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Exogenous female sex steroids may reduce lung ageing after menopause: A 20-year follow-up study of a general population sample (ECRHS)

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Abbreviations: BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HRT, hormone replacement therapy; IQR, interquartile range

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ABSTRACT

Objectives: Menopause involves hypoestrogenism, which is associated with numerous detrimental effects, including on respiratory health. Hormone replacement therapy (HRT) is often used to improve symptoms of menopause. The effects of HRT on lung function decline, hence lung ageing, have not yet been investigated despite the recognized effects of HRT on other health outcomes.

Study design: The population-based multi-centre *European Community Respiratory Health Survey* provided complete data for 275 oral HRT users at two time points, who were matched with 383 nonusers and analysed with a two-level linear mixed effects regression model.

Main outcome measures: We studied whether HRT use was associated with the annual decline in forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1).

Results: Lung function of women using oral HRT for more than five years declined less rapidly than that of nonusers. The adjusted difference in FVC decline was 5.6 mL/y (95%CI: 1.8 to 9.3, p = 0.01) for women who had taken HRT for six to ten years and 8.9 mL/y (3.5 to 14.2, p = 0.003) for those who had taken it for more than ten years. The adjusted difference in FEV_1 decline was 4.4 mL/y (0.9 to 8.0, p = 0.02) with treatment from six to ten years and 5.3 mL/y (0.4 to 10.2, p = 0.048) with treatment for over ten years.

Conclusions: In this longitudinal population-based study, the decline in lung function was less rapid in women who used HRT, following a dose-response pattern, and consistent when adjusting for potential confounding factors. This may signify that female sex hormones are of importance for lung ageing.

1. Introduction

Health after menopause becomes increasingly important as life spans lengthen. For many women, menopause is a midlife event [1], which might increase the risk of various diseases due to postmenopausal hypoestrogenism. The role of endocrine factors in respiratory health is increasingly acknowledged and studies have identified menopause as a predictor of new-onset asthma [2]. Menopause is further associated with lower lung function [3,4] as well as an acceleration of the naturally occurring lung function decline [5]. Postmenopausal hypoestrogenism is commonly systemically counteracted by oral hormone replacement therapy (HRT). Other options include dermal patches and vaginal preparations. It seems that HRT is a double-edged sword; it may hold benefits for some women while it may harm others. Originally developed to treat symptoms of the menopausal transition, it is now established that HRT largely prevents the long-term frailties of osteoporosis [6] and it has been associated with a reduced risk of lung and colorectal cancer [7,8]. Hormone replacement therapy is however also associated with an increased risk of ovarian and endometrial cancer [9,10] as well as asthma [11,12] Preparations containing progestins are amongst others associated with an increased risk of breast cancer [13,14]. The existing literature on the relationship between HRT and lung function consists of two cross-sectional studies and three small clinical trials, generally portraying HRT as being beneficial for the lungs [15–19]. The aim of the present study was to investigate whether oral HRT reduces the naturally

