**SHORT REPORT**

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# Low digit ratio (2D:4D) is associated with early natural menopause

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**Abstract**

**Objectives:** Intrauterine environmental conditions may affect the number of primordial follicles and in this way the timing of menopause. The aim of the present study was to investigate association patterns between right hand digit ratio, that is, 2D:4D - as an indicator of prenatal androgen and estrogen exposure, and age at menopause.

**Methods:** One hundred sixty-nine women, who had experienced natural menopause, were enrolled in the study. Length of second and fourth finger were measured directly from the palmar side and digit ratios of both hands were calculated. For further analyses the digit ratio of the right hand was used only. Additionally, smoking habits, body weight and body height, body mass index and the number of children were determined. Multiple regression analyses were used to test association patterns between digit ratio and age at menopause, body height, BMI, nicotine consumption as well as number of births and age at menopause.

**Results:** Age at menopause correlated significantly positively with the digit ratio. A more feminine digit ratio is associated with a higher age at menopause, while a low digit ratio, interpreted as a hint of a higher androgen exposure during prenatal phase was associated with a lower age at menopause.

**Conclusions:** Low digit ratio is associated with an earlier onset of natural menopause.

## 1 | INTRODUCTION

Menopause is the time when there has been no menstruations for at least 12 consecutive months. Therefore, menopause signifies the irreversible end of female reproductive capability and represents an important transition in female life history. Age at menopause is not only a marker of reproductive senescence and general aging, but also of general health (Gold, 2011). It is well known, that a later age at menopause is associated with greater life expectancy, reduced risk of cardiovascular disease and atherosclerosis, osteoporosis, but an increased risk of breast, ovarian and endometrial cancer (Gold, 2011). Therefore, the analysis of those factors that influence age at menopause has a special significance. The effects of various socioeconomic, life style and ecological factors on age at menopause are described extensively (Lujan-Barroso et al., 2018). Although it is well established that conditions in the prenatal environment have long lasting effects into postnatal life and even up to adulthood, only

few studies investigated the effects of intrauterine environment on the timing of menopausal transition, such as the association between birthweight, as an indicator of prenatal conditions and age at menopause (Tom, Cooper, Kuh, Guralnik, & Power, 2010). In the present study, the effect of another aspect of prenatal environment on menopausal age was tested. In detail, the early sex hormone exposure was focused on. A putative indicator of prenatal sex hormone levels is the ratio between second and fourth finger lengths (2D:4D) (Galis, Ten Broek, Van Dongen, & Wijnaendts, 2010). Prenatal testosterone correlates negatively with the 2D:4D ratio while prenatal estrogen levels are positively associated with 2D:4D ratio (Manning, 2011). The underlying mechanism for the correlation between 2D:4D and prenatal sex hormone levels may be the action of the Homeobox genes, which control the differentiation of digits but also of the gonads, that is, testes and ovaries (Manning, 2011). The 2D:4D ratio as a proxy of intrauterine sex hormone levels, correlates significantly with various somatic features, fertility parameters, behavioral traits (Fink, Manning, & Neave, 2004; Klimek, Galbarczyk, Nenko, Alvarado, & Jasienska, 2014; Klimek, Galbarczyk, Nenko, & Jasienska, 2016; Lyons, 2013; Manning, Scutt, Wilson, & Lewis-Jones, 1998) but also pathologies such as breast cancer risk (Muller et al., 2012). The aim of the present study was the analysis of association patterns between 2D:4D ratio and age at menopause.

## 2 | METHODS

### 2.1 | Participants

Hundred sixty nine postmenopausal women between the ages 47 and 66 years ($x = 57.2$; $\pm 5.4$) were enrolled in the present study. All participants met the following strict inclusion criteria: experience of natural menopause, last spontaneous menstrual bleeding was at least 1 year ago, no fractures of the index and/or ring finger, no injuries of the fingers, no disease affecting hands or fingers such as arthritis, gout or rheumatism, dominant right hand. Women with a history as competitive athletes were excluded from the sample. All participants were Austrian citizens and of Central European origin.

