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The Epidemiology of Otosclerosis in a British Cohort

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Objective: To analyse the epidemiology of otosclerosis in a British cohort collected between 2011 and 2017.
Design: Retrospective cohort study.
Setting: Five UK ENT Departments.
Patients: Patients with surgically confirmed otosclerosis.
Main Outcome Measures: Questionnaire data documented family history of otosclerosis, age of onset, medical history, and information on associated risk factors for 657 patients. Pre and post-surgical pure-tone audiometry was collected for 154 of these patients.
Results: The age of onset, incidence of bilateral disease, tinnitus and vertigo, a higher prevalence of women (65%) than men (35%) are similar to those reported previously for otosclerosis cohorts. No association with measles infection was detected. Patients with a family history (40%) have an earlier age of onset and a higher incidence of bilateral disease and vertigo than non-familial subjects. Pedigree analysis is consistent with an autosomal dominant inheritance with reduced penetrance being apparent in 44/91 pedigrees studied. Women who associate their hearing loss with pregnancy have an earlier age of onset than those that do not ($p = 6 \times 10^{-6}$).
Conclusions: This study confirms that otosclerosis is an early adult onset disease that is more prevalent in women than men with a large minority of patients having a family history of otosclerosis. We report new evidence to support a relationship between pregnancy and otosclerosis progression in a proportion of women. In addition, this is the first study to identify differences in severity between familial and non-familial cases of otosclerosis, highlighting the possibility that more than one etiology may be involved. **Key Words:** Bone remodeling—Epidemiology—Hearing loss—Middle ear—Otosclerosis—Stapes surgery.

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Otosclerosis is a common form of adult-onset hearing impairment, typically characterized by disordered bone remodeling in the otic capsule that leads to a progressive conductive hearing loss. The remodeling process often involves the stapedio-vestibular interface and can lead to fixation of the stapedial footplate. Patients often choose to undergo surgical treatment, by means of stapedectomy or stapedotomy. Both techniques are successful in improving the hearing loss to varying degrees (1). Although many patients with otosclerosis select surgical treatment, use of hearing aids to manage the hearing loss are advised before surgery and are an alternative for patients who are not candidates for stapes surgery (2–4).

Clinical otosclerosis is relatively common in White Europeans with a reported frequency of 0.1 to 2.1%, and is also common among individuals of Indian extraction (5–9). The age of onset is variable, although hearing loss typically begins in the third decade, with a range from first decade to the sixth decade (5,7,10). In most cases, hearing loss is bilateral (70–85%) and is usually asymmetrical, developing initially in one ear before progressing to the other (1,11–13). Otosclerosis has traditionally been regarded as a middle-ear disease but the inner ear can also be affected, with mixed or pure sensorineural hearing loss, tinnitus and sometimes vertigo (14,15).

Otosclerosis is considered a complex disease with both genetic and environmental factors that can occur in isolated cases with no family history (non-familial), or in cases with a strong familial inheritance pattern consistent with a monogenic cause (familial). A positive family history of otosclerosis has been previously reported in between 30 and 70% of cases (5,10,11,16,17).

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This wide range probably reflects a recruitment bias in these cohorts and variable ascertainment of relatives of the proband. The pattern of inheritance in familial otosclerosis is most often consistent with an autosomal dominant mutation that exhibits variable penetrance. Although reduced penetrance is common, the degree of penetrance can vary greatly between families and has been reported between 40 and 90% (5,10,18–23). To date, otosclerosis has proved resistant to analysis by conventional genetic techniques such as linkage analysis. In 2009, a genome-wide association study identified an association between *RELN* and otosclerosis (24), however, its biological role remains unclear. Recently, mutations and altered expression of *SERPINF1* have been identified in patients with familial otosclerosis (25).

In addition to the genetic component of otosclerosis, various other etiological factors have been suggested as playing a role in the pathogenesis of otosclerosis over the years. Clinical otosclerosis is consistently reported as more prevalent in women than in men, giving rise to the hypothesis that sex hormones may contribute to the development of disease (26–29). Other factors which have been associated with otosclerosis incidence include measles-virus infection (30–36), fluoride in drinking water (37), and co-incidence with certain systemic connective tissue disorders (38,39). However, despite its long history, many questions regarding the etiology of this condition remain unclear. One reason for this is a scarcity of empirical data on the epidemiology of otosclerosis in large well characterized cohorts. Although there have been several reviews of otosclerosis literature in recent decades which have included reiterations of the established epidemiology, these are largely based on a relatively limited number of studies some of which date back as far as the 1950s (5,10,16,18). There is therefore a need for a new analysis of otosclerosis epidemiology in sizeable cohorts to confirm or refute the conclusions inherited from much earlier studies.

