HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2024 December ; 76(12): 1733–1743. doi:10.1002/acr.25416.

Family History of Arthritis, Osteoporosis, and Carpal Tunnel Syndrome and Risk of These Conditions Among US Adults

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Abstract

Objective.—The aim was to estimate odds ratios (ORs) of associations between family history of arthritis, osteoporosis, and carpal tunnel syndrome and prevalence in a real-world population, uncovering family histories of related conditions that may increase risk because of shared heritability, condition pathophysiology, or social/environmental factors.

Methods.—Using data from 156,307 participants in the All of Us (AoU) Research Program, we examined associations between self-reported first-degree family history of five common types of arthritis (fibromyalgia, gout, osteoarthritis [OA], rheumatoid arthritis, and systemic lupus erythematosus [SLE]), osteoporosis, and carpal tunnel syndrome and prevalence. We evaluate associations across seven conditions and performed stratified analyses by race and ethnicity, sex, socioeconomic differences, body mass index, and type of affected relative.

Results.—More than 38% of AoU participants reported a family history of any arthritis, osteoporosis, or carpal tunnel syndrome. Adults with a family history of any arthritis, osteoporosis, and carpal tunnel syndrome exhibited 3.68 to 7.59 (4.90, on average) odds of having the same condition and 0.70 to 2.10 (1.24, on average) odds of having a different condition. The strongest associations observed were between family history of OA and prevalence of OA (OR 7.59; 95% confidence interval [95% CI] 7.32–7.88) and family history of SLE and prevalence of

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Rasooly confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Helsinki Declaration requirements.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The funders had no role in the study design, analysis, decision to publish, or preparation of this article.

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25416.

Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25416).

SLE (OR 6.34; 95% CI 5.17–7.74). We additionally uncover race and ethnicity and sex disparities in family history associations.

Conclusion.—Family history of several related conditions was associated with increased risk for arthritis, osteoporosis, and carpal tunnel syndrome, underscoring the importance of family history of related conditions for primary prevention.

INTRODUCTION

Arthritis is a leading cause of chronic pain and work disability among US adults[1-3]; it affects more than one in five US adults (21.2%)[4] and is projected to affect 78.4 million adults by 2040.[5] "Arthritis" is a general term for more than 100 conditions that affect the joints and tissues around the joint. Primary examples include fibromyalgia, gout, osteoarthritis (OA), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). Further, bone and joint conditions tend to cluster together. Individuals with an inflammatory form of arthritis, such as RA or SLE, are at an increased risk for osteoporosis, a chronic disease of progressive bone loss characterized by deterioration of bone microarchitecture leading to fractures, and carpal tunnel syndrome, a condition that causes pain, weakness, and numbness in the hand and wrist.[6-9] The early identification and management of arthritis, osteoporosis, and carpal tunnel syndrome is vital for preventing serious, lifelong complications and to reduce the ongoing public health burden of these conditions.

Family history reflects the effects of shared genetics, physical and social environment, lifestyle, and habits in a family, and is an established risk factor for arthritis and osteoporosis.[10-14] Genome-wide association studies have uncovered common variants that may increase risk of arthritis[15-17] and osteoporosis.[18] Although the pathophysiology of carpal tunnel syndrome remains largely obscure, 39% of cases have familial occurrence of carpal tunnel syndrome,[19] and genetic loci associated with the condition suggest genetic factors contribute to disease pathogenesis.[20] Family history can determine an individual's risk for developing disease beyond genetic factors,[21] capturing environmental and behavioral factors, including smoking, obesity, low physical activity, intergenerational poverty, intergenerational exposure to high risk occupations, and access to health care, that may contribute to disease progression. For example, it has been implicated that for RA, immune dysregulation and the presence of RA-associated autoantibodies are triggered by lung inflammation.[22-24] Early-life exposure to smoking[25] and air pollution,[26] which can be captured by family history, may exert a direct influence on RA risk by triggering biologic processes that produce RA-associated autoantibodies years before the onset of RA symptoms. Further, family history of interconnected conditions may increase risk for arthritis, osteoporosis, and carpal tunnel syndrome because of shared genetic background and overlapping disease mechanisms. For example, RA shares genetic overlap with osteoporosis[27] and SLE,[28] and carpal tunnel syndrome has a strong genetic correlation with OA.[20] In addition to shared genetics, these conditions are pathophysiologically linked. Arthritis involves chronic inflammation, which can lead to bone resorption and degradation of joint structures, increasing the risk of osteoporosis, and may play a role in the development of carpal tunnel syndrome.[8,29] Family history of related conditions may increase disease susceptibility through shared hereditary factors or disease mechanisms.