### 2.2 | Procedure

Recruitment of participants and data collection took place in the consulting rooms of various of Gynecologists, special Gyms for women and via snowball system in Vienna, Austria. Questionnaires containing questions about age at menopause, smoking habits, reproductive history and physical activity patterns were distributed. Age at menopause was determined using retrospective method exclusively. This technique relies on self-reported age at menopause and is reputed not to be exact. We are aware about the limitation of retrospective methods, especially in comparison with the status quo method. Nevertheless, this method was used, because status quo method was not applicable in this study. Smoking habits were estimated by number of cigarettes per week during premenopausal phase. Reproductive history was determined by number of births. Body weight and body height were measured and the body mass index (BMI calculated). Beside the objectives of the study, the right to withdraw at any time was explained.

### 2.3 | Digit ratio

The lengths of the ring fingers and the index fingers of both hands were measured directly from the hand twice by a trained examiner using digital Vernier calipers measuring to 0.01 mm. The mean finger length was calculated. While measuring, the hand of the participant was lying flat on a table, the palm facing up. Finger length was measured from the interphalangeal crease to the top of the fingertip. Digit ratio was calculated by dividing the length of the index finger to the ring finger, that is, 2D:4D. Based on digit ratio value, participants were divided into two groups: low or masculine 2D:4D <1 or high or feminine 2D:4D ≥1, following previously published studies (Klimek et al., 2014, 2016).

### 2.4 | Statistical analyses

Statistical analysis was carried out by using SPSS for Windows Program Version 24.0 (Microsoft Corp.). Descriptive statistics (means, SDs) and Kolmogorov-Smirnov tests were calculated. Since no normal distribution for the majority of metric variables could be assumed, Spearman rank correlation coefficients and Mann Whitney $U$ tests were performed. Additionally, a multiple regression analyses was carried out. $P$ value ≤0.05 was considered significant.

## 3 | RESULTS

Menopause occurred between the ages 40 and 56 years ($x = 49.8 \pm 4.3$). Right hand ($x = 0.983$; $\pm 0.047$) and left-hand digit ratio ($x = 0.981$; $\pm 0.050$) did not differ significantly. Nevertheless, statistically significant associations between digit ratio and age at menopause and number of

**TABLE 1** Association patterns between menopausal age and digit ratio, number of offspring, nicotine consumption and body mass index. Multiple regression analysis

| | $R^2$ | Regression coefficient | Sig. | 95% CI |
|---|---|---|---|---|
| Dependent variable: age at menopause | | | | |
| Digit ratio right hand | 0.36 | 21.41 | $P = 0.001$ | 10.17 to 31.19 |
| Body height | | −0.12 | $P = 0.019$ | −0.21 to −0.02 |
| Body mass index | | 0.05 | $P = 0.490$ | −0.09 to 0.19 |
| Nicotine consumption | | −2.35 | $P < 0.001$ | −3.01 to −1.69 |
| Number of children | | 0.34 | $P = 0.167$ | −0.15 to 0.89 |

**TABLE 2** Comparison between women with a more feminine digit ratio and women with a more masculine digit ratio (Mann–Whitney test)

| | More masculine 2D:4D (<1.0) | More feminine 2D:4D (≥1.0) | Sig. |
|---|---|---|---|
| | mean (SD) | mean (SD) | P value |
| Age at | menopause (years) | 48.8 ± 4.3 | 50.3 ± 4.1 |
| $P = 0.010$ | | | |
| Body height (cm) | 166.6 ± 6.0 | 164.5 ± 4.8 | $P = 0.046$ |
| Body mass index (kg/m²) | 24.23 ± 4.58 | 24.26 ± 3.41 | $P = 0.975$ |
| Number of children | 1.4 ± 1.2 | 1.6 ± 0.8 | $P = 0.003$ |

offspring were found for the right-hand digit ratio only. The digit ratio of the right hand correlated highly significantly positively with the age at menopause ($r = 0.35$; $P = 0.001$), and significantly with the number of children ($r = 0.16$; $P = 0.049$), that is, a more feminine digit ratio was significantly associated with a higher age at menopause and a higher number of children. Furthermore, body height correlated significantly negatively with age at menopause ($r = −0.24$; $P = 0.002$), a significant association between body height and digit ratio however, could not be demonstrated. In a second step, a multiple regression analysis was performed to test the association patterns between age at menopause and digit ratio of the right hand (dominant hand), body height, body mass index, number of cigarettes per week, and number of children.

