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Ultraviolet radiation as a predictor of sex hormone levels in postmenopausal women: A European multi-center study (ECRHS)

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ABSTRACT

Background: Solar ultraviolet radiation (UVR) affects the body through pathways that exhibit positive as well as negative health effects such as immunoregulation and vitamin D production. Different vitamin D metabolites are associated with higher or lower concentrations of estrogens and may thus alter the female sex hormone balance. *Objective:* To study whether exposure to UVR, as a modifiable lifestyle factor, is associated with levels of sex hormones (17β-estradiol, estrone, estrone 3-sulfate, testosterone, dehydroepiandrosterone sulfate), gonadotropins (follicle stimulating hormone, luteinizing hormone) as well as sex hormone binding globulin in postmenopausal women, and thus investigate whether managing UVR exposure can influence the hormone balance, with potential benefits for the biological aging process.

Abbreviations: CI, confidence interval; cL, centiliter; CV, coefficient of variation; daL, dekaliter; DHEA-S, dehydroepiandrosterone sulfate; dL, deciliter; ECRHS, European Community respiratory health survey; FSH, follicle stimulating hormone; IQR, interquartile range; LLQ, lower limit of quantification; IU/L, international units per liter; LC–MS/MS, liquid chromatography–tandem mass spectrometry; LH, luteinizing hormone; SHBG, sex hormone binding globulin; SED, standard erythema dose; UVR, ultraviolet radiation.

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Methods: The study included 580 postmenopausal women from six European countries, participating in the European Community Respiratory Health Survey (2010–2014). Average UVR exposure during the month before blood sampling was estimated based on personal sun behavior and ambient levels. Hormone concentrations were measured in serum using state-of-the-art methods. Subsequently we applied linear mixed-effects models, including center as random intercept, hormone concentrations (one at a time) as outcome and UVR, age, skin type, body mass index, vitamin D from dietary sources, smoking, age at completed full-time education and season of blood sampling as fixed-effect predictors.
Results: One interquartile range increase in UVR exposure was associated with decreased levels of 17β-estradiol (-15.6 pmol/L, 95 % Confidence Interval (CI): -27.69, -3.51) and estrone (-13.36 pmol/L, 95 % CI: -26.04, -0.68) and increased levels of follicle stimulating hormone (9.34IU/L, 95 % CI: 2.91, 15.77) and luteinizing hormone (13.86 IU/daL, 95 % CI: 2.48, 25.25).
Conclusions: Exposure to UVR is associated with decreased estrogens and increased gonadotropins in postmenopausal women, a status associated with osteoporosis, lung function decline and other adverse health effects. This study indicates that managing UVR exposure has potential to influence the hormone balance and counteract adverse health conditions after menopause.

1. Introduction

After menopause the female hormone balance changes drastically [1,2]. Low concentrations of estrogens and rising concentrations of gonadotropins affect many physiological pathways and accelerate the aging process [3]. Existing evidence suggests that this development may be influenced by utilizing lifestyle modifications to enhance the postmenopausal quality of life [4,5]. One easily modifiable lifestyle factor is the exposure to sunlight and thus ultraviolet radiation (UVR), which is a form of non-ionizing radiation that has both adverse and beneficial health effects. The sun is the principal source of UVR exposure, with short-term effects such as photokeratitis, sunburn and immunosuppression and long-term effects such as skin cancers, skin photoaging and cataracts [6]. A main known benefit of UVR is the stimulation of vitamin D production in the skin, which is essential for the calcium metabolism and for the maintenance of the musculoskeletal system [6,7]. Vitamin D in turn has been associated with endogenous concentrations of estrogens, as e.g. women with lower vitamin D were found to also have lower mean concentrations of 17β-estradiol across the menstrual cycle [8] and 1,25-dihydroxy vitamin D stimulates 17β-estradiol production [9]. A recent comprehensive review further highlights that vitamin D metabolizing enzymes are expressed in human reproductive tissues and that vitamin D deficiency is linked with impaired hormone production, thus attributing a mechanistic role for vitamin D in steroidogenesis [10]. Additionally an in vitro study of placental steroidogenesis showed, that calcitriol is a physiological regulator of 17β-estradiol [11]. Although, several studies suggest a link between concentrations of sex hormones and UVR exposure, to date there is no direct evidence on such a relationship [10,12,13]. We hypothesize that UVR exposure may affect the hormonal balance in postmenopausal women, which is of public health interest, as estrogens contribute to healthier reproductive aging through less pulmonary inflammation [14,15], faster wound healing and prevention of osteoporosis [16,17], while high gonadotropins are associated with lower cognitive function and a higher risk for Alzheimer's Disease [18]. The aim of the present study was to investigate whether UVR exposure is associated with serum concentrations of sex hormones, gonadotropins and sex hormone binding globulin (SHBG) after menopause and thus study whether managing UVR exposure can influence the hormone balance, with potential benefits for the biological aging process.