Motivated to better understand the potential role of familial predisposition in the development of these conditions, we extend prior studies that have assessed family history associations of these conditions using a single family history[11,30-32] or a single disease outcome[33] to examine a broad range of family history predictors and outcomes. The aim of this study is to examine the association between self-reported first-degree family history and personal history of five common types of arthritis (fibromyalgia, gout, OA, RA, and SLE),[34] osteoporosis, and carpal tunnel syndrome. We leverage data from the All of Us (AoU) Research Program to perform a "family history-wide association study" (FamWAS), a framework for comprehensively and systematically evaluating a range of family histories for their association with a disease outcome.[35] Inspired by the genome-wide association study,[36] which tests genetic variants across the genome to find associations with a disease outcome, FamWAS takes an untargeted, agnostic approach to assessing the contribution of family history to disease, enabling us to discover novel associations and to recapitulate known relationships.[35,37] Understanding disease risk may allow clinicians to better tailor targeted preventative approaches for patients at risk for developing these conditions and influence lifestyle changes that can reduce disease outcomes.[38,39]

Although arthritis affects people of all ages and backgrounds, certain groups of the population bear a disproportionate burden. Epidemiologic data have revealed racial and ethnic disparities for SLE, including higher incidence and prevalence of SLE among Black Americans and Hispanic Americans compared with non-Hispanic White Americans.[40] Although socioeconomic factors have been found to influence the development of RA,[41] disparities associated with RA have not been well studied compared with lupus, leaving a lack of clarity regarding the extent of disparities or the optimal interventions to address social determinants of health.[42] Several of these conditions display a distinct sex imbalance, including a 9:1 female-to-male ratio for SLE,[40] 3:1 female-to-male ratio for RA,[43] and 3:1 female-to-male ratio for carpal tunnel syndrome,[44] with unclear reasons for the overrepresentation of women. Further, genetics studies on these conditions have been predominantly performed in European-ancestry populations, limiting use across diverse populations, which can translate to diminished disease prediction and treatment for individuals of minority or under-represented ancestries.[10,18,20,45] As part of its goal, the AoU has emphasized enrollment of racial and ethnic minorities and individuals who have been historically under-represented in biomedical research (UBR) across various diversity categories including ancestry, age, sexual and gender minorities, income, educational attainment, access to care, geography, and disability.[46] To address disparities among these seven conditions, we evaluate family history associations in stratified groups by race and ethnicity, sex, income, body mass index (BMI), UBR status, and type of affected relative. We examined the role of BMI because obesity is a shared comorbidity of arthritis, osteoporosis, and carpal tunnel syndrome. Excess body weight increases mechanical stress on joints, negatively impacts bone density,[47] and contributes to the compression of the median nerve in the wrist.[48] Overall, our study improves our understanding of shared familial risk among seven bone and joint conditions, revealing differences among individuals by sex, race and ethnicity, BMI, and socioeconomic and social determinants of health factors, which can help identify individuals at elevated risk and can improve public health by promoting risk-based screening and prevention strategies.

MATERIALS AND METHODS

Data availability.

The data that support the findings of this study are openly available at the National Institutes of Health (NIH) AoU Research Program (https://www.researchallofus.org).

Study sample.—We conducted our investigation using data from the AoU Research program, a national effort sponsored by the NIH that has built a comprehensive research resource composed of personal medical and family history surveys, biosamples, and genetics data covering a diverse and inclusive population across the United States.[49] The AoU has a national network of research program partners and community partners focused on recruitment, which include regional medical centers, federally qualified health centers, and the Veterans Health Administration.[49] Additionally, participants are able to enroll in the AoU through a direct-volunteer mechanism, which allows individuals who are not patients in a health care provider organization to enroll in the AoU, complete the survey of demographic information, and provide physical measurements and biospecimen collection at a designated health clinic or facility.[49]

The AoU database Version 7 contains data on 413,457 participants. We removed participants with missing demographic, personal medical conditions, or family history information, resulting in a study sample of 156,307 participants (37.80% of total), all of whom had complete demographic data and who had completed the Personal and Family Health History survey. The data were accessed via the Curated Data Repository Release for Controlled Tier (C2022Q4R9), which includes deidentified participant data collected between May 30, 2017, and July 1, 2022. We accessed the AoU data using the Researcher Workbench, which is a cloud-based platform where registered researchers can access, store, and analyze data using an integrated Jupyter Notebook. All participants of the AoU Research Program have provided informed consent. The AoU surveys and protocols have been previously described[50] and have been approved by the AoU Institutional Review Board.

Main variables.—We obtained participant data on predictor and outcome measures from the Personal and Family Health History survey, which includes self-reported information about the biologic family history and personal medical history of participants. The predictors in this analysis were a self-reported first-degree family history for any of the following conditions: carpal tunnel syndrome, fibromyalgia, gout, OA, osteoporosis, RA, and SLE. Specifically, family history was determined by the following question: “Have you or anyone in your family ever been diagnosed with the following bone, joint, and muscle conditions? Think only of the people you are related to by blood.” Participants who responded to this question with “Mother,” “Father,” “Sibling,” “Daughter,” or “Son” were identified as having a self-reported first-degree biologic family history (Yes/No). The selection of the seven conditions was based on a prespecified list of “bone, joint, and muscle conditions” listed in the survey.

