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## ASSOCIATION OF DIGIT RATIOS (2D:4D) AND AGE AT MENOPAUSE: POSSIBILITY OF AN ECONOMIZING BIOMARKER

*ABSTRACT: Menopause represents an important transition in female life history. There is considerable variation in the timing of menopause (or age at menopause). Both the genetic factors and environmental exposures (both intra and extra uterine environments) are thought to contribute to an early or later initiation of it. Measurement of "Digit Ratio" (2D:4D) could be used as a non-invasive biomarker of age at menopause as prenatal sex hormones controls the differentiation of digits. As the numbers of postmenopausal women are increasing day by day both globally and nationally therefore researches should focus on this age group of women. Since the vulnerability of getting multiple illnesses is higher among them but very few studies are there on the association of 2D:4D ratio and age at natural menopause and perhaps not undertaken from India. In this backdrop the present attempt is to understand the association of digit ratio (2D:4D) with age at natural menopause from Eastern India (Bengalee Hindu Population). The present study conducted on 187 apparently healthy ever married natural post-menopausal women without nullipara. Structured schedule was used to take socio demographic and reproductive data. Digit ratios has been measured using standard technique. No Bilateral Asymmetry for 2D:4D ratio was found. Significant ( $p < 0.05$ ) difference between low and high digit ratio (2D:4D) with age at menopause was found, indicating significant ( $p < 0.05$ ) association with early age at menopause ( $\leq 50^{\text{th}}$  percentile) and low digit ratio (2D:4D). Hence the present study envisaged, the possibility to use of the digit ratio (2D:4D) as an economizing biomarker to predict/assess age at menopause to ameliorate the health consequences.*

*KEY WORDS: Digit Ratio (2D:4D) - Menopause - Intra Uterine Environment - Biomarker*

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## INTRODUCTION

Reproductive health has occupied a central place in the field of health, illness and medicine. It goes beyond the narrow confines of family planning and encompasses all aspects of human sexuality and reproductive health needs during the various stages of women's lives (Nagar 2020) that is from menarche to menopause. Menopause represents an important transition in female life history (Kirchengast *et al.* 2020). The post-menopausal years are associated with abundant physical (hypertension, heart disease, osteoporosis) and psychological (Dementia, depression, cognitive changes, insomnia) complications (Nagata *et al.* 1998, AARon *et al.* 2002, Meeta *et al.* 2020) such as decline in the overall quality of life (Figure 1). There is considerable variation in the timing of age at natural menopause (Fraser *et al.* 2020). Various factors (Brand *et al.* 2013) can contribute to an early or later initiation of menopause, including genetic factors,

environmental exposures (both intra and extra uterine environments), health related and socio-demographic (Figure 1) factors. The most important determinants of age at natural menopause are considered to be those factors that affect the duration of decline in ovarian follicle reserve (Gold *et al.* 2001) and also prenatal sex hormone exposure (Kirchengast *et al.* 2020). From the aforementioned information it appears that there is an urgent need to comprehend the factors pertained of prenatal sex hormone exposure that might influence the age at natural menopause.

It has long been hypothesized that prenatal sex hormones, particularly testosterone controls the differentiation of digit (Manning *et al.* 1998, Manning 2011). Therefore, accurate measurement of this prenatal testosterone exposure can be made using the "Digit Ratio" (2D:4D) (Manning *et al.*, 1998; Galis *et al.*, 2010) that is the ratio of the relative lengths of the second digit (the "index" finger) and the fourth digit (the "ring"