2. Methods

2.1. Study population

The present analysis was based on the second follow-up of the European Community Respiratory Health Survey (ECRHS), a population-based cohort study [19,20] that recruited random participants throughout Europe, reflecting a mostly Caucasian population. The current analysis included 580 postmenopausal women from eleven study centers in six countries in the south, center and north of Europe (Huelva, Albacete and Galdakao in Spain, Bordeaux, Grenoble and Paris in France, Aarhus in Denmark, Uppsala and Umea in Sweden, Reykjavik in Iceland as well as Bergen in Norway). The examinations took place during 2010 and 2014 and consisted of an interviewer-led questionnaire on anthropometrics, lifestyle factors, sun behavior and reproductive health as well as blood sampling. Vitamin D intake from dietary was estimated using the GA^{2}LEN food frequency questionnaire, a standardized instrument, designed to ascertain dietary intake internationally [21].

We included only women in a stable hormonal state, reporting no menstrual periods within the last 12 months, surgical removal of the ovaries or FSH serum levels greater or equal to 70 IU/L [1]. Therefore, we excluded pre- and perimenopausal women, as well as women who reported taking exogenous hormones such as hormone replacement therapy or treatments for (not specified) gynecological conditions at the time of the survey. Ethical approval was obtained from the appropriate ethics committees of each study center and all participants provided informed written consent.

2.2. Individual UVR exposure

We obtained satellite data on the ambient vitamin D effective UVR dose at wave lengths between 290 and 315 nm [22,23] at each study center, from the Royal Netherlands Meteorological Society (www.temis.nl) [24,25]. These data account for the attenuation of UVR due to clouds, varying Sun-Earth distance, axial tilt, surface albedo, surface elevation as well as presence of aerosols. Additionally, we collected data on personal sun behavior, including time spent outdoors during daylight, vacation destinations, clothing and frequency of sunscreen use through a standardized sun behavior questionnaire (Online data supplement section 2). Furthermore we gathered self-reported data on skin type, as an indicator of sun sensitivity [26,27]. Subsequently, we applied the following modeling approach integrating data on personal sun behavior, with data on ambient UVR to estimate the daily exposure [24,28,29]:

$$E_{id} = UVR_d \times EF_{id} \times (1 - (1 - h_{id} / H_d)^2)$$

where E_{id} is the facial UVR exposure in subject i during day d, UVR_d is the ambient UVR level in day d, EF_{id} is the exposure fraction (i.e. the fraction of ambient UVR received on the face relative to ambient during the same period of exposure in subject i during day d), h_{id} is the time spent outdoors during daylight by subject i during day d and H_d is the number of daylight hours for the mid-point of the month that includes day d and at the latitude of interest. The exposure fraction for subject i on day d, EF_{id}, was assumed to be distributed according to a uniform probability distribution. Specifically:

$$EF_{id} = EF_{min,\,d} + r_i\,(EF_{max,\,d} - EF_{min,\,d})$$

where $EF_{min,d}$ and $EF_{max,d}$ are the minimum and maximum exposure fractions on day d for any subject, respectively and r_i, between 0 and 1, is drawn from the uniform distribution. $EF_{min,d}$ was set at 0.05 in all cases and $EF_{max,d}$ was set at 0.25, 0.30, 0.40 and 0.50 for the weekdays, winter weekends, summer weekends and holidays respectively [28]. We previously validated the modeling framework against measurements of UVR exposure by personal UVR dosimeters in outdoor and indoor workers over a period of six months (covering the warm and the cold season). Modeled UVR exposure levels strongly correlated with dosimeter measured personal UVR exposure levels (correlation coefficient: 0.87) (Manuscript submitted).