The outcomes in this analysis were a personal medical history (Yes/No) for any of the seven conditions with family history information. Specifically, participants who responded “Self” to the survey question “Have you or anyone in your family ever been diagnosed with the

following bone, joint, and muscle conditions?," with the options for carpal tunnel syndrome, fibromyalgia, gout, OA, osteoporosis, RA, and SLE, were identified as cases for our study.

Demographics and covariates.

We ascertained participant demographic information from the Basics survey. We adjusted models for participant age, sex-at-birth, racial and ethnic categories, and income. We calculated age by subtracting birth-date from the date of the survey. Sex-at-birth included "female" and "male"; participants who reported "intersex" or "none of these" were removed from analyses because of a sample size less than 20 participants in accordance with the AoU Data and Statistics Dissemination Policy. Survey responses to the question "Which categories describe you? Select all that apply. Note, you may select more than one group" (options included "White," "Black," "Asian," "Hispanic," and "Other") were collapsed into five racial and ethnic categories (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic, and other or multiple races). Income was ascertained by the survey question "What is your annual household income from all sources" (options included <$25,000, $25,000–$75,000, $75,000–$100,000, >$100,000 annual income). To calculate BMI, we used participant height and weight, which was obtained by being collected in a clinical setting, via extrapolation from the electronic health record (EHR), and/or via self-reporting. Based on the AoU Guide for Diversity and Inclusion,[46] we identified participants who are UBR by examining participant data across the following 10 diversity categories: race and ethnicity (individuals who identify as other than White and non-Hispanic), age (adults ≥65 years), annual household income (individuals with household incomes ≤200% of the Federal Poverty Level), physical or cognitive disability, educational attainment (individuals with less than a high school degree or equivalent), gender identity (individuals who identify as sexual or gender minority), sex assigned at birth (individuals who are neither male nor female), sexual orientation (individuals who do not identify as straight), geography (individuals who live in rural and nonmetropolitan areas), and individuals with inadequate access to medical care.

Statistical analysis.

We used logistic regression to estimate the adjusted odds ratio (OR) of family history of arthritis, osteoporosis, and carpal tunnel syndrome for personal medical history of each condition, controlling for age, sex, racial and ethnic category, income, and BMI, and reported on findings with a P value of less than 0.05. Age was treated as a continuous variable, and sex-at-birth, racial and ethnic categories, income, and BMI were treated as categorical variables. The reference groups for each categorical variable, respectively, were male, White non-Hispanic, above $100,000 annual income, and BMI between 18.5 and 24.9. Racial, ethnic, sex, and socioeconomic disparities exist among several of these conditions.[42,51,52] To evaluate health disparities in familial influences on arthritis, osteoporosis, and carpal tunnel syndrome, we computed ORs in stratified AoU study samples based on racial and ethnic category, sex-at-birth, income (<$25,000, $25,000–$75,000, $75,000–$100,000, >$100,000 annual income), BMI (<18.5, 18.5–24.9, 25.0–29.9, >30), and UBR status. In all stratified analyses, we used logistic regression to estimate the OR of family history for personal medical history, controlling for age, sex, racial and ethnic category, and income (except for the relevant stratified variable). In the stratified

analyses, the full dataset is divided into different subgroups (strata) based on the levels of a variable of interest, and a separate logistic regression analysis is performed within each subgroup.[53] Stratifying the full analysis by a variable is similar to including an interaction term[54] between the stratum variable and every parameter included in the model; it allows us to measure how the relationship between the independent variables and the outcome differs across various subgroups. Prior work has established that increased BMI has a protective impact on bone density[55] and a negative impact on incidence and progression of OA.[56] To assess influences of BMI, we examined family history associations stratified by BMI ranges for underweight, healthy weight, overweight, and obesity. In accordance with the AoU Data and Statistics Dissemination Policy, we do not report association results on participant case counts of less than 20. Because of the large number of tests conducted in the stratified analyses, we used Bonferroni correction to account for multiple hypothesis testing and to require stringent control over type 1 errors and denote statistical significance by a P value of less than 0.05/49 or 0.001. The preliminary dataset was generated using the AoU Researcher Workbench, which was subsequently analyzed in a Jupyter Notebook. All analyses were conducted using R (Version 4.0) statistical software.[57]

RESULTS

Study sample characteristics.