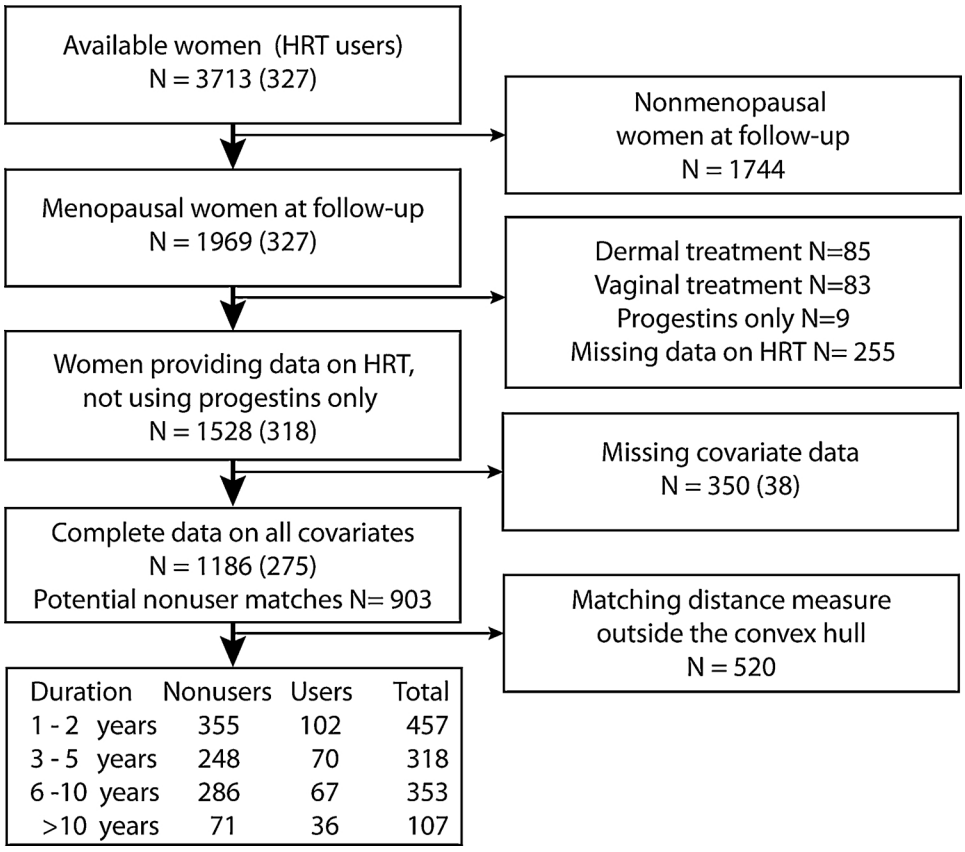

Fig. 1. Flow chart of the study population.

occurring lung function decline over a 20-year period in matched subsets of a large, population-based cohort.

2. Methods

2.1. Study population

The European Community Respiratory Health Survey (ECRHS) is a population-based international and prospective cohort study (www.ecrhs.org). The present analysis includes 658 women (275 HRT ever users, 383 nonusers) from 22 study centres in nine countries (see online supplement). We used data from baseline in 1991–1994 and follow-up in 2010–2012 with a median observation time of 20.0 years (range: 17.9–22.4). The examinations consisted of an interviewer-led questionnaire on respiratory health and lifestyle factors as well as spirometry. At follow-up, women also answered a questionnaire on reproductive health. The ECRHS provided serum samples at follow-up for a subgroup of the study population (N = 169). These samples were analysed for 17β-estradiol at the Core Facility for Metabolomics, University of Bergen (Norway) by liquid chromatography – tandem mass spectrometry. We performed the regression analysis on 275 HRT ever users, containing 125 past users and 150 current users. Eighty-four current users reported HRT constituents: estradiol combined with a progestin (N = 50), tibolone (N = 18), estradiol only (N = 16). The study did not provide details of the HRT constituents of past users. Ethical approval was obtained from the appropriate ethics committees of each study centre at each wave and all participants provided informed written consent.

2.2. Statistical analysis and inclusion criteria

Our exposure measure was the number of years women used oral HRT. This information was extracted from the answers to the following two questions at follow-up: 1) *"How long in total did you take the following types of hormonal treatments for the menopause (oral preparations)?"* and 2) *"For each year of age between 40 and now, please tick the years when you took the following types of hormonal treatments for the menopause (oral preparations)"*. Women using dermal patches or vaginal preparations were excluded from the analysis. The outcome, lung function, was recorded at baseline and follow-up, according to standardized spirometry procedures [20]. The specific outcome variables were the difference of FVC, respectively FEV_1 between baseline and follow-up, divided by the individual follow-up time, which can be interpreted as the annual lung function decline [mL/y]. A positive regression coefficient thus indicates a less rapid decline of lung function, respectively a smaller change in lung function between study waves in the corresponding group. Interviewers, who also gathered the information about age, pack-years of cigarettes and age at completed full-time education, measured the covariates weight and height. As *age at menopause*, we used the age at bilateral oophorectomy or the age at the last menstruation. All included participants reached menopause, as they reported amenorrhea for more than 12 months at follow-up. The specific questions were: 1)*"Do you have regular periods?"* Options: *"Yes", "No, they have never been regular", "No, they have been irregular for a few months", "No, my periods have stopped"* and 2) *"When was your last period?"*. We identified 327 menopausal women who reported use of oral HRT (range: 1–19 years). We performed a complete case analysis and excluded women with missing data on pack-years, age at menopause, weight at follow-up, and age at completed full-time education. The remaining 275 HRT users were matched with suitable nonusers (N = 383), who reported never using oral HRT. We analysed four similar-sized subgroups of women taking HRT according to duration of use: 1–2 years, 3–5 years, 6–10 years and more than 10 years (Fig. 1). HRT users and nonusers were matched non-parametrically using the Mahalanobis distance measure for matching according to a 1:n matching scheme [21]. Since the analyses of the four subgroups were separate from each other, nonusers were matched multiple times as long as their distance measure was within the convex hull. Matching enables a more robust and less sensitive subsequent regression analysis by selecting the best control matches for each HRT user [22]. We matched HRT users and nonusers by age, age at menopause, height (baseline), weight (baseline), age at completed full-time education. We evaluated the balance between HRT users and nonusers in the full data set, and in the matched data, using quantile-quantile plots of each matching variable (see online data supplement). To compare the