It was difficult to choose a proper window of exposure because the involved pathways were likely to be complex and intertwined. For our main analyses, we averaged the daily estimates of UVR exposure over a period of one month preceding the examination visit for each participant, in order to abstract their individualized mean UVR exposure over this period. To investigate the robustness of our findings to this choice, we abstracted two alternative exposure times of one week and three months. We repeated the analyses using these exposure estimates.

2.3. Serum sex hormone analysis

Non-fasting blood samples were collected and centrifuged within three hours after collection and blood serum was stored at −80 °C until analysis. In the current study we included total concentrations of steroid hormones (17β-estradiol, estrone, estrone 3-sulfate, testosterone and dehydroepiandrosterone sulfate (DHEA-S)), measured with a high sensitivity liquid chromatography-tandem mass spectrometry method [30] and peptides (follicle stimulating hormone (FSH), luteinizing hormone (LH) and sex hormone binding globulin (SHBG)), determined with enzyme-linked immunosorbent assays (Demeditec Diagnostics, Kiel, Germany). Measurements were carried out at the Core Facility for Metabolomics (University of Bergen, Norway) and all liquid handling steps were fully automated [31,32]. Concentrations below the lower limit of quantification (LLQ) for 17β-estradiol (3.6 pmol/L), estrone (2.1 pmol/L), estrone 3-sulfate (0.24 nmol/L) testosterone (106 pmol/L), DHEA-S (0.21 μmol/L), FSH (5.0 IU/L) LH (10.0 IU/L), and SHBG (4.0 nmol/L) were included as "lower limit of quantification / 2" [33]. This was the case for the following percentage of women of our study population: 17β-estradiol: 7.0 %, estrone: 0.2 %, estrone 3-sulfate: 5.1 %, testosterone: 1.4 %, DHEA-S: 0.2 %, FSH: 2.3 %, LH: 0.0 % and SHBG: 2.8 %. All assays were specific for the respective compound, only LH showed cross reactivity with FSH (2.6 %) and thyroid stimulating hormone (1.25 %).

2.4. Statistical analyses

We fitted linear mixed effects model with study center as random intercept, sex hormones and SHBG (untransformed, as residuals were normally distributed) one at a time as outcome and the mean UVR exposure during the last month as a fixed effect predictor. Models were adjusted for an a priori selected set of covariates: age (continuous), skin type (white sensitive; white non-sensitive; olive, brown or black) [34], body mass index (continuous), vitamin D intake from dietary sources (continuous) [35], smoking habit (lifelong non-smoker, ex-smoker and current smoker), age at completed full-time education (<17 years (Middle school); 17–20 years (High school); >20 years (University)) as a proxy for socio-economic status and season of blood sampling (spring, summer, autumn, winter). Missing values for the age at completed full-time education (n = 12) where included as ">20 years" for managers and professionals and "17–20 years" for non-manual laborers.

We fitted several additional models: We 1) repeated the main analyses using the average UVR exposure during the last week as well as during the last three months instead of the last month to approximate the window of susceptibility; 2) evaluated the direct association of dietary vitamin D intake with hormones; 3) additionally adjusted the model of the main analyses for physical activity as total metabolic equivalents of task and in a separate model for the answers to the sun behavior questions, not included in the exposure assessment: 1. "For the last 12 months, where did you spend your summer holidays?" (Options: "Home country", "Mediterranean and Adriatic countries, including Northern African", "Northern European countries, above Brussels", "Central European countries, below Brussels and above Mediterranean and Adriatic countries", "Other"), 2. "During the summer days, which parts of your body are usually exposed to sunlight when you are outside?" (Options: "Face and hands", "Arms", "Legs", "Trunk" on either of the following "Working days", "Non-working days", "Holidays"), 3. "How often do you use sunscreen when you are outside during the summer days?" (Options: "Never", "Sometimes", "Usually", "Always" on either of the following "Working days", "Non-working days", "Holidays") and 4. "What Sunscreen sun protection factor (SPF) do you usually use?" 4) stratified the analysis by season of exposure (winter/spring and summer/autumn), to elaborate the influence of seasonality and get an indication of the role of dietary Vitamin D intake, which may be of importance for exposure during the winter/spring months but is likely negligible during the summer/autumn months; and 5) stratified the analysis by skin complexion ("white, sensitive or non-sensitive" and "non-white skin type"). All analyses were performed using the R statistical package [36–41] (Fig. 1).