Table 1 shows the demographic characteristics of the study sample (n = 156,307). The mean age of the participants was 55.22 years, and most participants were female sex-at-birth (65.06%) and non-Hispanic White (74.81%) (Table 1). Of the respondents in the AoU, 38.67% of participants reported having a positive family history of any arthritis, osteoporosis, and/or carpal tunnel syndrome; 61.33% reported no family history of any of the conditions. Prevalence of family history for the seven conditions was highest for maternal relationships (26.97%), followed by paternal (12.71%) and sibling relationships (12.48%) (Table 1). The prevalence of family history was highest for OA (19.61%; 95% confidence interval [95% CI] 19.41–19.81), followed by osteoporosis (11.66%; 95% CI 11.51–11.82), RA (10.22%; 95% CI 10.07–10.37), and gout (8.02%; 95% CI 7.89–8.16) (Figure 1, Supplementary Table 1). Among individuals who identified as non-Hispanic White, the prevalence of family history of disease was highest for OA (22.10%; 95% CI 21.87–22.34), followed by osteoporosis (13.06%; 95% CI 12.86–13.25) (Figure 1). Among individuals who identified as non-Hispanic Black, the prevalence of family history of disease was highest for OA (11.95%; 95% CI 11.41–12.49), followed by RA (11.31%; 95% CI 10.78–11.84) and gout (8.61%; 95% CI 8.14–9.08) (Figure 1). Family history of RA was most prevalent among individuals who identified as Hispanic (12.18%; 95% CI 11.68–12.69) (Figure 1). Compared with persons assigned male at birth, persons assigned female at birth reported higher prevalence of family history for all seven conditions (Figure 1).

Family history associations of arthritis, osteoporosis, and carpal tunnel syndrome.

Overall, adults with a family history of any arthritis, osteoporosis, and carpal tunnel syndrome exhibited 0.70 to 2.10 (1.24, on average) odds of having a different bone, joint, or muscle condition and 3.68 to 7.59 (4.90, on average) odds of having the same condition

(Figure 2), controlling for age, sex, racial and ethnic categories, income, and BMI. As shown in Figures 2 and 3, family history of OA, fibromyalgia, osteoporosis, RA, and SLE displayed significant associations across all personal medical conditions. Of the findings with the highest magnitude of association, family history of OA was associated with a personal diagnosis of OA (OR 7.59; 95% CI 7.32–7.88), followed by a family history of SLE with a personal diagnosis of SLE (OR 6.34; 95% CI 5.17–7.74), and family history of fibromyalgia and a personal diagnosis of fibromyalgia (OR 4.69; 95% CI 4.35–5.05). Of the associations between family history and personal diagnosis of a different condition, the highest magnitude in association was between a family history of OA and a personal diagnosis of fibromyalgia (OR 2.10; 95% CI 1.97–2.23), a family history of fibromyalgia and a personal diagnosis of SLE (OR 1.76; 95% CI 1.44–2.13), and a family history of RA and a personal diagnosis of SLE (OR 1.67; 95% CI 1.42–1.95) (Figure 3, Supplementary Table 1).

We identified a greater magnitude of association between family history of osteoporosis and a personal diagnosis of osteoporosis for participants with obesity (OR 4.14; 95% CI 3.72–4.55) compared with participants with a healthy weight (OR 3.32; 95% CI 3.04–3.61) (Supplementary Table 2). We also identified a greater magnitude of association between family history of OA and a personal diagnosis of OA for participants who were overweight (OR 7.02; 95% CI 6.57–7.46) and obese (OR 7.32; 95% CI 6.93–7.72), compared with participants with a healthy weight (OR 5.92; 95% CI 5.51–6.34) (Supplementary Table 2). However, these are not clinically relevant differences.

Race and ethnicity, income, and UBR analyses.

In race and ethnicity analyses, the finding with the highest magnitude of association was between a family history of SLE and a personal diagnosis of SLE for participants who identify as non-Hispanic White (OR 8.70; 95% CI 6.93–10.47) and Hispanic (OR 9.50; 95% CI 5.72–13.27), which was lower in magnitude of association for participants who identify as non-Hispanic Black (OR 4.90; 95% CI 2.76–7.04) (Supplementary Tables 3-5). Although there were notable differences between race and ethnicity groups, the composite analysis indicates strong associations in all three groups assessed. We did not find meaningful differences across all conditions by income ranges (Supplementary Table 6). Although the association between a family history of carpal tunnel syndrome was stronger in magnitude of association for individuals who were classified as UBR (OR 4.98; 95% CI 4.54–5.42) compared with individuals who did not classify as UBR (OR 3.92; 95% CI 3.52–4.32), the composite analysis indicates strong associations in both groups assessed (Supplementary Tables 7 and 8).

Association of family history of disease and personal diagnosis, stratified by sex assigned at birth.

Overall, persons assigned male at birth with a family history of any arthritis, osteoporosis, and carpal tunnel syndrome exhibited a 4.53 to 9.68 (6.72, on average) odds of having a personal diagnosis of the same condition, compared with 3.57 to 8.16 (5.20, on average) for persons assigned female at birth (Supplementary Tables 9 and 10). Among conditions with the largest difference in magnitude of association between persons assigned male and female

at birth included a family history of fibromyalgia and personal diagnosis of fibromyalgia, which was higher in males (OR 8.74; 95% CI 7.06–10.42) compared with females (OR 5.82; 95% CI 5.13–5.82), and family history of OA and personal diagnosis of OA, which was also higher in persons assigned male at birth (OR 8.04; 95% CI 7.57–8.51) compared with persons assigned female at birth (OR 6.80; 95% CI 6.55–7.04).