Table 1
Anthropometrics, pack-years and pulmonary function of the matched study participants using HRT for 1–2 years and 3–5 years, mean (Standard deviation) unless indicated otherwise.

	Nonusers	HRT (1-2y)	p[1]	Nonusers	HRT (3-5y)	p[1]
n	355	102		248	70	
Age (baseline) [y]	35.94 (4.32)	36.26 (5.71)	0.53	38.48 (2.92)	39.87 (4.30)	< 0.001
Age (follow-up) [y]	55.88 (4.24)	56.32 (5.63)	0.39	58.47 (2.84)	59.88 (4.08)	< 0.001
Age (menopause) [y]	49.35 (3.15)	49.00 (4.44)	0.37	50.18 (2.94)	49.94 (4.41)	0.59
Age (compl. education) [y]	20.89 (3.01)	21.20 (5.44)	0.46	20.17 (2.91)	21.71 (5.81)	< 0.001
Weight at baseline [kg]	62.38 (7.24)	63.48 (9.57)	0.21	62.52 (7.70)	62.53 (11.55)	0.99
Δ Weight [kg]	9.37 (8.39)	9.69 (10.03)	0.75	8.07 (7.79)	7.21 (7.62)	0.41
Height (baseline) [m]	1.63 (0.05)	1.64 (0.06)	0.26	1.64 (0.04)	1.63 (0.06)	0.42
Δ Height [m]	−0.01 (0.02)	−0.01 (0.02)	0.04	−0.01 (0.02)	−0.01 (0.02)	0.64
Pack-years [median (IQR[2])]	0.00 [0.00, 8.00]	0.00 [0.00, 11.88]	0.41	0.00 [0.00, 8.00]	0.00 [0.00, 6.44]	0.84
Δ Pack-years [median (IQR[2])]	0.00 [0.00, 1.81]	0.00 [0.00, 3.18]	0.34	0.00 [0.00, 0.00]	0.00 [0.00, 1.38]	0.45
FVC[3] (baseline) [mL]	3.88 (0.50)	3.87 (0.51)	0.89	3.88 (0.48)	3.75 (0.56)	0.05
Δ FVC[3] [mL/y]	−0.03 (0.01)	−0.03 (0.02)	0.07	−0.03 (0.02)	−0.03 (0.02)	0.23
FEV_1[4] (baseline) [mL]	3.20 (0.43)	3.18 (0.47)	0.68	3.18 (0.42)	3.10 (0.44)	0.17
Δ FEV_1[4] [mL/y]	−0.03 (0.01)	−0.04 (0.02)	0.18	−0.04 (0.01)	−0.03 (0.02)	0.55
Predicted FVC[3] (baseline) [%]	102.91 (11.42)	102.05 (9.92)	0.49	102.91 (11.25)	100.94 (12.86)	0.21
Predicted FEV_1[4] (baseline) [%]	102.42 (12.29)	101.16 (11.64)	0.36	102.58 (12.62)	101.96 (12.98)	0.72
Predicted FVC[3] (follow-up) [%]	101.64 (12.98)	99.79 (12.50)	0.20	101.56 (13.32)	101.40 (15.66)	0.94
Predicted FEV_1[4] (follow-up) [%]	97.25 (14.16)	95.09 (15.21)	0.18	96.93 (14.57)	97.17 (15.39)	0.91
Respiratory symptoms[5] N (%)	39 (11.0)	8 (7.8)	0.46	33 (13.3)	10 (14.3)	0.99