The aim of this study was to report the epidemiological findings from a British cohort recently recruited for a genetic study of otosclerosis (25) and examine factors such as age of onset, pattern of inheritance, hearing loss symptoms, as well as investigate the differences between the various demographic subgroups of the cohort including sex, familial inheritance, and pregnancy characteristics to reveal any potentially distinct pathological mechanisms.

METHODS

Patient Recruitment

Between 2011 and 2017 individuals with a confirmed diagnosis of otosclerosis were recruited from the Royal National Throat Nose and Ear Hospital (London), Princess Margaret Hospital (Windsor), Sunderland Royal Hospital (Sunderland), Freeman Hospital (Newcastle upon Tyne), and Ninewells Hospital (Dundee). The diagnosis of otosclerosis was made on clinical and audiometric examination, and then confirmed during surgery. Two recruitment pipelines were used, one via individuals attending for surgical treatment and another involved a retrospective recruitment of past surgical patients from the same centres. The study was approved by the London Bloomsbury NRES Ethics committee (11/LO/0489) and patients were recruited by informed consent. Patient reported outcomes were recorded using a structured questionnaire regarding medical history (see Supplemental Digital Content 1, http://links.lww.com/MAO/A688). All female subjects answered a second questionnaire detailing history of pregnancies and hormonal medication use (see Supplemental Digital Content 2, http://links.lww.com/MAO/A689).

Family Pedigrees

In 96 patients who reported a strong family history of otosclerosis a family pedigree was constructed based on further investigation with the proband and recruitment of other family members to the study. We investigated at least three generations per family and following detailed assessment, a pattern of inheritance was assigned for each pedigree. The number of affected parents of probands was used to estimate the penetrance in otosclerosis.

Audiometry

Pure-tone audiometry was performed not earlier than 3 months before surgery and 3 months after. Air-conduction (AC) and bone-conduction (BC) included frequencies 0.5, 1, 2, 3 and 4 kHz. The guidelines from the Committee on Hearing and Equilibrium regarding the four-tone pure-tone average (0.5, 1, 2, and 3 kHz) were followed (40). Pure-tone average (PTA) values (0.5, 1, 2, and 3 kHz) were calculated regarding AC and BC thresholds, as well as the air-bone gap (ABG). We used the parameters of successful surgery as: postoperative ABG less than or equal to 10 dB; AC improvement more than or equal to 20 dB; or BC not worsened by more than or equal to 5 dB (41).

Data Analysis

Univariate analyses were performed on questionnaire data, comparing different demographics using the χ^2 test. Audiometric data were analyzed to establish normal distribution and Student's *t*-tests were conducted to establish if data were significant. Results with values of $p < 0.05$ were considered statistically significant. SigmaPlot 11.0 software (Systat Software Inc., San Jose, CA) was used to perform all statistical analysis.

RESULTS AND DISCUSSION

Characteristics of the Study Cohort

A total of 1,025 subjects with a confirmed diagnosis of otosclerosis were invited to join the study: 368 either declined to take part or did not respond to a written invitation (36%). Questionnaire data were obtained from a total of 657 subjects and the cohort demographics are summarized in Table 1.

The characteristics of this British otosclerosis cohort are largely consistent with those of other published otosclerosis cohorts and the reported epidemiology of otosclerosis (5,10,11). As has been reported previously there are more women (65%) than men in this British cohort. Regarding ethnicity, the make-up of the cohort is very similar to the ethnicities reported for the UK population in the 2011 UK Census (n = 63,182,178) of 86% White/White British, 7% Asian/Asian British, and 3% Black/Black British (42). Most participants report the age of onset of the disease as in the 3rd and 4th decades (62%, Fig. 1A), with onset above the age of 50 (4%) or below the age of 10 (6%) being rare. Familial clustering has

TABLE 1. *Demographic characteristics of otosclerosis cohort.*

	Variables	n = 657
Sex	Male	35%
	Female	65%
Age at consent	Years (mean ± SD)	50 ± 13.3
Ethnicity	White/White British	85%
	Asian/Asian British	7%
	Black/Black British	3%
	Other	2%
	No entry	3%
Age of onset	≤10 years	6%
	11–20 years	11%
	21–30 years	30%
	31–40 years	32%
	41–50 years	17%
	≥51 years	4%
Family history	≥2 family members	16%
	1 family member	24%
	No family history	60%
Hearing loss	Bilateral	62%
	Unilateral	38%
	No entry/DK (n = 13)	
Tinnitus	Yes	68%
	No	32%
	No entry/DK (n = 10)	
Vertigo	Yes	31%
	No	69%
	No entry/DK (n = 22)	