Association of family history of disease and personal diagnosis, stratified by parental relationship.

The disease with the highest prevalence of family history was OA for both maternal and paternal family history (14.97% and 7.39%, respectively [Supplementary Tables 11 and 12]). The prevalence of maternal family history of disease was second highest prevalence for osteoporosis (9.92%, compared with 1.07% for paternal family history, *t*-test *P* value < 0.001), whereas for paternal family history it was gout, at a prevalence of 4.82% (compared with 1.88% for maternal, *t*-test *P* value < 0.001). Adults who reported their father had fibromyalgia exhibited a greater odds of having a personal diagnosis of fibromyalgia (OR 9.30; 95% CI 7.38–11.22; $P < 2.0 \times 10^{-16}$) compared with adults who reported their mother had fibromyalgia (OR 6.29; 95% CI 5.79–6.79; $P < 2.0 \times 10^{-16}$; *t*-test $P < 0.05$). We identified a high magnitude of association for SLE for both parental relationships, in which a family history of SLE was associated with a 9.15 and 10.30 odds of SLE for paternal and maternal family history, respectively.

DISCUSSION

This study finds that individuals with a first-degree relative with any of five common types of arthritis, osteoporosis, and carpal tunnel syndrome have, on average, a 4.90-fold increased odds of having the same condition and a 1.24-fold increased odds of having a different condition, compared with individuals without a family history, implying that family history of these related conditions may be useful for primary prevention. We reveal family history disparities by race and ethnicity, in which a family history of any of the seven conditions was associated with a 4.35 to 8.37 (6.28, on average) fold increased odds of having the same condition for participants who identify as non-Hispanic Black, compared with 3.84 to 9.50 (6.65, on average) fold for those who identify as Hispanic, and 3.69 to 8.70 (5.36, on average) fold for those who identify as non-Hispanic White. We identify sex disparities, with a stronger magnitude of family history association in male participants than in female participants, which was larger for same compared with different family history-disease associations. Although we identified disparities between subgroups in terms of magnitude of association, many of the differences in risk estimates are likely not meaningful in terms of clinical interpretation and action. Overall, our findings suggest that these family histories are shared risk factors across seven distinct bone and joint conditions. This suggests the value of family history of several related conditions to facilitate early screening and targeted interventions, thereby enhancing primary prevention efforts for arthritis, osteoporosis, and carpal tunnel syndrome.

The results of this study align with what is reported in the literature regarding genetic and family history ties to the five common types of arthritis, osteoporosis, and carpal tunnel

syndrome. About 50% of RA cases appear to have a genetic link/familial risk contribution.[58] Many of the risk factors for SLE are related to genetic, environmental, and hormonal factors. Major histocompatibility complex encoded genes are associated with susceptibility to SLE.[59] Family history of OA and gout are both associated with an increased risk of OA and gout, respectively.[60,61] Fibromyalgia aggregates in families,[31] and osteoporosis is highly heritable, at an estimated heritability of 50% to 80%.[18] Carpal tunnel syndrome has a genetic component with more than 50 genome-wide associations that may contribute to disease pathogenesis.[20]

The FamWAS methodology allows for a comprehensive and systemic analysis of family history and family experiences in association with a personal condition on a broad scale, echoing known relationships and uncovering novel associations. We identified that a family history of SLE is associated with an increased prevalence of RA (OR 1.31; 95% CI 1.11–1.54), which is consistent with a previous case-control study in a prospectively recorded Swedish population that found a family history of lupus is associated with seropositive RA.[62] This finding also corresponds to an elevated risk identified in a nationwide cohort study in Denmark (hazard ratio 1.64); however, our study has a much larger sample size of 7,221 compared with 103 cases.[63] Among the novel associations, we reveal the association between a family history of fibromyalgia and personal diagnosis of SLE. We also reveal a stronger association between family history of fibromyalgia and personal diagnosis of fibromyalgia in male patients compared with female patients, even though the prevalence of fibromyalgia is higher in female patients than in male patients. The strength of family history as a risk factor depends on various factors including the genetic component of the disease, inheritance patterns, environmental factors, and gene-environment interactions.