[1] T-test for continuous variables, X^2-test for categorical variables, Kruskal-Wallis test for nonnormal variables (pack-years).
[2] Interquartile range.
[3] Forced vital capacity.
[4] Forced expiratory volume in one second.
[5] Asthma attack during the last 12 months, breathless while wheezing at any time in the last 12 months, woken up with a feeling of tightness in your chest at any time in the last 12 months, or woken by an attack of shortness of breath at any time in the last 12 months.

groups, we used two-level linear mixed effects regression models (level 1 unit: subject; level 2 unit: centre) with a random intercept term at level 2. The models were further adjusted for study centre, the difference in weight, height and pack-years between baseline and follow-up (extant exposure during the time period over which lung function change was measured), as well as the type of spirometer, as spirometers differed between centres and study waves (see online data supplement). We further stratified the analysis into current and past users. To investigate a potential trend, we performed a Mann-Kendall trend test without continuity correction. All analyses were performed using RStudio (Version 1.0.136, The R Foundation for Statistical Computing).

3. Results

Anthropometrics, pack-years and pulmonary function of the matched subgroups are presented in Tables 1 and 2. With the 1:n matching scheme (with multiple use of nonuser observations), each of the suitable 383 nonusers were matched on average 2.5 times leading to a total of 960 observations of nonusers being matched to the 275 HRT users (included total observations: 1235). Detailed information on the balance before and after matching (quantile-quantile plots for matching variables) can be found in the online data supplement. We evaluated serum 17β-estradiol in a subset of the population (N = 169). In the exposure group, consisting of past and current users of oral HRT, we calculated a median concentration of 73.3 pmol/L (Inter quartile range (IQR): 12.1–169.3) for current users and 10.0 pmol/L (IQR: 5.6–18.6) for past users. Nonusers had a median estradiol concentration of 10.5 pmol/L (IQR: 5.4–16.5).

The adjusted regression analysis showed that the use of oral HRT for more than 5 years was associated with a reduced decline of FVC and FEV_1 compared with non-use. Associations were statistically significant for treatment durations greater than five years (Table 3 and Fig. 2). Overall, FVC and FEV_1 showed a very similar pattern as well as a dose-response like relationship (p_{trend} = 0.04). The stratified analysis into current and past users showed that the association was more pronounced amongst current HRT users (online data supplement).

Table 3
Differences in the change of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) of hormone replacement therapy (HRT) users compared with nonusers (A positive regression coefficient indicates a less rapid decline of lung function).

	FVC		FEV_1	
HRT treatment	β [mL/y] (95% CI)[1]	p	β [mL/y] (95% CI)[1]	p
None	Reference		Reference	
1–2 years (n = 86)	−2.2 (−5.2 to 0.8)	0.16	−2.1 (−4.7 to 0.5)	0.12
3–5 years (n = 72)	2.2 (−1.7 to 6.0)	0.28	2.0 (−1.7 to 5.6)	0.30
6–10 years (n = 70)	5.6 (1.8–9.3)	0.01	4.4 (0.9–8.0)	0.02
> 10 years (n = 39)	8.9 (3.5–14.2)	0.003	5.3 (0.4–10.2)	0.048

[1] Coefficients and 95% confidence intervals of the linear mixed effects model adjusted for age, age at menopause, weight (baseline), weight change, height, height change, pack-years since baseline, age at completed full-time education, type of spirometer and study centre.

4. Discussion

This study on matched subgroups of a population-based international cohort found that lung function decline was significantly reduced in women taking oral HRT for more than five years, compared to women who never used oral HRT. For the individual women the effect sizes might not be of practical importance, but the results indicate that oral HRT compensates roughly one third of the postmenopausal acceleration of lung function decline [5] if it is used for six to ten years, respectively, and half if it is used for more than ten years. The results seem plausible, as elevated estrogens are likely to protect lung function [23,24]. In animal studies, increased systemic estrogen levels have been shown to improve metabolic and inflammatory profiles [24,25] and a comprehensive review concluded that estradiol overall has an anti-inflammatory effect on the lungs [23]. Estrogens also protect from osteoporosis, which might preserve the integrity of thoracic vertebrae and maintain an optimal expansion of the thoracic cage during inspiration [26].