DK indicates do not know; SD, standard deviation.

long been identified in otosclerosis with evidence of a monogenic, reduced penetrance familial form of the disease proposed to exist alongside the more common sporadic disease (5,10,11,16,17), and as in other cohorts a large minority of patients (40%) report having at least one other family member diagnosed with otosclerosis, although only 16% of cases report having at least two affected family members.

Although most patients in our cohort have bilateral disease (62%) this is lower than the often quoted figure of 70 to 85% (1,11,12). In addition, most patients report suffering from tinnitus (68%) and a significant minority of subjects also reported symptoms of vertigo (31%). The incidence of tinnitus in our cohort is consistent with figures found in the literature of 50 to 85% (16,43,44). However, the incidence of vertigo is higher than the 9 to 24% found in previous studies (11,16,43).

We examined the progression of symptoms with increased duration of hearing loss (Fig. 1B). In patients who had less than 10 years of hearing loss, 45% of subjects reported bilateral symptoms, with this figure increasing to 70 to 85% of subjects after more than 30 years of hearing loss, which is in line with what is found in published literature. Incidence of vertigo also increased from 25 to 45% with duration of hearing loss. The relationship with tinnitus over time is less clear, which may be a result of improved hearing after surgery.

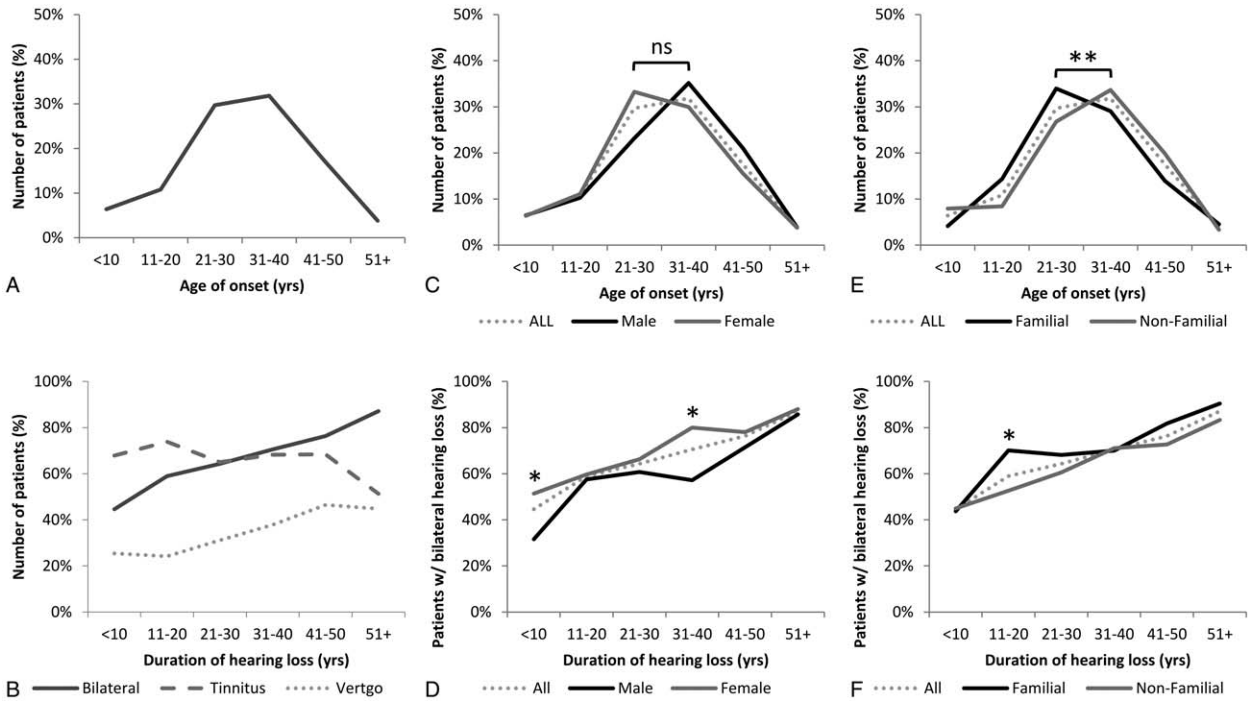

FIG. 1. Characteristics of otosclerosis cohort. (*A*) Age of onset and (*B*) incidence of hearing phenotypes in otosclerosis cohort according to duration of hearing loss (n = 657). (*C*) Age of onset and (*D*) incidence of bilateral hearing loss in male and female cases according to duration of hearing loss (male, n = 233; female; n = 424). (*E*) Age of onset and (*F*) bilateral hearing loss in familial and non-familial cases according to duration of hearing loss (familial, n = 265; non-familial; n = 392). Familial cases were defined as having 1 or more affected family member. ns indicates not significant; *, $p < 0.05$; **, $p < 0.01$.

TABLE 2. *Demographic characteristics of otosclerosis cohort stratified by sex and family history*

	Variables	Male (n = 233)	Female (n = 424)	*p*-value	Familial (n = 265)	Non-familial (n = 392)	*p*-value
Sex	Male	n/a	n/a	n/a	33%	37%	0.36
	Female				67%	63%	
Age at consent	Years (mean ± SD)	51 ± 12.7	50 ± 13.6	0.23	52 ± 13.5	49 ± 13.1	$\mathbf{8 \times 10^{-3}}$
Ethnicity	White/White British	85%	84%	0.11	86%	84%	0.85
	Asian/Asian British	7%	8%		8%	7%	
	Black/Black British	3%	2%		2%	3%	
	Other	1%	4%		2%	3%	
	No entry	4%	2%		2%	3%	
Age of onset	≤10 years	7%	6%	0.11	4%	8%	$\mathbf{6 \times 10^{-3}}$
