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Original article

# Association between index-to-ring finger length ratio and risk of severe knee and hip osteoarthritis requiring total joint replacement

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## Abstract

**Objective.** The data are conflicting for the association between the index-to-ring finger length ratio (2D:4D) and the risk of OA. The aim of this cohort study was to examine the relationship between 2D:4D and the risk of severe knee and hip OA requiring total joint replacement.

**Methods.** A total of 14 511 participants in the Melbourne Collaborative Cohort Study had 2D:4D assessed from hand photocopies. The incidence of total knee replacement and total hip replacement between 2001 and 2011 was determined by linking the cohort records to the Australian Orthopaedic Association National Joint Replacement Registry.

**Results.** Over an average 10.5 years of follow-up, 580 participants had total knee replacement and 499 had total hip replacement. Greater right 2D:4D [hazard ratio (HR) 0.91 for a s.d. increase in 2D:4D, 95% CI 0.84, 0.99, $P = 0.03$] and average right and left 2D:4D (HR 0.91 for a s.d. increase in 2D:4D, 95% CI 0.84, 0.99, $P = 0.02$) were associated with a reduced incidence of total knee replacement. These associations persisted when participants whose fingers had any features that might have affected the validity of 2D:4D measurements were excluded. No significant associations were observed between 2D:4D and the incidence of total hip replacement.

**Conclusion.** A lower 2D:4D is associated with an increased risk of severe knee OA requiring total knee replacement, but not the risk of severe hip OA. The underlying mechanisms for the association warrant further investigation.

**Key words:** index-to-ring finger length ratio, osteoarthritis, total knee replacement, total hip replacement.

CLINICAL SCIENCE

## Introduction

OA is a major public health problem with significant morbidity and disability associated with OA of the knees and hips [1]. Hormonal factors are thought to play a role in the pathogenesis of OA, and possibly account for some of the well-described sex differences in the prevalence of OA [2, 3].

Anthropological studies suggest that there are consistent sex differences in the ratio of the lengths of the index (2D) and ring (4D) fingers (expressed as 2D:4D) such that men have a lower average 2D:4D than women [4, 5]. 2D:4D has been suggested as a proxy indicator of prenatal testosterone levels, with low 2D:4D reflecting higher *in utero* testosterone exposure [4–7]. There is evidence that 2D:4D reflects the effects of prenatal sex steroids

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on 19 skeletogenic genes [8] and 2D:4D is strongly associated with the skeletogenic *SMOC1* gene [9], suggesting a possible underlying genetic determinant of 2D:4D.

Previous studies of 2D:4D and the risk of knee OA have yielded inconsistent results. These are summarized in Table 1. While two case–control studies showed a linear relationship between lower 2D:4D and increased risk of radiographic knee OA [10, 11] and one cross-sectional study found type 3 finger length pattern (longer ring finger than index finger) to be associated with increased risk of total knee replacement (TKR) for OA [12], the Framingham study found no association between 2D:4D and the risk of radiographic knee OA [13]. There are more consistent data for the association between 2D:4D and the risk of hip OA. One case–control study found no significant association between 2D:4D and the risk of radiographic hip OA [10], and a recent cross-sectional study showed no association between finger length patterns and the risk of total hip replacement (THR) for OA [12]. Due to the nature of these studies, being case–control or cross-sectional, temporal relationships cannot be examined. Identification of the association between 2D:4D and OA risk from large cohort studies would provide stronger evidence and thus increase understanding of disease pathogenesis.

One method for defining OA is to use total joint replacement, which signifies severe clinical knee and hip OA relevant to the symptomatic disease burden and economic impact of OA [14, 15]. Thus the aim of this study was to determine whether 2D:4D was associated with the risk of severe knee or hip OA requiring TKR or THR in a large cohort study.

## Patients and methods

### Study participants

The Melbourne Collaborative Cohort Study (MCCS) is a prospective cohort study of 41 514 people (24 469 women) between 27 and 75 years of age (99.3% age 40–69 years) at baseline [16]. Participants were recruited via the electoral rolls (enrolment to vote is compulsory for Australian adults), advertisements and community announcements in local media between 1990 and 1994 in the Melbourne metropolitan area. All participants provided written informed consent and the study protocol was approved by the Cancer Council Victoria Human Research Ethics Committee.