The main reason to start an HRT regiment is distress caused by symptoms of the menopausal transition, which lasts on average five

Table 2
Anthropometrics, pack-years and pulmonary function of the matched study participants using HRT for 6–10 years and more than 10 years, mean (Standard deviation) unless indicated otherwise.

	Nonusers	HRT (6-10y)	p[1]	Nonusers	HRT (> 10y)	p[1]
n	286	67		71	36	
Age (baseline) [y]	38.15 (3.89)	40.37 (4.88)	< 0.001	41.32 (2.21)	42.15 (3.75)	0.15
Age (follow-up) [y]	58.15 (3.85)	60.48 (4.78)	< 0.001	61.40 (2.14)	62.00 (3.59)	0.29
Age (menopause) [y]	49.19 (3.27)	49.15 (4.43)	0.94	47.29 (4.24)	45.25 (6.72)	0.06
Age (compl. education) [y]	19.55 (3.03)	19.87 (5.17)	0.51	19.42 (2.41)	20.53 (4.53)	0.10
Weight at baseline [kg]	61.91 (6.61)	62.54 (10.62)	0.54	61.62 (6.33)	60.94 (10.69)	0.68
Δ Weight [kg]	8.23 (8.22)	7.77 (7.91)	0.68	7.81 (7.65)	10.23 (8.30)	0.14
Height (baseline) [m]	1.64 (0.05)	1.65 (0.07)	0.17	1.63 (0.04)	1.63 (0.06)	0.57
Δ Height [m]	−0.01 (0.02)	−0.01 (0.01)	0.37	−0.01 (0.02)	−0.02 (0.02)	0.63
Pack-years [median (IQR[2])]	0.00 [0.00, 9.00]	0.00 [0.00, 9.50]	0.81	0.00 [0.00, 2.45]	0.00 [0.00, 11.29]	0.20
Δ Pack-years [median (IQR[2])]	0.00 [0.00, 0.00]	0.00 [0.00, 2.80]	0.28	0.00 [0.00, 0.00]	0.00 [0.00, 6.07]	0.04
FVC[3] (baseline) [mL]	3.91 (0.50)	3.76 (0.59)	0.04	3.73 (0.50)	3.56 (0.49)	0.11
Δ FVC[3] [mL/y]	−0.03 (0.01)	−0.02 (0.02)	0.07	−0.03 (0.01)	−0.02 (0.01)	0.01
FEV_1[4] (baseline) [mL]	3.21 (0.43)	3.05 (0.50)	0.01	3.06 (0.39)	2.95 (0.48)	0.22
Δ FEV_1[4] [mL/y]	−0.04 (0.01)	−0.03 (0.02)	0.07	−0.04 (0.01)	−0.03 (0.01)	0.07
Predicted FVC[3] (baseline) [%]	102.70 (11.14)	98.43 (11.20)	0.01	101.26 (11.20)	97.02 (13.51)	0.09
Predicted FEV_1[4] (baseline) [%]	102.59 (12.45)	97.69 (12.74)	< 0.001	101.93 (11.87)	98.65 (15.65)	0.23
Predicted FVC[3] (follow-up) [%]	101.86 (13.42)	100.91 (12.75)	0.60	99.89 (14.47)	100.25 (15.32)	0.91
Predicted FEV_1[4] (follow-up) [%]	97.15 (14.49)	94.98 (13.92)	0.27	95.88 (15.28)	96.14 (16.55)	0.94
Respiratory symptoms[5] N (%)	38 (13.3)	12 (17.9)	0.43	7 (9.9)	6 (16.7)	0.48

[1] T-test for continuous variables, X^2-test for categorical variables, Kruskal-Wallis test for nonnormal variables (pack-years).
[2] Interquartile range.
[3] Forced vital capacity.
[4] Forced expiratory volume in one second.
[5] Asthma attack during the last 12 months, breathless while wheezing at any time in the last 12 months, woken up with a feeling of tightness in your chest at any time in the last 12 months, or woken by an attack of shortness of breath at any time in the last 12 months.