	11–20 years	10%	11%		14%	8%	
	21–30 years	23%	33%		34%	27%	
	31–40 years	35%	30%		29%	34%	
	41–50 years	21%	16%		14%	20%	
	≥51 years	4%	4%		5%	3%	
Family history	Familial	38%	42%	0.36	n/a	n/a	n/a
	Non-familial	62%	58%				
Hearing loss	Bilateral	56%	66%	**0.03**	69%	58%	$\mathbf{6 \times 10^{-3}}$
	Unilateral	44%	34%		31%	42%	
Tinnitus	Yes	62%	72%	**0.02**	70%	67%	0.47
	No	38%	28%		30%	33%	
Vertigo	Yes	26%	33%	0.06	36%	28%	**0.04**
	No	74%	67%		64%	72%	

Familial cases were defined as having one or more affected family member. SD indicates standard deviation. Significant differences in bold.

Sex and Otosclerosis

There are a greater number of women than men in the cohort with a ratio of 1.9:1, which is in keeping with previous reports of a sex bias of 1.5 to 2:1 in the female to male prevalence of otosclerosis (11,41,45,46). Dichotomising this British cohort by sex (Table 2) shows that the age of women at recruitment and self-reported age of onset is not significantly different from men (Fig. 1C). Furthermore, there is evidence that women experience greater severity of symptoms at an earlier age than men. Women report significantly higher rates of bilateral disease ($p = 0.03$), tinnitus ($p = 0.02$), and a greater incidence of vertigo although this latter difference is not statistically significant ($p = 0.06$). The higher rate of bilateral disease in women was maintained throughout progression of the disease although was only statistically significant at two time-points (Fig. 1D).

It has previously been proposed that the greater prevalence of women in otosclerosis cohorts might be explained by women seeking earlier clinical treatment than men (47). However, the consistency and degree of the female bias across different cohorts seems unlikely to be fully explained by this factor leading to the hypothesis that estrogen may play a role in the etiology of the disorder (26–29). In our cohort the similar age of onset reported in men and women does not support an earlier attendance of women in audiological clinics and instead is more consistent with the hypothesis that women are at a higher risk of developing clinical otosclerosis than men.

Familial Inheritance and Otosclerosis

Otosclerosis is unusual in that in some populations it is a relatively common disorder with a familial form of the disease that is thought to have a monogenic origin, and a non-familial form. We examined the profile of otosclerosis comparing familial and non-familial cases (Table 2). Familial cases were defined as having one or more family members with otosclerosis. No significant differences were observed between familial cases with one affected relative and familial cases with two or more affected relatives (Table S1, Supplemental Digital Content 3, http://links.lww.com/MAO/A690).