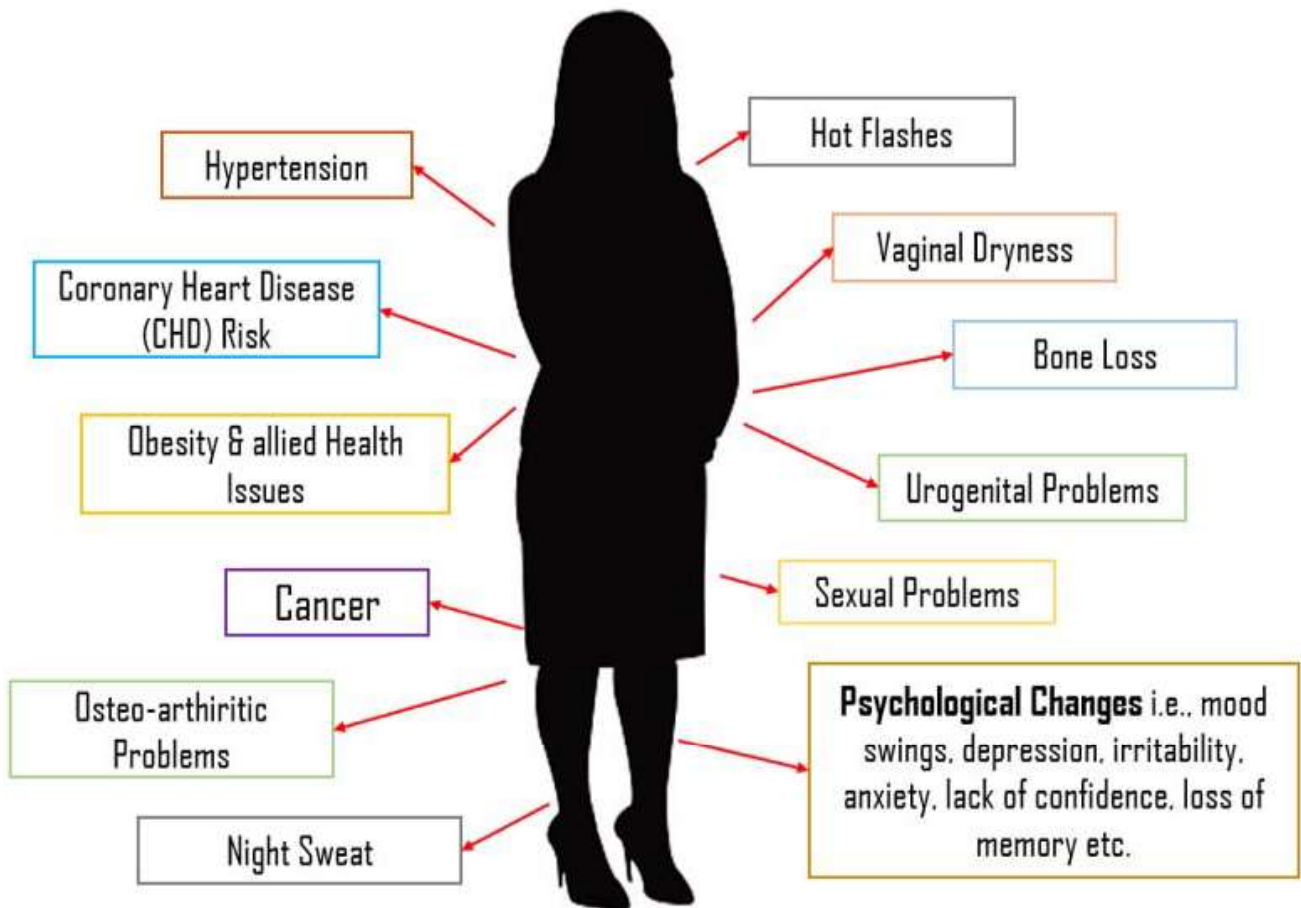


FIGURE 1: Postmenopausal Health Ailments.

finger) (McIntyre 2006, Manning *et al.* 2014). Even in recent study (Butovskaya *et al.* 2021) on large participants from three large world populations with age cohorts reported, the 2D:4D magnitude and its sexual dimorphism (Warrington *et al.* 2018) remained stable throughout the ontogeny, both sex and population origin were permanent reliable predictors of 2D:4D and sex differences in 2D:4D are not an artifact of allometry.

The underlying mechanism for the correlation between 2D:4D and prenatal sex hormone levels may be the action of the Homeobox genes as it controls both the differentiation of digits and gonads (Manning *et al.* 1998, 2000, 2011, Brown *et al.* 2002). It was suggested that a balance of foetal testosterone (FT) and foetal oestrogen (FE) influences the formation of 2D:4D, such that low 2D:4D indicates high FT and low FE and high 2D:4D indicates low FT and high FE (Galís *et al.* 2010) which varies substantially by ethnicity (Hönekopp 2010, Butovskaya *et al.* 202). The 2D:4D ratio as a proxy measure of intrauterine sex hormone levels, correlates significantly with various somatic features, fertility parameters, behavioural traits (Fink *et al.* 2004, Klimek *et al.* 2016), and also non-communicable disease such as breast cancer risk (Muller *et al.* 2012), behavioural disorders (Vladeanu *et al.* 2012, Dey *et al.* 2021) and even in drug dependence (Kim *et al.* 2022) could therefore be used as a non-invasive economizing biomarker of prenatal hormonal exposure.