From a clinical point of view, our findings suggest potential use of incorporating family histories of multiple related bone, joint, and muscle conditions for informing early diagnosis and disease prognosis. This could inform patient-provider shared decisionmaking for the development and implementation of individualized, comprehensive treatment plans including low-cost behavior changes (eg, physical activity, diet, weight management, smoking cessation) alongside medical and pharmaceutical treatments[64-66] aiming to prevent or delay disease progression. Incorporating family history of arthritis and osteoporosis in the clinic may align with the Healthy People 2030 goals for osteoporosis and arthritis, which include increasing the proportion of older adults screened for osteoporosis, decreasing the proportion of adults diagnosed with osteoporosis, increasing the proportion of adults with arthritis who get health care provider counseling for physical activity, reducing the proportion of adults with arthritis who have moderate or severe joint pain, and reducing the proportion of adults with arthritis whose arthritis limits their work or activities. Specifically, incorporating family history of arthritis and osteoporosis might be useful in developing tailored risk-specific recommendations for primary prevention of these conditions. Existing literature has found early identification of RA can affect disease course, prevent the development of joint erosions, and may affect disease outcomes to a remission state.[67-69] Family history information can also be used to motivate individuals at increased familial risk to engage in health-modifying behaviors,[70] such as increasing physical activity, which can reduce arthritis pain and fall risk.[71] Our findings suggest that common fracture risk assessment tools such as the Fracture Risk Assessment Tool (FRAX), which evaluates

osteoporosis-related bone fracture risk by integrating clinical risk factors, bone mineral density, as well as history of a hip fracture in the patient's mother or father,[72] may benefit from the addition of multiple interconnected family histories, such as including the first-degree family history of SLE and fibromyalgia for enhanced predictive ability of the assessment tool.

There are several limitations to our study. First, our findings cannot be generalized to the US population because the AoU is not a nationally representative sample. As participants voluntarily responded to the surveys, selection bias may impact our findings. The participants who volunteered to respond were more likely to be female sex assigned at birth and non-Hispanic White (t-test P value < 0.00001), compared with the participants who did not respond to the survey (Supplementary Table 13). Second, an inherent limitation of the AoU study design is the lack of temporality of reported information, because if family history is to be useful for prediction of disease risk, that information must be collected before a diagnostic workup. Third, self-reports of personal history may be subject to both random error and recall bias. However, a review examining the diagnostic accuracy of self-reported OA and RA found the accuracy to be acceptable at a pooled sensitivity and specificity of 0.75 and 0.89 for OA and 0.88 and 0.93 for RA.[73] Although survey data are susceptible to recall bias, we did not use EHR data because this was limited to data collected by a single health care network, and therefore may not capture fragmented care by out-of-network or other providers, and additionally may bias results, because AoU participants of younger age, female sex, and high school or higher education were significantly associated with declining to share EHR data.[74] Further, prior studies comparing medical and family history data derived from the EHR and survey responses in the AoU have found that survey data can identify missingness in EHR data,[75] and that surveys provided more extensive family history information than the EHR.[76] Fourth, self-reported first-degree family history may be inaccurate, and respondents may not have access to accurate information about past diagnoses of family members, especially those who are deceased. Further, participants who were diagnosed with a condition may be more likely to know their family history of that condition or a related condition. Another source of imprecision is ambiguity in diagnostic categories. For example, participants may not be able to reliably distinguish between diagnoses of the type of arthritis. Fifth, the AoU does not capture the number of affected relatives for us to determine contribution to risk with increasing numbers of relatives. Sixth, the variables for racial and ethnic category, sex, and gender identity status may represent a combination of biologic, physical, and societal factors that may increase risk of disease, diagnosis of disease, and, ultimately, disease symptoms and outcomes, as well as availability of these variables in the AoU data.

The pathogenesis of these conditions is very complex, with susceptibility determined by genetic factors, physical and social environmental factors, and their interactions. Family history represents the contribution of shared genetics, physical and social environment, lifestyle, and behavioral factors that are present within or experienced by families and has been used to guide risk assessment and to support clinical and shared decision-making. Future research should assess the potential effectiveness of an intervention based on family history on health risk behavioral changes and explore the integration of genetic and environmental data as captured by family history for enhancing disease prediction models.

By broadening our search to evaluating seven family histories, our findings suggest the use of multiple family histories of interconnected conditions for primary prevention of arthritis, osteoporosis, and carpal tunnel syndrome, which can potentially inform future guidance development about screening strategies, lifestyle changes, and early treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The All of Us Research Program would not be possible without the partnership of its participants.

The All of Us Research Program is supported by the NIH Office of the Director: regional medical centers (grants 1 OT2 OD026549, 1 OT2 OD026554, 1 OT2 OD026557, 1 OT2 OD026556, 1 OT2 OD026550, 1 OT2 OD 026552, 1 OT2 OD026553, 1 OT2 OD026548, 1 OT2 OD026551, 1 OT2 OD026555); IAA (grant AOD 16037); federally qualified health centers (grant HHSN 263201600085U); data and research center (grant 5 U2C OD023196); biobank (grant 1 U24 OD023121); the participant center (grant U24 OD023176); participant technology systems center: (grant 1 U24 OD023163); communications and engagement: (grants 3 OT2 OD023205, and 3 OT2 OD023206); and community partners (grants 1 OT2 OD025277, 3 OT2 OD025315, 1 OT2 OD025337, and 1 OT2 OD025276.