3. Results

Anthropometric and endocrine characteristics of the included participants are presented in Table 1. The imprecision and accuracy for the sex hormone and SHBG measurements is presented in Supplementary Table 1. Characteristics of the study population, stratified by skin complexion, are presented in Supplementary Table 2.

The median daily UVR exposure during the last month was 55.1 J/m^2 (Interquartile range (IQR): 13.6–163.2 J/m^2). Fig. 2 illustrates the ambient UVR levels and personal UVR exposure separately for each study center.

The averaged one-month exposure to UVR was associated with decreased 17β-estradiol (-15.6 pmol/L, 95 % CI: -27.69, -3.51), estrone (-13.36 pmol/L, 95 % CI: -26.04, -0.68) and an increase in concentrations of follicle stimulating hormone (9.34IU/L, 95 % CI: 2.91, 15.77) and luteinizing hormone (13.86IU/daL, 95 % CI: 2.48, 25.25) (Fig. 2).

Further analyses with other exposure windows of one week and three months, showed very similar results with overall somewhat lower effect sizes (Supplementary Fig. 1 and 2). Investigating the direct association of dietary vitamin D intake with hormones did not yield any statistically significant results (Supplementary Fig. 3). The analyses with additional

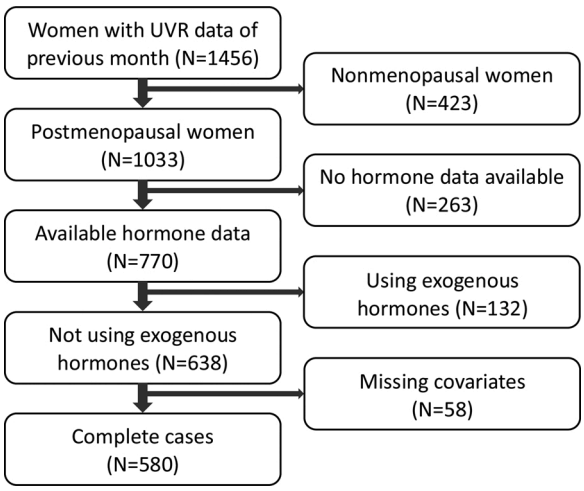

Fig. 1. Flowchart of the study population with inclusion criteria.

Table 1
Description of the study population; Median [interquartile range] for continuous variables and number (%) for categorical variables;

N	580
Age [years]	56.8 [52.4, 61.4]
BMI [kg/m^2]	25.6 [23.0, 29.4]
Smoking habit	
Lifelong non-smoker	274 (47.2)
Ex-smoker	224 (38.6)
Current smoker	82 (14.1)
Skin type	
White, sensitive	110 (19.0)
White, non-sensitive	341 (58.8)
Olive, brown or black	129 (22.2)
Dietary vitamin D [µg/d]	7.0 [4.4, 11.0]
Age at completed education	
<17 years	110 (19.0)
17–20 years	178 (30.7)
>20 years	292 (50.3)
Sex hormones and SHBG	
17β-Estradiol [pmol/L]	12.2 [6.6, 26.8]
Estrone [pmol/L]	67.8 [47.9, 108.4]
Estrone 3-sulfate [pmol/cL]	9.0 [5.0, 18.9]
Testosterone [pmol/dL]	53.0 [36.5, 69.9]
DHEA-S [nmol/dL]	166.0 [100.6, 251.6]
FSH [IU/L]	125.7 [84.1, 166.2]
LH [IU/daL]	278.8 [203.0, 362.0]
SHBG [nmol/L]	58.9 [36.5, 91.1]