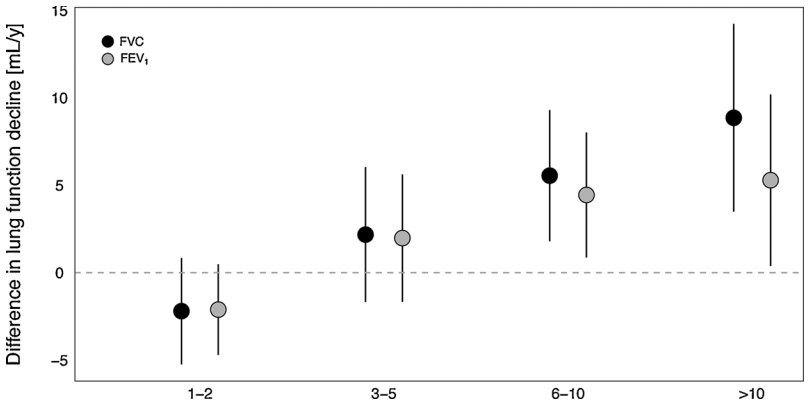

Fig. 2. Decline of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) of hormone replacement therapy (HRT) users compared with nonusers. The size of the markers represents group size.

years [27]. During this phase, concentrations of estradiol may differ substantially and even be elevated [28]. The process of the transition possibly overshadows the early effect of HRT on lung function decline. This may contribute to the non-significant results for using HRT for less than five years. It might further be possible that women, who chose to use HRT have more severe menopausal symptoms, thus the beneficial effect of HRT may have been observed mainly in this group. However, this does not necessarily limit the potential benefit to women with severe menopausal symptoms.

This study focuses on oral HRT as it represents a systemic as well as the most frequent treatment. A potential issue with HRT treatment over a long time is compliance. Women may have stopped the treatment periodically to evaluate the continuity of transitional symptoms. This may introduce a minor bias, and the results would underestimate the true effect. Further when the Women's Health Initiative study was published in 2002, many women worldwide stopped taking HRT. As our study is retrospective and covering this time point, it is likely that this applies to some women in our study population and this might attenuate associations.

To our knowledge, this is the first longitudinal study investigating HRT and the decline of lung function. Of two previous cross-sectional studies, Carlson et al reported that current HRT users older than 65 years, had higher FEV_1 compared to nonusers [15], whereas Jarvis et al observed this association only in overweight, past HRT-users [16]. Due to the different study designs, comparability is limited between studies. Cevrioglu et al, in one of two clinical trials on volunteers, lasting three months, found an increased lung function in 23 women treated with a continuous estrogen and progestin preparation compared to 25 women who did not take HRT [17]. Pata et al, in the second trial on volunteers (N = 75) reported an increased lung function after treatment with Tibolone, combined estrogens and progestins as well as estrogen only preparations, but this study did not have a control group [18]. A drawback of both studies on volunteers might be that they are underpowered and subject to selection bias. Stipic et al in the third trial reported increased FEV_1 in 30 HRT users who underwent surgery because of genital prolapse compared to nonusers after six months of treatment [19]. Overall, our results are in agreement with the previous work in the field. Our analysis adds external validity and the use of objective hormone measurements, the long follow-up time and the high response rates are strengths of our study [29]. Weaknesses of the study are the unknown history of HRT types, which did not allow stratification according to the active ingredients (estrogen with and without progestin) and the non-randomized use, as users could have more menopausal symptoms or be more health conscious [30]. The latter is accounted for by matching HRT users with the most similar nonusers. There was no statistically significant difference in the age at completed full-time education within the groups yielding statistically significant results (our proxy for socio-economic status) and it seems unlikely that the observed associations could be explained by unobserved differences.

5. Conclusions

Oral hormone replacement therapy for six years or more is associated with a reduced decline of lung function. Even though the effect size might be irrelevant for the individual women, this supports the idea that the accelerated loss of lung function during menopause may be explained by hypoestrogenism. Our findings are relevant for the necessary further research on lung ageing.

Contributors

Kai Triebner is the principal author, responsible for conception and design of the work, statistical analysis, interpretation of data, and drafting of the manuscript.

All other authors participated in the conception and design of the work, acquisition or interpretation of data and revising the draft for important intellectual content.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

The study was funded by the European Medical Research Council (Grant Number 92091) and carried out according to the Helsinki Declaration II and approved by local ethics committees at each centre. Every participant was required to give written informed consent. Details can be found at http://www.ecrhs.org/progress.htm.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.maturitas.2018.11.007.

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