The age at recruitment of familial cases was older than non-familial cases by an average of 3 years ($p = 8 \times 10^{-3}$). Two recruitment pipelines were used, one via individuals attending for surgical treatment and another involved a retrospective recruitment of past surgical patients. Patients recruited retrospectively are therefore likely to be older than those recruited at surgery. Therefore, we examined the characteristics of our cohort comparing surgical and retrospective recruitment (Table S2, Supplemental Digital Content 3, http://links.lww.com/MAO/A690). The age at recruitment of the retrospective cases was significantly older than surgical cases (55 and 48 yr, respectively, $p = 1 \times 10^{-9}$). A significant difference is also observed in the reporting of family history, where 35% of current surgical cases compared with 51% of retrospective cases report a family history of otosclerosis ($p = 2 \times 10^{-4}$). It is therefore possible that the older age of familial patients at recruitment may be explained by a greater motivation of patients with family history to respond to the retrospective recruitment method and hence, that 35% represents a better estimate of familial incidence. This also highlights why such a wide range is observed in the published literature, with a positive

family history reported between 30 and 70% of cases (5,10,11,16,17), and probably reflects a recruitment bias within the cohorts.

Despite the older age at recruitment familial patients report a significantly earlier age of onset than non-familial subjects with a mode age of onset in the 3rd decade compared with 4th decade for non-familial patients ($p = 6 \times 10^{-3}$; Fig. 1E). Familial patients also report a higher incidence of bilateral disease and vertigo than non-familial subjects consistent with an earlier, more severe disease ($p = 6 \times 10^{-3}$ and $p = 0.04$, respectively). Incidences of tinnitus were similar in both groups. As familial subjects reported significantly higher rates of bilateral disease, we looked at the correlation between the duration and bilaterality of hearing loss in familial and non-familial participants (Fig. 1F). In those patients who reported hearing loss for between 11 and 20 years, familial subjects reported significantly higher rates of bilateral disease compared with non-familial (70% and 53%, respectively, $p = 0.02$). This difference was not observed after a longer duration of otosclerosis but suggests familial otosclerosis may be quicker to progress to bilateral disease.

Previous studies have suggested the possibility of a differing etiology for the two forms of otosclerosis (5,43). However, most studies have not documented family history and therefore did not compare the characteristics of familial and non-familial cases of otosclerosis. In 2001, one study that evaluated a relatively small retrospective cohort of 183 patients found no difference in the degree of clinical severity between sporadic and familial cases (43). This may explain why this is the first study to report that familial patients have a significantly earlier age of onset, and report a higher incidence of bilateral disease and vertigo than non-familial subjects, consistent with an earlier, more severe disease in familial cases suggesting that distinct pathological mechanisms may be involved.

Pedigree Analysis

Otosclerosis is commonly described as having an autosomal dominant mode of inheritance, with evidence of incomplete penetrance (5,10,18,19), although the empirical evidence available to support this is limited. To investigate the inheritance pattern of familial otosclerosis in our cohort, family pedigrees were constructed from 96 patients who reported a strong family history of otosclerosis. In 91 of the 96 families the apparent mode of inheritance was most consistent with an autosomal dominant pattern, with evidence of incomplete penetrance observed in 44 of these 91 families. The remaining five families having insufficient information to ascribe a mode of inheritance. In estimating the degree of penetrance in otosclerosis, we examined the number of affected parents of probands. Of the 96 pedigree probands, there are 62 affected parents indicating an estimated penetrance of at least 65%. Before this study very little data has been published since the 1980s regarding the commonly recognized mode of inheritance found in the literature. Therefore, our study is important in establishing this further.

Pregnancy, Breastfeeding, and Oral Contraception

The preponderance of female patients with otosclerosis has led to speculation that estrogen signaling may be involved in the etiology of the disease (26–29). The typical age of onset of otosclerosis is concurrent with typical age of pregnancy and a link between the two has been suggested although remains disputed (27,29). To clarify the relationship of pregnancy and hormones with otosclerosis, female specific questionnaire data were examined in more detail (Table 3). From the 424 women in the cohort, there were 409 responses for the female only questionnaire, where 313 (77%) had experienced at least one pregnancy (Preg_Y) and 96 had no history of pregnancy (Preg_N). Age at recruitment is significantly associated with pregnancy as might be expected since younger female reported fewer pregnancies ($p = 1 \times 10^{-6}$). Overall no significant differences were observed in the age of onset, family history, bilateral disease, incidence of tinnitus, or vertigo between Preg_Y and Preg_N women providing no evidence for an interaction between pregnancy and risk of disease. Both Preg_Y and Preg_N women have an earlier age of onset than men, but very similar to each other (Fig. 2A).