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SIGNIFICANCE & INNOVATIONS

- This study reports 49 family history associations of five common types of arthritis (fibromyalgia, gout, osteoarthritis, rheumatoid arthritis, and systemic lupus erythematosus), osteoporosis, and carpal tunnel syndrome and the prevalence of these conditions in a large-scale cohort of diverse US adults from the All of Us Research Program.
- This study leverages a comprehensive and systematic search strategy, termed "Family History-Wide Association Study," for testing a range of family histories for their association with disease prevalence and uncovers family history risk factors that have not previously been studied for their association with these conditions.
- Using data on 156,307 participants, this study reports that participants with a first-degree relative with any of five common types of arthritis, osteoporosis, and carpal tunnel syndrome have, on average, a 4.90-fold increased odds of having the same condition and a 1.24-fold increased odds of having a different condition, compared with individuals without any family history.
- Our findings suggest the clinical utility of multiple family histories of interconnected conditions for primary prevention of arthritis, osteoporosis, and carpal tunnel syndrome.

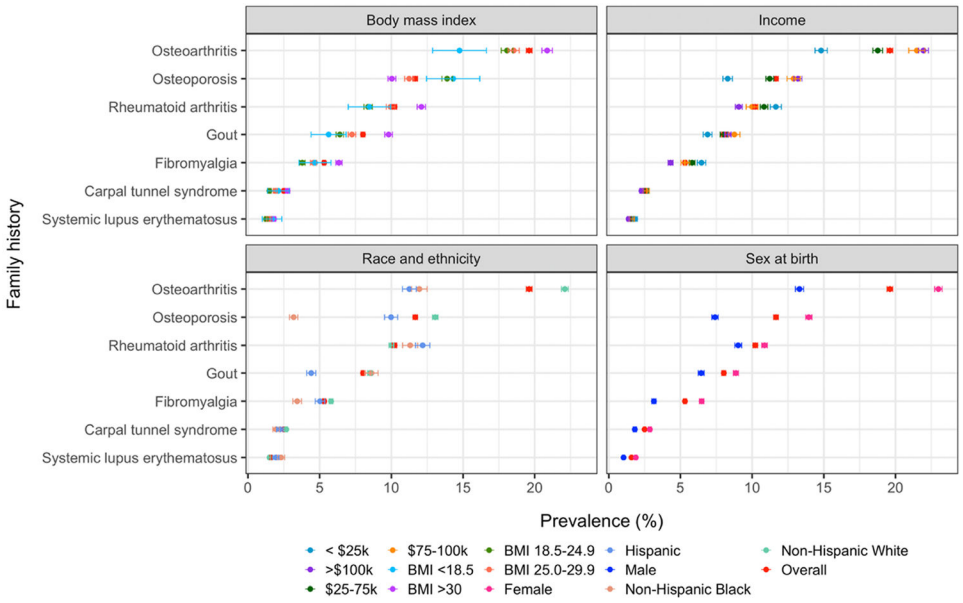

Figure 1.

Prevalence (%) of self-reported first-degree family history of arthritis, osteoporosis, and carpal tunnel syndrome in the All of Us Research Program and by BMI, income, race and ethnicity, and sex assigned at birth. “Overall” indicates the All of Us Research Program study sample. The error bars represent 95% confidence intervals. BMI, body mass index.

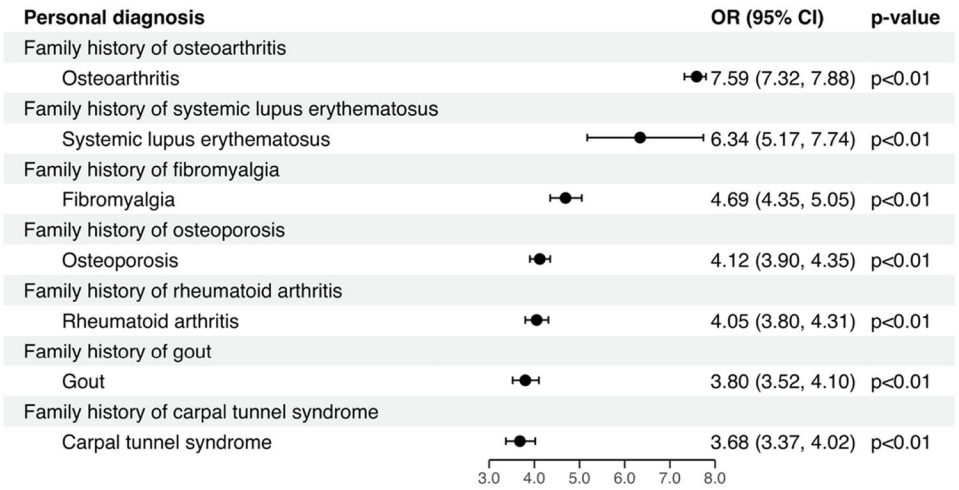

Figure 2.