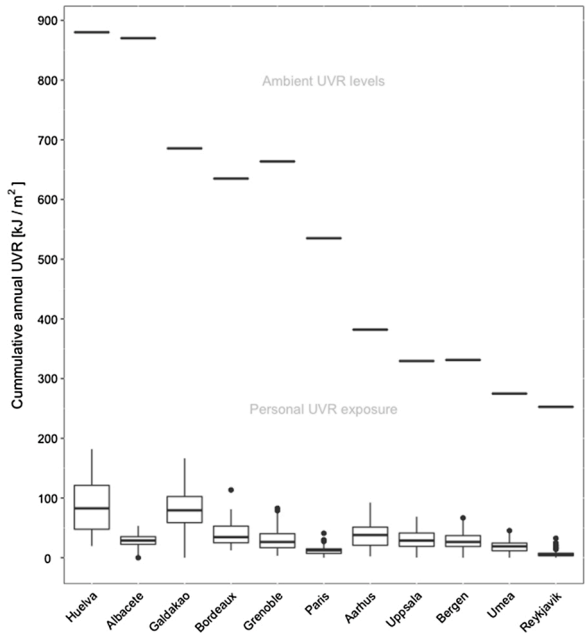

Fig. 2. Ambient UVR levels and personal UVR exposure by study center, arranged by geographical latitude from south to north; Cumulative annual ambient UVR levels are displayed as horizontal lines and cumulative annual personal UVR exposures are displayed as boxplots. The lower and upper hinges correspond to the 25th and 75th percentile. The upper and lower whiskers extend from the hinge to the largest, respectively smallest value, yet no further than 1.5 interquartile ranges. Data beyond the end of the whiskers are plotted individually.

adjustment for physical activity and detailed sun behavior resulted in similar effect estimates (Supplementary figures 4 and 5). The stratified analyses by season of exposure showed stronger associations for exposure during the sun-rich months (Supplementary figures 6 and 7) and stratification by skin complexion showed very similar results for white skin complexion (Supplementary figure 8), as compared to the whole study population, whereas no statistically significant results could be observed for non-white skin complexion (Supplementary figure 9) (Fig. 3).

4. Discussion

In this study we evaluated the association of UVR exposure and concentrations of sex hormones and SHBG in postmenopausal women. This study used data from a representative sample of women living across Europe at different latitudes, cultures and climates. We observed that higher exposure to UVR was associated with lower 17β-estradiol and estrone levels as well as with elevated FSH and LH levels. This was most pronounced for an exposure time of one months as compared to one week or three months. Additional adjustment for physical activity and personal sun behavior (vacation destination, body exposure and sunscreen use) yielded very similar results. We further investigated the direct association of dietary vitamin D intake with hormone concentrations, without being able to establish statistically significant associations, indicating that the role of dietary intake of vitamin D is not a driving force of the observed associations. The stratified analyses by season of exposure showed that the associations were considerably stronger for exposure during the sun-rich months, which strengthens the hypothesis that dietary vitamin D intake may be negligible. We found similar results for women with white skin complexion (compared to the main analysis), while for women with non-white skin complexion the associations were less clear. This could however be due to the small numbers of individuals with non-white skin complexion, decreasing the statistical power for the analyses conducted on this subsample.

To our knowledge, this is the first large-scale epidemiological study to combine personal sun behavior with ambient UVR levels. This individualization is important, given that most of the variation in actual exposure is due to personal behaviors and not due to the ambient, latitude-dependent exposure in the place of residence [29,42–44]. Given there is no available literature on our studied association, it is not possible to compare our findings with those of others; however, our results are in line with a number of previous observations, which we elaborate below separately for estrogens and gonadotropins.

It is likely that steroid hormones and gonadotropins are affected by different, yet tangled, mechanisms: Sex steroid concentrations are directly associated with vitamin D metabolites [9,45], which are derived from exposure to UVR radiation, while on the other hand, visible light, received by the retina, modulates the actions of the pineal and pituitary gland and thus could exhibit an effect on gonadotropins [46,47].

4.1. Estrogens

One possible mechanism explaining the statistically significant negative association between estrogens and UVR exposure is based on UVR derived vitamin D (cholecalciferol) being metabolized into calcidiol [48], and 17β-estradiol enhances the conversion of calcidiol to calcitriol, the active form of vitamin D, in the kidneys [45]. This pathway might also, at least in part, explain the observed association on estrone, a metabolic intermediate of 17β-estradiol [9]. This mechanism may be further supported by vitamin D being stored in adipose tissue, the major estrogen production site in postmenopausal women [49].