However, 33% of Preg_Y women responded <Yes> to ''Did you notice any changes in your hearing ability during your pregnancy/pregnancies?'' When these third of Preg_Y women who reported awareness of changes in their hearing (Preg_HC) were compared with women that reported no changes in their hearing during pregnancy (Preg_NC), Preg_HC women were on average 4 years younger at recruitment than Preg_NC women ($p = 6 \times 10^{-3}$, Table 3). In addition, there was a highly significant association between the reported age of onset of otosclerosis and whether women reported a change in hearing with pregnancy ($p = 6 \times 10^{-6}$, Fig. 2B). Preg_HC women have an earlier age of onset than both men and Preg_NC women. The age of onset in Preg_NC women is very similar to that of men. Hence, 43% of men and 40% of Preg_NC women have onset of symptoms before the age of 30, in contrast this figure rises to 65% of Preg_HC women. Preg_N women also have a lower age of onset, similar to that of Preg_HC women. One possibility is that this might be related to long-term use of oral contraceptives; 66% of Preg_N women have used oral contraception for more than 5 years compared with 52% of Preg_Y ($p = 0.049$).

In the whole study group, women reported a higher incidence of bilateral disease than men ($p = 0.03$). Preg_HC women reported a higher incidence of bilateral hearing problems compared with Preg_N women and men ($p = 0.04$ and $p = 7 \times 10^{-3}$ respectively, Fig. 2C). For Preg_HC women, a significantly higher proportion breastfed after their pregnancies compared with Preg_NC women (90% compared with 78%, $p = 0.02$). There was no significant difference between Preg_HC and Preg_NC women in the total time of breastfeeding (Fig. 2D) or in the total number of pregnancies (Fig. 2E).

In previous studies, it has been reported that in a proportion of women with otosclerosis a deterioration

TABLE 3. *Demographic characteristics of female otosclerosis cases stratified by the effect of pregnancy on hearing loss*

	Variables	Preg_Y (n = 313)	Preg_N (n = 96)	*p*-value	Preg_HC (n = 100)	Preg_NC (n = 204)	*p*-value
Age at consent	Years (mean ± SD)	52 ± 12.8	44 ± 14.5	**$1x10^{-6}$**	49 ± 12.5	53 ± 12.8	**6×10^{-3}**
Age of onset	≤10 years	6%	8%	0.27	6%	6%	**6×10^{-6}**
	11–20 years	11%	15%		14%	9%	
	21–30 years	32%	36%		45%	25%	
	31–40 years	29%	29%		32%	28%	
	41–50 years	18%	10%		3%	26%	
	≥51 years	4%	2%		0%	6%	
Family history	Familial	41%	45%	0.54	41%	40%	0.99
	Non-familial	59%	55%		59%	60%	
Hearing loss	Bilateral	68%	58%	0.10	73%	65%	0.21
	Unilateral	32%	42%		27%	35%	
Tinnitus	Yes	69%	77%	0.19	72%	69%	0.72
	No	31%	23%		28%	31%	
Vertigo	Yes	36%	27%	0.17	32%	37%	0.45
	No	64%	73%		68%	63%	
Number of pregnancies	1	n/a	n/a	n/a	15%	20%	0.07
	2				37%	45%	
	3				26%	25%	
	4				15%	6%	
	5+				7%	4%	
Breastfed	Yes	n/a	n/a	n/a	90%	78%	**0.02**
	No				10%	22%	
Time spent breastfeeding	<1 month	n/a	n/a	n/a	11%	20%	0.19
	2–5 months				21%	23%	
	6–12 months				27%	28%	
	>1 year				40%	29%	
Oral contraception	≤5 years	48%	34%	**0.05***	46%	49%	0.69
	>5 years	52%	66%		54%	51%	

Preg_HC indicates pregnant with hearing changes; Preg_N, no history of pregnancy; Preg_NC, pregnant no hearing changes; Preg_Y, history of pregnancy; SD, standard deviation. Significant differences in bold.

*$p < 0.05$

of hearing can occur during pregnancy (5,10,27). Similar to these studies, it must be noted that the reporting of a patient's impression of deterioration of hearing during pregnancy requires a subjective response. With that in mind, our data further confirms that in a proportion of women pregnancy leads to a deterioration of hearing. Furthermore, our data suggest that in this significant minority of women pregnancy may accelerate the progression of otosclerosis with a significant shift forward in the age of onset in these women.

