centre study	Takeda et al. ⁸⁰
Dietary risk factors				
Food additive consumption	Exposure vs no exposure	OR, 3.17 (2.25–4.46)	Single-centre study	Shen et al. ⁸¹
Use of soybean milk	Consumption vs no consumption	OR, 2.52 (1.89–3.35)	Single-centre study	Shen et al. ⁸¹

BMI, body mass index; CI, confidence interval; DMPA, depot medroxyprogesterone acetate; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk; UFs, uterine fibroids.

Multivariate-adjusted RRs, ORs and IRRs.

Bold values indicates reported magnitude of risk and protective factors compared with race. If lower 95% CI ≥ 1.5 then included as a risk factor; if upper 95% CI ≤ 0.67 then included as a protective factor.

(Table 1).⁷⁸ Similar protective effects but of smaller magnitude were reported in the Nurses' Health Study II, in which UF risk was 20% lower in all current oral contraceptive users and 53% lower in those with a history of 4–5 years' oral contraceptive use than in women who had never used them,⁴⁶ and in a multicentre case–control study in Thailand, in which UF risk was 24% lower in all women who had ever used oral contraceptives than in those who had never used them.⁷⁷ In addition, women who had used the injectable contraceptive depot medroxyprogesterone acetate (DMPA) were less than half as likely to have UFs than those who had never used it (Table 1).⁷⁷

Disease status

Women with hypertension, defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication, had an almost fivefold increased risk of UFs compared with those with normal blood pressure in a Japanese single-centre, case–control study (Table 1).⁸⁰

Dietary factors

In a large case–control survey conducted at a hospital in China, exposure to food additives in processed, sweetened or preserved foods increased the risk of UFs more than

threefold compared with no exposure (Table 1).⁸¹ The same study found that women who consumed soybean milk had a 2.5-times greater risk of UFs than those who did not (Table 1).⁸¹

Other factors

Many other factors, associated with a smaller risk of developing UFs than that seen with race, were described in the selected studies (Table S2). These potential risk factors include additional demographic factors, other aspects of reproductive status, diseases such as cervical neoplasia, diabetes mellitus, polycystic ovary syndrome and metabolic syndrome, additional dietary factors and other environmental factors, including pollution and physical or sexual abuse.

Discussion

Main findings

This systematic review examined the incidence and prevalence of UFs and risk factors for their development. There was a large variation in the data on UF prevalence, ranging from 4.5% to 68.6% (Figure 2),⁹ and no consistent associations between prevalence and country/region, study methodology or population were seen across the studies. The reported incidences of UFs also ranged widely (217–3745 cases per 100 000 women-years; Figure 1A).^{48,66} Only one study reported solely on women with asymptomatic UFs,⁴⁷ and at least one third of studies described mixed populations of women with symptomatic and asymptomatic UFs.

There was a marked difference in UF incidence between racial groups, confirming that UFs are much more common in black than in white women (Figure 1B). Additionally, being of black race was the only factor consistently found in this review to increase UF risk, by up to three times in black women than in white women (Figure 3A; Table 1).^{27,44,48,54} This higher incidence in black women was not associated with differences in the prevalence of other putative risk factors, suggesting that it may have a genetic basis.^{7,40,44}

Over 30 factors relating to demographic characteristics, reproductive and disease status, dietary and other environmental conditions were found to have a significant effect on UF risk (Table S2). We confined our discussion to 11 important risk factors, by selecting those with a magnitude similar to or greater than the well-established risk factor of race in at least one study (Table 1).

The factor that exerted the largest impact on UF risk is age, which can increase it by up to ten times in women in their fifth or sixth decade compared with those in their third decade.^{73,74} This effect did not persist beyond the sixth decade, reflecting the protective effect of postmenopausal status.^{48,75}

Positive family history was also found to increase UF risk.^{77,79,81} This effect may, however, be at least partly due to more frequent screening in relatives of women with UFs than in the general population. It may also be attributable to the role played by genetic factors in the development of UFs.^{82,83}

Smoking was found to reduce UF risk, but only in women with a low BMI, in one registry study.⁷⁵ This may result from a putative anti-estrogenic action of smoking, which may be counteracted in women with high BMI by the associated elevated estrogen levels.^{84–86} In addition, some women with low BMI may have hypothalamic dysfunction and associated chronic hypoestrogenism, which may compound any effect of smoking on estrogen activity.⁸⁷

Reproductive status plays a notable role in UF development. Time since last birth was reported to increase UF risk in two registry studies.^{51,60} In some analyses, however, this risk was not adjusted for age and may therefore be partly due to the effect of increasing age.