Participants who attended face-to-face follow-up between 2003 and 2009 and had their hands photocopied were eligible for inclusion in this study ($n = 14\,917$); 406 (3%) were excluded from the current analysis because they died or left Australia before 1 January 2001, reported a joint replacement performed before 1 January 2001 at the MCCS follow-up, left Australia before the date of a primary joint replacement or had a revision surgery as the first procedure recorded in the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR). These exclusions left 14 511 participants available for analysis.

### Demographic, lifestyle factors and physical measurements

At baseline, information was obtained on demographic and lifestyle factors, including date of birth, country of birth (Australia, United Kingdom, Italy, Greece), smoking status, alcohol consumption, physical activity during leisure time and highest level of education. Height and weight were measured according to written protocols using standard procedures [17]. Weight was measured to the nearest 0.1 kg using digital electronic scales and height was measured to the nearest 1 mm using a stadiometer. BMI was calculated as weight in kilograms divided by the square of height in metres.

### Measurement of 2D:4D

During the face-to-face follow-up conducted during 2003–9, participants had their hands photocopied for the purpose of measuring 2D:4D. The length of the index and ring fingers were measured from photocopies of the surface of the hand using vernier callipers with a resolution of 0.01 mm [18]. Measurements were taken from the tip of the finger to the basal crease. Where two creases were visible at the base of the digit, the crease proximal to the palm was chosen. The length of the index finger was divided by the length of the ring finger to obtain the 2D:4D. Any features that made measurement difficult or might have affected the validity of the measurements, such as finger deformities potentially due to hand arthritis or injuries, were also recorded. The measurement was undertaken by a team of trained research assistants at Cancer Council Victoria. One hundred photocopies were measured by each research assistant twice to assess the inter- and intraobserver reliability of the digit measurements. Inter- and intraobserver reliability was high for raw digit measurements, with intraclass correlation coefficients (ICCs) for left and right index and ring fingers all being >0.95. The ICCs for 2D:4D were slightly lower than those for raw digit measurements (0.80 for right and 0.73 for left 2D:4D), but still suggest that the observed variability in digit ratio is largely due to between-individual differences rather than measurement error [18].

### Identification of incident primary knee and hip joint replacement

Cases were identified from the AOA NJRR. The registry began data collection in September 1999, with staged implementation across the Australian states and territories. Victoria commenced data collection in 2001, and national data on arthroplasty procedures in Australia is available from 2002 [19]. Hip and knee joint replacements are monitored with detailed information available on prostheses, demographics, reasons for revisions and types of revision. Data are collected from both public and private hospitals and validated using a sequential multilevel matching process against State and Territory Health Department unit record data. Following the validation process and retrieval of unreported records, the registry collects an almost complete set of data relating to hip and knee replacement in Australia [20].

TABLE 1 Association between 2D:4D and OA, data from three published studies

| Author and year | Study design | Participants | Measurement of exposure | Measurement of outcome | Main results |
|---|---|---|---|---|---|
| Zhang *et al.* 2008 [10] | Case–control study | 2049 cases with symptomatic knee or hip OA seen by an orthopaedic surgeon or rheumatologist. 1123 controls undergoing i.v. urography | Visual classification of finger patterns. 2D:4D ratio measured from radiographs of both hands by taking the mean of the ratio of the right and left hand | Radiography of the knee before knee joint replacement due to OA. Radiography of the pelvis for hip OA | The type 3 finger pattern (longer ring finger than index finger) was associated with knee OA, and the risk was greater in women. There was a linear relationship between both the 2D:4D ratio and the risk of knee OA. The risk of hip OA was inconsistent |
| Ferraro *et al.* 2009 [11] | Nested case–control study from the Clearwater OA Study | 236 cases with knee OA. 236 controls randomly selected | Visual classification of finger patterns. 2D:4D ratio measured from digitized films of hand radiographs | Radiographic knee OA | The type 3 finger pattern was associated with knee OA. Women demonstrated a stronger association of visual type 3 finger pattern and knee OA |
| Haugen *et al.* 2011 [13] | Cross-sectional study | 1039 participants from the Framingham community cohort | Right 2D:4D phalangeal and metacarpal bones measured from hand radiographs. Left hand was measured if measurement of the right hand was not possible. | Radiographic knee OA. Self-reported knee injury. Meniscal lesions from MRI | There were no significant associations between 2D:4D and radiographic knee OA, severe symptomatic knee OA or meniscal lesions |

TKR: total knee replacement; 2D:4D: index-to-ring finger length ratio.