Since, menarche and menopause are hormone related and plausible imperative influence of prenatal hormonal activities, but few studies were conducted on the association of 2D:4D ratio and age at natural menopause (Muller *et al.* 2011, Kalichman *et al.* 2020, Kirchengast *et al.* 2020) from abroad with mixed results. But Indian Study is lacking and yet to be made. Moreover, the number of postmenopausal women is increasing (Xi *et al.* 2014) both globally and nationally. Thus, health policies in the country should focus on this age group of women, as the vulnerability of getting multiple general health concomitants of reproductive health seems to be higher among the mid-life women.

In this background, the present study attempts to understand the association of digit ratio (2D:4D) with age at natural menopause form Eastern India among the Bengalee Hindu Population.

## MATERIAL AND METHODS

The present study conducted on 187 apparently healthy ever married natural post-menopausal women (mean age

46.78 ± 1.71 Years) without nullipara from Bengalee Hindu Population, India. Prior to the study verbal and written consent were obtained from the participants and Institutional ethical clearance has also sanctioned (CU/EC/02/15/2022-23, dated January 01, 2023).

In addition to that, general socio-demographic variables were obtained. Moreover, information on reproductive data (Age at menarche and menopause) and reproductive performances (parity, Living Children, miscarriages and still births) were collected. Age at menopause was determined using retrospective method exclusively. This technique relies on self reported age at menopause. Although there is limitation of retrospective methods, especially in comparison with the status quo method, but status quo method was not applicable in this study. Digit ratios has been measured using standard technique (Xi *et al.* 2014). After taking the measurements, Technical Error measurement (TEM) was checked (Ulijasek, Kerr 1998) and found with no deviation. 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 there is deviation from normal distribution for the variables, Mann Whitney *U* tests were performed.

Participants were divided into two groups as low 2D:4D ≤ 50<sup>th</sup> percentile and high 2D:4D ≥ 50<sup>th</sup> percentile. Likewise, Participants were also categorized as early age at menopause (≤ 50<sup>th</sup> percentile) and late age at menopause (≥ 50<sup>th</sup> percentile). The cut off was set as p=0.05.

## RESULTS

No Bilateral Asymmetry for 2D:4D ratio was found. Significant (p < 0.05) difference between low and high digit ratio (2D:4D) with age at menopause was found (*Table 1*), indicating significant (p < 0.05) association with early age at menopause (≤ 50<sup>th</sup> percentile) and low digit ratio (2D:4D). Examination on socio-demographic variables, such as parity, educational attainments, and physical activity revealed no association with age at natural menopause.

## DISCUSSION

The present study revealed a significant (p < 0.05) association between age at menopause and 2D:4D, and envisaged low digit ratio is associated with early age at

TABLE 1: Distribution of digit ratio (cm) in respect of age at menopause (years). \*p&lt;0.05.

Variable	Early age at menopause (years) (n=88) 50 <sup>th</sup> percentile	Late age at menopause (years) (n=99) 50 <sup>th</sup> percentile
Mean digit ratio (cm)	0.95 (±0.006)	1.20 (±0.05) *

menopause in this population, plausibly imply that, a low digit ratio suggested high prenatal (intrauterine) androgen exposure which is associated with a lower menopausal age and thereby decreased reproductive span. In contrast, a high digit ratio, denotes higher estrogen levels during intrauterine phase and significantly associated with a higher menopausal age. This result of the present study found to be in corroboration with the earlier findings (Lyons 2013, Kirchengast *et al.* 2020). Nevertheless, the age at menopause and digit ratio, has population variation, therefore, the present study stimulates for more studies from different population group.

Finally, in conclusion it perhaps the situation that intrauterine sex hormone exposure, indicated by 2D:4D, was found to be significantly associated with menopausal age, hence the present study envisaged plausibility of digit ratio as an economizing biomarker of age at menopause for early assessment and amelioration of the health consequences.

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