As demonstrated in Table 1, according to the multiple regression analysis right hand digit ratio was significantly positively associated with the age of menopause, independent of body mass index, body height, number of children and nicotine consumption.

A more masculine digit ratio (<1.0) could be observed among 64.3% of the participants, while only 35.7% exhibited a more feminine digit ratio (≥1.0). The comparison between women showing a more feminine digit ratio and those showing a more masculine one yielded a significantly higher age at menopause ($x = 49.4 \pm 4.5$) vs ($x = 50.3 \pm 4.1$; $P = .04$) and significantly higher number of children ($x = 1.4 \pm 1.2$) vs ($x = 1.6 \pm 0.8$; $P = .003$) among women with a more feminine digit ratio (see Table 2).

## 4 | DISCUSSION

The present study provides information regarding the association patterns between prenatal sex hormone exposure, estimated by digit ratio and timing of natural menopause. To our knowledge, this is the first study focusing on these association patterns. Nevertheless, the effects of intrauterine hormone exposure, estimated by 2D:4D, on female life history traits and fertility patterns were tested in some previous studies. Klimek et al. (2016) reported a higher reproductive success among women with a more feminine digit ratio. In detail, these women had a higher number of offspring, gave birth to their last child at a later age and exhibited a longer reproductive life span. Unfortunately, age at menopause was not considered in this study. Few studies considered the association patterns between 2D:4D and the onset of reproductive phase, such as Matchok (2008) who reported a significant negative association between 2D:4D and age at menarche, indicating a delayed menarche in association with higher androgen exposure during intrauterine phase. Helle (2010), however, found no significant association between menarcheal age and 2D:4D ratio. The present study focused on effects of prenatal sex hormone levels at the end of reproductive phase.

Before we start with a detail discussion of the results, we have to state that we are aware of the limitation of the present study. The sample size is very small, only 169 women corresponded to the strict criterion of inclusion, age at menopause was determined by retrospective method only and prenatal sex hormone exposure was only estimated by digit ratio, which is a putative indicator of prenatal sex hormone exposure. Despite these limitations, a significant association between age at menopause and

2D:4D was found independent of body mass index, and nicotine consumption. A high digit ratio, indicating higher estrogen levels during intrauterine phase was significantly associated with a higher menopausal age. A low digit ratio, indicating high prenatal androgen exposure, in contrast, was significantly associated with a lower age at menopause indicating a decreased reproductive span. This observation corresponds with the findings of Klimek et al. (2016). The present results may be interpreted as an indication of an association between intrauterine environment and age at menopause. From a physiological viewpoint, menopause is the consequence of the progressive depletion of oocytes and the follicle pool (Lambalik, van Disseldorp, de Koning, & Broekmans, 2009). The primordial follicle pool represents the reserve of follicles available and determines in this way the fertility potential of a female (Lebbe & Woodruff, 2013). The maximum number of primordial follicles, 6 to 7 million, is already present at the fifth month of fetal development. From this time onwards, a gradual decrease starts. Consequently, early life development and intrauterine environment may be critical for the timing of menopause. Prenatal sex hormone levels may affect the quantity of primordial follicles but also the decline of them. In the present study 2D:4D is not only significantly associated with age at menopause, but also with the number of children. Higher prenatal estrogen levels are associated with a higher number of children. This result is in accordance with the findings of Klimek et al. (2016).

The analyses of the association patterns between body height, which might be used as an indicator of life circumstances during subadult phase as well as social status and age at menopause as well as digit ratio yielded a significant negative association between body height and age at menopause. Consequently, the taller the women, the earlier menopause occurred. A significant association between body height and digit ratio, however, could not be observed.

Finally, we can conclude that intrauterine sex hormone exposure, indicated by 2D:4D, is significantly associated with menopausal age.

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## AUTHOR CONTRIBUTIONS

S.K. and E.D. conceived and designed the study. E.D., E.P., and S.K. collected the data. J.H. organized data collection. E.D. and S.K. analyzed the data. S.K. wrote the manuscript.

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