Identifying information for MCCS participants, including first name, last name, date of birth and gender, was provided to the AOA NJRR in order to identify those participants who had had a primary or revision joint replacement between 1 January 2001 (commencement of Victorian data collection) and 31 December 2011. The matching was performed on these data using U.S. Bureau of the Census Record Linkage software. Exact matches were identified and probabilistic matches were reviewed. The AOA NJRR forwarded this information to the MCCS, which was added to the MCCS database. The data linkage was approved by the Cancer Council Victoria Human Research Ethics Committee and Monash University Human Research Ethics Committee.

### Statistical analysis

Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% CI for the first recorded TKR and THR associated with each 2D:4D measurement, with age as the time scale. Follow-up for TKR and THR (i.e. calculation of person-time) began at 1 January 2001 and ended at the date of the first TKR or THR for OA or the date of censoring. Participants were censored at either the date of the first TKR or THR for indications other than OA, the date of death, the date they left Australia or the end of follow-up (i.e. 31 December 2011, when ascertainment of joint replacement by AOA NJRR was complete), whichever came first.

The right and left 2D:4D were examined separately. Due to the strong correlation between the right and left 2D:4D ($r = 0.58$ in this sample), the average of the right and left 2D:4D was also examined. 2D:4D was examined as a standardized continuous variable (measured 2D:4D divided by the sex-specific s.d. of the ratio). 2D:4D was also categorized into approximate sex-specific tertiles based on the analysis sample. The highest tertile was used as the referent category. Linear associations between the 2D:4D and the risk of TKR and THR were investigated by comparing regression models with the 2D:4D as a categorical variable and a pseudo-continuous variable (using the median value in each 2D:4D category) using the likelihood ratio test. Tests for trends across categories of the 2D:4D (calculated using the 2D:4D as a pseudo-continuous variable) were presented only when there was no statistical evidence of a departure from a linear association with the risk of joint replacement. To assess whether associations between 2D:4D and the risk of total joint replacement were modified by sex or country of birth, interaction terms between sex or country of birth and 2D:4D were fitted and models with and without these interaction terms were compared using the likelihood ratio test. Sensitivity analyses were also conducted excluding any participants whose fingers had features that might have affected the validity of the measurements. All analyses were adjusted for BMI and country of birth and stratified by sex.

Tests based on Schoenfeld residuals and graphical methods using Kaplan–Meier curves showed no evidence that proportional hazard assumptions were violated. All statistical analyses were performed using Stata/IC 12.1 (StataCorp, College Station, TX, USA).

## Results

Over the 10.5 years (s.d. 1.7) of follow-up, 580 incident TKRs and 499 incident THRs were identified. The characteristics of the study participants are shown in Table 2. When the 2D:4D ratios were examined as continuous variables, greater right and average 2D:4D was associated with a reduced incidence of TKR (HR 0.91, 95% CI 0.84, 0.99 for both) with no significant association observed for left 2D:4D (Table 3). When the 2D:4D ratios were examined as categorical variables, there was a linear trend for an association between left and average 2D:4D and the incidence of TKR, with a lower ratio being associated with an increased risk of TKR. For left 2D:4D, the HR was 1.15 (95% CI 0.93, 1.42) for middle tertile and 1.28 (1.04, 1.57) for the lowest tertile. For average 2D:4D, the HR was 1.01 (95% CI 0.82, 1.26) for middle tertile and 1.29 (1.05, 1.59) for the lowest tertile. No significant associations were observed between 2D:4D and the incidence of THR. There was no evidence that sex or country of birth