Premenopausal state was associated with a significantly higher UF risk than postmenopausal state, reflecting the role of female gonadal steroid hormones in stimulating UF growth.^{26,48,75,88} UFs may, however, be under-reported by postmenopausal women because they do not experience menstruation-associated symptoms.

The factor with the greatest protective effect was parity: giving birth was associated with a fivefold reduction in risk of UFs requiring surgical treatment than nulliparity in a single-centre study.⁷⁹ The effect of parity on UF prevalence may result from changes in hormone exposure due to pregnancy and decreased menstrual cycling, or from myometrial ischaemia involution and remodelling during and after parturition.^{40,41,60,89–93} The role of parity in UF risk is, however, difficult to evaluate due to possible confounding effects such as the negative impact of UFs on fertility.

Oral contraceptive use was also found to reduce the risk of developing UFs. UF risk was up to 70% lower in women who currently used oral contraceptives than in those who had never used them.^{46,77,78} In addition, use of the injectable contraceptive DMPA was found to protect against UF development, more than halving UF risk.⁷⁷ The mechanism of action of steroidal contraceptives responsible for this effect is not clear. Reduction of myometrial exposure to unopposed estrogen activity by exogenous progestogens may diminish estrogen-mediated stimulation of UFs.^{26,77,78} This result may, however, represent a selection bias, because UFs and other confounding indications, such as polycystic ovary syndrome, have historically been relative contraindications for steroidal contraceptives.^{78,94}

Finally, hypertension, food additive and soybean milk consumption were identified to increase UF risk in single-centre studies.^{80,81}

Strengths and limitations

Our comprehensive literature searches used pre-specified search terms to select the publications included in this review, to ensure that all relevant data on the epidemiology of symptomatic and asymptomatic UFs were extracted without bias. Study and reporting quality was good in all the registry studies and most of the 'other observational' studies, but poorer in over two thirds of the single-centre studies. Almost all the included studies were subject to selection bias (Table S3). Much of the information available on UF prevalence came from single-centre studies with populations that were not representative of the general population (e.g. women undergoing investigations for possible UF symptoms).

Over half the studies relied on self-report and may therefore have been affected by recall bias. Additionally, the variety of diagnostic methods and data sources used may have resulted in detection bias in some studies (Table S3). The use of pelvic examination is likely to result in an overestimation of UF incidence as it is not a specific or sensitive test.

Considering the influence of black race on UF risk,^{7,27,43,44,95} the underrepresentation of African women in the available data may have introduced some bias into the analysis of UF occurrence and risk factors.

Interpretation

In our systematic review of the epidemiology of UFs, we found wide variations in both the methodology and quality of the 60 selected studies, and also in the epidemiological data they report, with UF incidence ranging between 217 and 3745 cases per 100 000 women-years and UF prevalence ranging between 4.5% and 68.6%. In addition, we have evaluated the relative strengths of over 30 factors reported to have a significant effect on UF risk and identified black race as the only factor consistently reported to increase UF risk, and 11 other factors that affect it to a similar or greater magnitude. This evaluation reveals the important risk factors to be age, premenopausal state, hypertension, family history, time since last birth, and food additive and soybean milk consumption. The important protective factors were oral or injectable contraceptive use, smoking in women with low BMI and parity.

Conclusions

This is the first systematic review of the epidemiology of UFs to analyse the incidence and prevalence of UFs and evaluate the risk factors associated with the condition, and to identify those risk factors with the largest effects. This analysis supports the finding that black women are at greater risk of UFs than white women. The quality of the epidemiological data varies widely between the studies reviewed, however. Only one study specifically described women with asymptomatic

UFs; the rest did not distinguish between symptomatic and asymptomatic UFs. Further observational data from large well-conducted prospective studies on the occurrence of both symptomatic and asymptomatic UFs will therefore prove invaluable in improving our understanding of the aetiology of this often debilitating disease, and may thus facilitate progress in its management.

Disclosure of interest

Full disclosure of interests available to view online as supporting information.

Contributions to authorship

EAS, CC, RAG and RSR contributed to the design of the study, and the analysis and interpretation of the data. CC conducted the database searches and extracted the data; CC and RAG drafted the manuscript. EAS, CC, RAG and RSR were involved in revising the manuscript for important intellectual content and approving the final version for publication.

Details of ethics approval

This study did not require ethical approval as the data used have been published previously.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. PRISMA flow diagram of the literature search and article selection process.

Table S1. Study design, demographic characteristics and prevalence and incidence of UFs, and significant associated risk factors and protective factors, in studies included in systematic review.

Table S2. Significant risk and protective factors for UFs in studies included in systematic review.

Table S3. Study and reporting quality according to the STROBE checklist⁴⁵ and risk of bias in studies included in systematic review. ■

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