4.2. Gonadotropins

We observed a statistically significant positive association with the gonadotropins FSH and LH, which are closely related to each other and to estrogens through negative feedback regulation. When the gonadal production of estrogens stops due to menopause, the gonadotropins rise. Therefore, lower estrogen concentrations due to UVR exposure may also promote higher concentrations of gonadotropins. Further, bright versus dim light exposure has been associated with increased concentrations of gonadotropins as well as more ovulatory cycles [50]. A study on light therapy, for example, has suggested a direct action of visible light on the

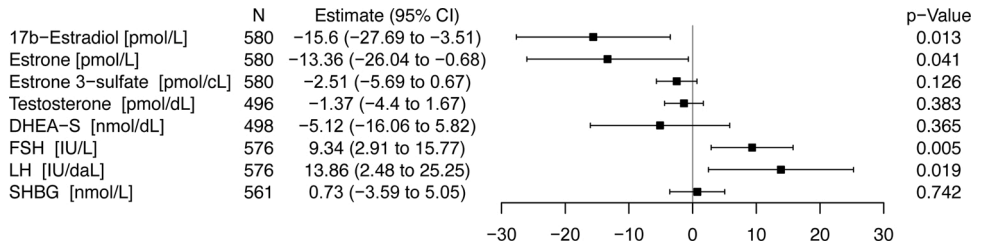

Fig. 3. Results of the main model, adjusted for skin type, age, BMI, dietary vitamin D intake, smoking habit, age at completed full-time education and season of blood sampling. The x-axis represents the expected change in the mean level of each hormone when increasing the average personal one-month exposure to UVR by a quantity equivalent to the interquartile range observed in the study sample. The units of the hormones are given behind the respective name.

hypothalamic–pituitary–gonadal axis [51], modulation of the actions of the pineal and pituitary gland, and thus an effect on gonadotropins [46, 47]. It seems plausible, that brighter light occurs predominantly outdoors, which is also where UVR exposure takes place. This simultaneous exposure likely contributes to the results on gonadotropins. Moreover, there is evidence that LH is negatively associated with melatonin, which accumulates in the pineal gland during daylight hours and secretion is restricted until darkness [47]. It is however unclear in how far this might be relevant to our observed findings.

4.3. Strengths and limitations

The major strengths of this study are the representative study population, state-of-the-art hormone measurements and the individualized exposure assessment. The cross-sectional design on the other hand limited the capability in establishing a causal relationship. It seems however considerably more likely that exposure to UVR is the cause, rather than the consequence of an altered hormone balance. A limitation of the study is that the dietary assessment of vitamin D did not include supplements or medication and that serum vitamin D levels were not available, which restricted our ability to evaluate the mechanisms underlying the associations between UVR exposure and sex hormone concentrations. Further, melatonin measurements would have allowed a more detailed insight into mechanisms at work and we cannot exclude that factors such as shift work [52], high intensity physical activity [53] or the exclusion of women receiving hormonal treatment may have influenced our observed associations somewhat.

4.4. Conclusions

We conclude, that high exposure to UVR is associated with an adverse hormone balance in postmenopausal women and may negatively affect healthy aging of a large part of the population. This study indicates, that managing UVR exposure has potential to influence the hormone balance and counteract adverse health conditions after menopause. Future studies continuing this pioneering work and focusing on pathways, could consider including several vitamin metabolites, not only the routinely measured vitamin D3.

Contributors

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

Ersilia Bifulco, Jose Barrera-Gómez, Xavier Basagaña, Bryndís Benediktsdóttir, Bertil Forsberg, Karl A Franklin, Vanessa Garcia-Larsen, Bénédicte Leynaert, Eva Lindberg, Jesús Martínez-Moratalla, Nerea Muniozguren-Agirre, Isabelle Pin, Chantal Raherison, Antonio Pereira-Vega, Vivi Schlünssen, Antonia Valentin, Steinar Hustad, Francisco Gómez Real and Payam Dadvand contributed to the conception and design of the work, acquisition or interpretation of data and revision of the draft of the paper for important intellectual content.

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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.

Ethics statement

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Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of Competing Interest

The authors report no declarations of interest.

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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.2020.12.011.

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