**Table 2** Characteristics of study participants

| | TKR ($n = 580$) | THR ($n = 499$) | Without knee or hip replacement ($n = 13432$) |
|---|---|---|---|
| Age at study entry (1990–4), years | 57.7 (7.1) | 57.5 (7.5) | 53.8 (8.3) |
| Female, *n* (%) | 356 (61.4) | 314 (62.9) | 7928 (59.0) |
| BMI at study entry, kg/m$^2$ | 29.5 (4.8) | 27.3 (4.6) | 26.7 (4.2) |
| Country of birth, *n* (%) | | | |
| Australia/UK | 470 (81.0) | 426 (85.4) | 9603 (71.5) |
| Italy/Greece | 110 (19.0) | 73 (14.6) | 3829 (28.5) |
| Right 2D:4D | 0.950 (0.042) | 0.952 (0.038) | 0.956 (0.037) |
| Left 2D:4D | 0.957 (0.040) | 0.960 (0.037) | 0.961 (0.037) |
| Average 2D:4D | 0.954 (0.035) | 0.956 (0.033) | 0.958 (0.033) |

Data presented as mean (s.d.) unless otherwise indicated. 2D:4D: index-to-ring finger length ratio; TKR: total knee replacement; THR: total hip replacement.

modified the association between 2D:4D and the incidence of TKR or THR.

There were 830 participants whose fingers had features that might have affected the validity of the measurements. Sensitivity analyses were performed by excluding these participants (Table 4). Among the remaining 13 681 participants, there were 524 TKRs and 454 THRs. The estimates were similar to those obtained from the complete sample. Greater right (HR 0.89, 95% CI 0.81, 0.97, $P = 0.01$) and average (HR 0.90, 95% CI 0.83, 0.99, $P = 0.03$) 2D:4D were associated with a reduced incidence of TKR, with consistently significant associations when the ratios were examined in tertiles. For right 2D:4D, the HR was 0.97 (95% CI 0.77, 1.21) for the middle tertile and 1.29 (1.05, 1.60) for the lowest tertile. For average 2D:4D, the HR was 0.98 (95% CI 0.78, 1.23) for the middle tertile and 1.30 (1.05, 1.61) for the lowest tertile. No significant association was seen for left 2D:4D and TKR. There were no significant associations between 2D:4D and the incidence of THR.

There was no association between 2D:4D and participation in vigorous physical activity at recruitment. Including physical activity in the regression models did not alter the results (data not shown).

**Table 3** Association between 2D:4D and risk of total knee or hip replacement for OA ($n = 14\,511$)

| | TKR | | THR | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Right 2D:4D | 0.91 (0.84, 0.99) | 0.03 | 0.95 (0.86, 1.03) | 0.21 |
| Tertile 3 | 1 | | 1 | |
| Tertile 2 | 0.94 (0.76, 1.16) | | 1.15 (0.91, 1.44) | |
| Tertile 1 | 1.20 (0.98, 1.46) | 0.06* | 1.25 (1.00, 1.56) | 0.05* |
| Left 2D:4D | 0.93 (0.86, 1.01) | 0.09 | 0.99 (0.91, 1.08) | 0.84 |
| Tertile 3 | 1 | | 1 | |
| Tertile 2 | 1.15 (0.93, 1.42) | | 0.92 (0.74, 1.14) | |
| Tertile 1 | 1.28 (1.04, 1.57) | 0.02* | 0.95 (0.77, 1.18) | 0.65* |
| Average 2D:4D | 0.91 (0.84, 0.99) | 0.02 | 0.97 (0.89, 1.06) | 0.49 |
| Tertile 3 | 1 | | 1 | |
| Tertile 2 | 1.01 (0.82, 1.26) | | 0.98 (0.78, 1.22) | |
| Tertile 1 | 1.29 (1.05, 1.59) | 0.01* | 1.12 (0.90, 1.39) | 0.30* |

2D:4D: index-to-ring finger length ratio; TKR: total knee replacement; THR: total hip replacement; HR: hazard ratio. All models adjusted for BMI and country of birth and stratified by sex. *P for trend.