Measles Virus as a Risk Factor

The reported data on the role of measles infection in the pathogenesis of otosclerosis has been contradictory. In several studies, measles virus antigens and RNA have been detected in otosclerotic foci and it was hypothesised that this may be an inflammatory trigger during the active phase of otosclerosis (30,31,33). In contrast, other studies failed to demonstrate any viral antibodies in otosclerotic foci or find any evidence of measles virus RNA in stapes samples or bone cell cultures (32,34,36). We examined the profile of otosclerosis comparing cases that reported measles infection and cases without measles infection (Table S3, Supplemental Digital Content 3, http://links.lww.com/MAO/A690). Age at recruitment was significantly associated with measles infection which might be expected as more older patients who did not receive vaccination reported measles infection. Interestingly, patients with measles infection report a significantly later age of otosclerosis onset than subjects with no measles infection, with a mode age of onset in the 4th decade compared with 3rd decade, respectively ($p = 2 \times 10^{-3}$; Figure S1, Supplemental Digital Content 3, http://links.lww.com/MAO/A690).

Hence, we find no evidence to support a relationship between measles infection and risk of otosclerosis in our British cohort. Previously, studies in German cohorts have suggested that the incidence of otosclerosis has declined since the introduction of measles vaccination (35), as well as highlighting the increasing age of otosclerosis patients at the time of surgery over this period (48). Similar to the contradictions with measles virus antigens and RNA studies, our data do not support previous suggestions that measles infection is an otosclerosis risk factor. However, there is still a need for a definitive study that does not rely on retrospective self-reporting of measles infections which may explain our failure to detect an association here.

Audiometry and Surgery

Audiological data were obtained from 154 subjects and the demographics of this study population was