Association of family history and personal diagnosis. ORs between self-reported first-degree family history of arthritis, osteoporosis, and carpal tunnel syndrome and personal diagnosis of the same conditions are shown. The ORs were computed from the multivariable logistic regression of personal medical history on self-reported first-degree family history, controlling for all seven family histories, age, sex-at-birth, racial and ethnic categories, income, and body mass index. The 95% CIs and *P* values are reported. 95% CI, 95% confidence interval; OR, odds ratio.

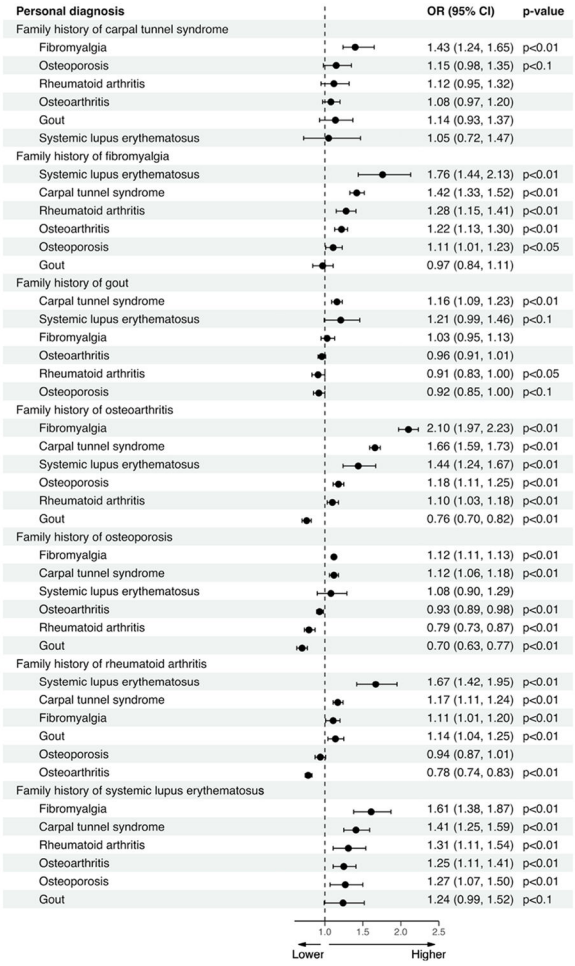

Figure 3.

Association of family history and different personal diagnosis. ORs between self-reported first-degree family history of arthritis, osteoporosis, and carpal tunnel syndrome and personal diagnosis of different conditions are shown. The ORs were computed from the multivariable logistic regression of personal medical history on self-reported first-degree family history, controlling for all seven family histories, age, sex-at-birth, racial and ethnic categories, income, and body mass index. The 95% CIs and *P* values are reported. 95% CI, 95% confidence interval; OR, odds ratio.

Table 1.

Descriptive statistics for the study sample (n = 156,307) from the All of Us Research Program [*]

Characteristics	Proportion of total participants
Female, n (%)	101,700 (65.06)
Age, y, mean (SD)	55.22 (17.00)
Race and ethnic category, n (%)[a]	
Non-Hispanic White	116,931 (74.81)
Hispanic	16,365 (10.47)
Non-Hispanic Black	13,854 (8.86)
Non-Hispanic Asian	5,298 (3.39)
Positive family history for at least one of the seven conditions by type of affected relative,[b] n (%)	60,443 (38.67)
Mother[c]	42,157 (26.97)
Father[c]	19,869 (12.71)
Sibling[c]	19,502 (12.48)
Child[c]	4,501 (2.88)
Positive family history by condition,[c] n (%)	
Carpal tunnel syndrome	3,235 (2.07)
Fibromyalgia	7,002 (4.48)
Gout	11,723 (7.50)
Osteoarthritis	29,135 (18.64)
Osteoporosis	17,756 (11.36)
Rheumatoid arthritis	15,771 (10.09)
Systemic lupus erythematosus	2,407 (1.54)
No family history of any of the seven conditions[d]	95,864 (61.33)
Personal medical condition among participants with a positive family history,[e] n (%)	
Carpal tunnel syndrome	9,994 (16.49)
Fibromyalgia	4,848 (8.02)
Gout	2,662 (4.40)
Osteoarthritis	18,513 (30.63)
Osteoporosis	5,982 (9.90)
Rheumatoid arthritis	3,811 (6.31)
Systemic lupus erythematosus	795 (1.32)
None of these	30,006 (49.38)

[*] This table includes participant data collected between May 30, 2017, and July 1, 2022, by the All of Us Research Program.

[a] 2.47% of the participants are multiracial or other race and ethnic category.

[b] 38.67% of the study sample (n = 156,307) have reported a positive first-degree (mother, father, sibling, and/or child) family history for any of the 7 conditions.

[c] The denominator for the percentages for family history of mother, father, sibling, and child is 156,307. Note that these categories are not mutually exclusive and a participant can select more than 1 family member for any of the 7 conditions.

[d] Participants with unknown or unreported family history have been removed from the study sample of 156,307 participants.

[e] The denominator for the conditions among participants with first-degree relatives is 60,443.