**Table 4** Association between 2D:4D and risk of total knee or hip replacement for OA in sensitivity analyses ($n = 13\,681$)

| | TKR | | THR | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Right 2D:4D | 0.89 (0.81, 0.97) | 0.01 | 0.94 (0.86, 1.04) | 0.22 |
| Tertile 3 | 1 | | 1 | |
| Tertile 2 | 0.97 (0.77, 1.21) | | 1.11 (0.88, 1.41) | |
| Tertile 1 | 1.29 (1.05, 1.60) | 0.01* | 1.23 (0.98, 1.55) | 0.08* |
| Left 2D:4D | 0.94 (0.87, 1.03) | 0.20 | 0.98 (0.89, 1.07) | 0.65 |
| Tertile 3 | 1 | | 1 | |
| Tertile 2 | 1.10 (0.88, 1.37) | | 0.93 (0.74, 1.17) | |
| Tertile 1 | 1.21 (0.98, 1.51) | 0.08* | 0.97 (0.77, 1.21) | 0.77* |
| Average 2D:4D | 0.90 (0.83, 0.99) | 0.03 | 0.96 (0.87, 1.06) | 0.40 |
| Tertile 3 | 1 | | 1 | |
| Tertile 2 | 0.98 (0.78, 1.23) | | 0.93 (0.74, 1.18) | |
| Tertile 1 | 1.30 (1.05, 1.61) | 0.01* | 1.11 (0.88, 1.40) | 0.34* |

2D:4D: index-to-ring finger length ratio; TKR: total knee replacement; THR: total hip replacement; HR: hazard ratio. All models adjusted for BMI and country of birth and stratified by sex. *P for trend.

## Discussion

To our knowledge, this is the first cohort study examining the relationship between 2D:4D and the incidence of severe OA requiring TKR or THR. We found that lower 2D:4D was associated with an increased incidence of TKR but not THR.

We showed that lower 2D:4D was associated with an increased incidence of TKR when the ratio was examined on either the right or left hand or the average. The findings were consistent with those from two previous case–control studies that showed an association between lower 2D:4D and an increased risk of radiographic knee OA [10, 11] when 2D:4D was measured from hand radiographs using the average ratio of both hands [10] or the ratio of the right hand [11]. Although there is no cohort study examining the temporal relationship between 2D:4D phalangeal ratios and hand OA, the findings from the Framingham OA study suggest that hand OA may contribute to a lower 2D:4D phalangeal ratio, as the index finger is more frequently affected by OA than the ring finger, due to joint space narrowing, bone attrition, malalignment or deformity [21]. Neither of the two case–control studies took into account whether the participants had hand OA, which might be an important confounder [10, 11], whereas in our study the associations for right and average 2D:4D persisted when participants with finger deformities potentially due to arthritis or injury were excluded from analysis. We observed a stronger association of right 2D:4D than left 2D:4D with TKR risk. This is supportive of this being a real effect, as this pattern is common in 2D:4D work and there is evidence that right 2D:4D is inversely associated with prenatal exposure and sensitivity to testosterone, with weak evidence for any association with left 2D:4D [4, 22]. Our findings were also supported by a recently published cross-sectional study showing that type 3 finger length pattern was associated with an increased risk of TKR for OA, with the results persistent in sensitivity analyses of participants with no evidence of hand OA on photographs [12]. However, in this study finger length ratios were assessed visually on photographs of both hands with no actual measurement of finger length, which is prone to misclassifications of finger length pattern [12]. In contrast, the Framingham study, which assessed 2D:4D on right hand radiographs, did not find an association between 2D:4D and a risk of knee OA [13]. A significant difference with our study was that we examined severe knee OA as defined by needing a TKR, whereas the Framingham study used radiographic knee OA as the outcome measure, which may have reduced the sensitivity for detecting this relationship. In support of this, the Framingham study found a non-significant trend for lower 2D:4D to be associated with an increased risk of knee OA in sensitivity analyses of men without evidence of hand OA [adjusted odds ratio (OR) 1.76, 95% CI 0.87, 3.57, $P$ for trend = 0.11] [13]. The Framingham study was cross-sectional and had a modest sample size, which may have reduced its power to show an effect.