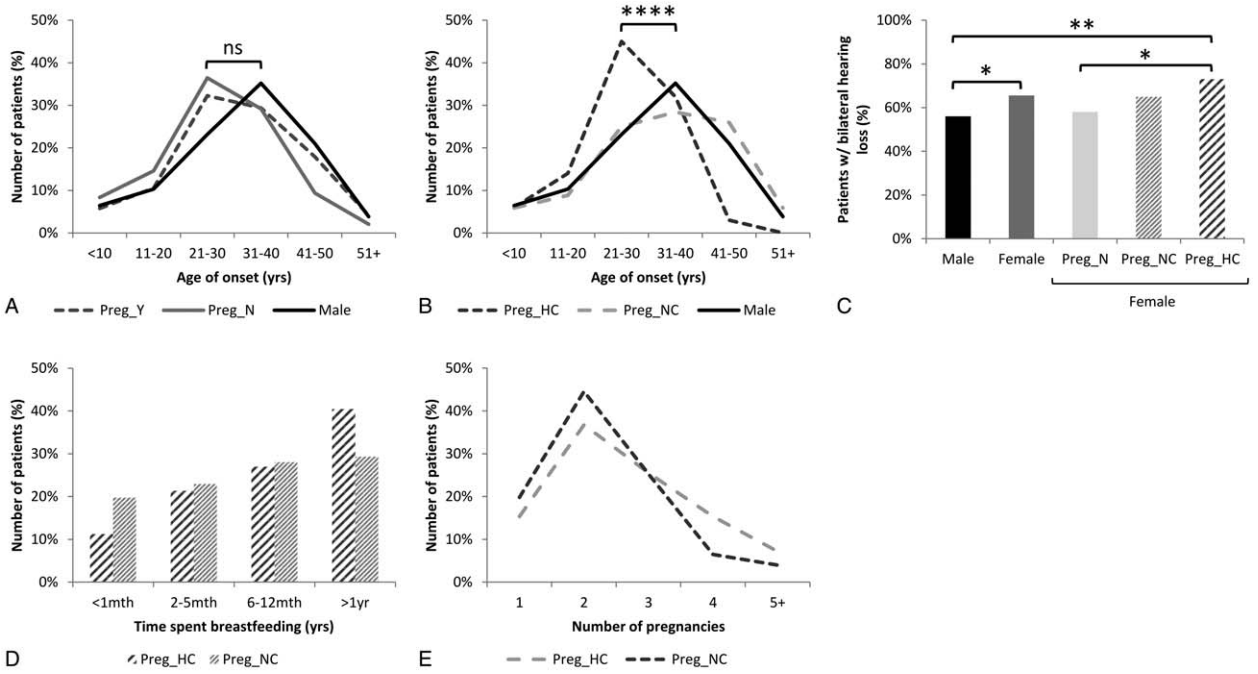

FIG. 2. Comparison of otosclerosis characteristics in patients when stratified by the effect of pregnancy on hearing loss. (*A*) Age of onset in women who had experienced pregnancy (Preg_Y, n = 313) and those that had not (Preg_N, n = 96). (*B*) Age of onset in women who report changes in hearing associated with pregnancy (Preg_HC, n = 100) and those who report no change during pregnancy (Preg_NC, n = 204). (*C*) Bilateral hearing loss in pregnancy subgroups. (D) Time spent breastfeeding and (E) number of pregnancies in Preg_HC and Preg_NC women. Male data used as control comparison in panels A to C (n = 233). ns indicates not significant; *, $p < 0.05$; **, $p < 0.01$; ****, $p < 0.0001$.

consistent with our main cohort (Table S4, Supplemental Digital Content 3, http://links.lww.com/MAO/A690). The audiometric results from our study are presented in Table S5 and S6 (see Supplemental Digital Content 3, http://links.lww.com/MAO/A690). The mean preoperative pure-tone average (PTA) air-conduction (AC) threshold was 57 dB HL, and the bone-conduction (BC) was 28 dB HL. The air-bone gap (ABG) was 29 dB. After surgery, the corresponding results were AC 31 dB HL, BC 25 dB HL, and ABG 5 dB. The mean hearing gain after surgery, expressed as improvement of the AC, was 27 dB and in 75% of patients the AC threshold improved by more than 20 dB. After surgery, the BC was maintained or not worsened by more than 5 dB in 86% of the patients. In 88% of patients, the postoperative ABG was within less than or equal to 10 dB, and in 98% it was within 20 dB. Importantly, the mean pure-tone air and bone hearing thresholds of our cohort are consistent with those of other published cohorts (41,46).

As highlighted above, clinical differences can be observed in the epidemiology and severity of otosclerosis between groups and we wanted to evaluate whether these differences are reflected in pre- and postoperative audiometric thresholds between groups. We compared AC, BC, and ABG between male and female patients (Figure S2A-C, Supplemental Digital Content 3, http://links.lww.com/MAO/A690) and no significant differences were observed in the preoperative data. However, in postoperative data male patients had a significantly higher ABG (7 dB male and 5 dB female; $p = 0.04$). Even though this is significant, the surgical outcome would still be considered successful. When comparing familial and non-familial surgical patients no significant differences were observed (Figure S2D-F, Supplemental Digital Content 3, http://links.lww.com/MAO/A690).

Finally, we compared hearing thresholds between Preg_Y and Preg_N women (Figure S3A-C, Supplemental Digital Content 3, http://links.lww.com/MAO/A690) and found no significant differences, which is consistent with other published data (29). Even when we compared Preg_HC and Preg_NC women no significant impact was observed (Figure S3D-F, Supplemental Digital Content 3, http://links.lww.com/MAO/A690).

Similar surgical outcomes between subgroups are perhaps understandable considering the relatively short-term follow-up of the study and participants would have sought medical advice at a point when their hearing loss constitutes a disability. This is more likely to be the case the greater the hearing loss, rather than the duration of the hearing loss. It would therefore be more informative to undertake a prospective study beginning from the age of onset of otosclerosis to evaluate whether clinical differences observed in the epidemiology and severity of otosclerosis can be reflected in hearing thresholds between groups. Additionally, these results suggest that while disease processes may be distinct between groups,

the effect they have on the stapes footplate and bone conduction are similar.

CONCLUSION

In summary, this study has identified that familial otosclerosis has a more rapid onset, with a higher incidence of bilateral disease than non-familial otosclerosis. This is the first study to identify differences in the degree of clinical severity between familial and non-familial cases of otosclerosis. Therefore, suggesting that more than one etiology may be involved and highlighting a need for further investigation. In addition, we have found further evidence to support the hypothesis that women are at a higher risk of developing clinical otosclerosis than men and pregnancy may accelerate disease progression, at least in a proportion of women. Despite these differences in otosclerosis onset and progression, patients choose to undergo surgery at similar times, with similar outcomes. Finally, our British otosclerosis cohort also confirms several characteristics largely consistent with previous published literature, including age of onset, sex ratio, family history, and hearing loss symptoms associated with otosclerosis. Otosclerosis is a common cause of adult-onset hearing loss, resulting in a significant annual surgical load. There remain several unresolved questions with respect to certain etiological factors that continue to limit the confidence of evidence-based patient information. We believe there is a further need for modern cohort observations, including longitudinal studies, and that our present cohort adds significantly to the literature on this elusive disease.

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