While the Framingham study found an association between lower 2D:4D and an increased risk of knee injury [13], we did not find an association between 2D:4D and participation in vigorous activity, or evidence to suggest that the association between 2D:4D and the risk of knee OA can be explained by physical activity. This finding is consistent with the findings of the Genetics of Osteoarthritis and Lifestyle Study [10]. Although there is some evidence that sporting ability and achievement in sports and athletics are negatively related to 2D:4D [23], this might not reflect levels of regular physical activity in the general population. In our study, the measure of physical activity did not directly assess sporting ability, nor did the measure report past physical activity, which may also be important in this regard.

We found an increased incidence of severe knee OA but no association for severe hip OA in relation to lower 2D:4D. This is consistent with the findings from the Genetics of Osteoarthritis and Lifestyle Study [10] and the Age, Gene/Environment Susceptibility (AGES) Reykjavik study [12], which found that measured 2D:4D or visually assessed finger length pattern was related to knee OA but not hip OA. The site difference in OA risk in relation to 2D:4D may be explained, at least in part, by the different susceptibility of knee and hip OA in response to injury. The Johns Hopkins Precursors Study, a prospective study conducted in medical students, revealed that early knee injuries were associated with a 2.95 (95% CI 1.35, 6.45) times relative risk of symptomatic knee OA, with no association between hip injuries and later development of hip OA [24]. Moreover, this study reported higher prevalence and incidence of knee injury than hip injury [24], indicating that the knee is more prone to injury than the hip. There is evidence for effects of hormones on the growth of bone, cartilage and soft tissue [25, 26]. It may be that the differences seen in the relationship between 2D:4D and the risk of knee and hip OA reflect the increasingly described differences in the mechanisms of disease in the two joints [27, 28].

Our study has several strengths and limitations. The large size of the population-based cohort with complete follow-up in terms of total joint replacement since 2001 and inclusion of participants from different ethnic backgrounds are the major strengths. Digit measurements were made with a high degree of reliability by trained research assistants. Additionally we examined the relationship between 2D:4D and the risk of knee and hip OA in the same population, for right and left 2D:4D separately, and demonstrated that the mechanism of disease differs in these joints. One of the limitations is that we used photocopies of the hand, which tend to yield lower 2D:4D values compared with direct measurement from hand radiographs [29]. However, we used this measurement technique in all the participants. This would tend to result in non-differential misclassification of 2D:4D, which is not related to the outcome. Including participants whose fingers had features that might have affected the validity of the measurements in the analysis would have resulted in non-differential misclassification of 2D:4D categories, which may have underestimated the observed associations. Thus sensitivity analyses were performed by excluding these participants and the results were similar. Another limitation of our study is that not all participants attended the follow-up during 2003–9, thus we do not have 2D:4D measures available for every participant. While the 2D:4D measurements were made between 2003 and 2009, the follow-up for total joint replacement commenced in 2001 and ended in 2011. Thus the 2D:4D data are a mixture of prospective and retrospective collection. As there is evidence that 2D:4D is stable over time [6], we consider it appropriate to analyse these data prospectively. Defining OA based on total joint replacements identifies partial evidence of the true problem. Whether patients undergo total joint replacement as a treatment of OA may be influenced by a number of factors, such as access to health care, physician bias and patient-level factors, in addition to disease severity [30]. Thus we performed the analysis on an age scale, stratified by sex and adjusted for country of birth to counter this issue.

In conclusion, in a large cohort study of middle-aged and older people, lower 2D:4D is associated with an increased risk of severe knee OA requiring TKR. This is not observed for severe hip OA. Although these results may be explained in part by joint injuries associated with high-level physical activity in those with lower 2D:4D and the greater susceptibility of knee OA in response to injury than hip OA, they may also reflect hormonal influences on the growth of bone, cartilage and soft tissue, which warrants further investigation.

**Rheumatology key messages**

- Lower index-to-ring finger length ratio (2D:4D) is associated with an increased risk of severe knee OA.
- 2D:4D is not associated with the risk of severe hip OA.
- There may be different mechanism of disease for knee and hip OA.

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