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Heritability of the Fibromyalgia Phenotype Varies by Age

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Objective. Many studies suggest a strong familial component to fibromyalgia (FM). However, those studies have nearly all been confined to individuals with primary FM, i.e., FM without any other accompanying disorder. The current 2011 and 2016 criteria for diagnosing FM construct a score using a combination of the number of painful body sites and the severity of somatic symptoms (FM score). This study was undertaken to estimate the genetic heritability of the FM score across sex and age groups to identify subgroups of individuals with greater heritability, which may help in the design of future genetic studies.

Methods. We collected data on 26,749 individuals of European ancestry undergoing elective surgery at the University of Michigan (Michigan Genomics Initiative study). We estimated the single-nucleotide polymorphism–based heritability of FM score by age and sex categories using genome-wide association study data and a linear mixed-effects model.

Results. Overall, the FM score had an estimated heritability of 13.9% (SE 2.9%) ($P = 1.6 \times 10^{-7}$). Estimated FM score heritability was highest in individuals ≤50 years of age (23.5%; SE 7.9%) ($P = 3.0 \times 10^{-4}$) and lowest in individuals >60 years of age (7.5%; SE 8.1%) ($P = 0.41$). These patterns remained the same when we analyzed FM as a case–control phenotype. Even though women had an ~30% higher average FM score than men across age categories, FM score heritability did not differ significantly by sex.

Conclusion. Younger individuals appear to have a much stronger genetic component to the FM score than older individuals. Older individuals may be more likely to have what was previously called "secondary FM." Regardless of the cause, these results have implications for future genetic studies of FM and associated conditions.

INTRODUCTION

Fibromyalgia (FM) is a symptom complex characterized by widespread pain accompanied by somatic symptoms such as fatigue and sleep and memory problems. Nearly all recent research studies of FM have focused on what is termed "primary FM," which is FM without any other identifiable autoimmune or structural causes of pain. However, similar symptom complexes are observed in individuals with identifiable causes of pain such as autoimmune disorders and chronic diseases. This form of FM is thought to be more similar to animal and human studies of central sensitization, where ongoing nociceptive input is required to drive the processes of central sensitization, at the level of both the spinal cord and the brain (1–6).

Individuals with primary FM typically begin developing pain in their childhood or teens and are often diagnosed as having regional pain conditions early in their life before finally being diagnosed as having FM. Primary FM occurs preferentially in women, is strongly familial, and coaggregates with other regional pain conditions in both individuals and families (7–12). In contrast to primary FM, pain with identifiable causes can be caused by pain-related diseases such as osteoarthritis, which often occur later in life, and less is known about the heritability of pain with identifiable causes. Understanding the pathogenic differences between FM with and FM without identifiable causes of pain may lead to different treatments for the 2 forms of FM. For example, central nervous system drugs and primary FM therapies may be less effective than identification and treatment of the ongoing nociceptive input (7,13).

Candidate gene and genome-wide association studies (GWAS) comparing variant allele frequencies in FM cases and controls have been performed, but many of the results have been inconsistently noted or replicated (14). However, the studies to date

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have been small in size (n < 1,000) and would only have been able to identify common genetic variants with very large effects (14,15).

Population- (16) or hospital-based (17) cohorts provide an opportunity to study the genetics of a wider spectrum of pain in much larger samples, although it may not always be possible to differentiate between patients with and those without any identifiable causes of pain given available survey or medical records and the high prevalence of individuals with peripheral sources of ongoing nociceptive input. Large studies of quantitative pain phenotypes can potentially contribute to the understanding of disease processes. A multisite chronic pain (MCP) GWAS (18) performed using data from the large-scale UK Biobank found 76 independent MCP-associated variants at 39 loci and an estimated MCP heritability of 10.2%.

Estimates of disease or trait heritability are of interest because they give a sense of the genetic contribution to the measured trait. Heritability has traditionally been estimated from family and twin studies, which require intensive participant recruitment. But narrow-sense heritability (additive components) can also be estimated from cohort- or case–control–based GWAS data (19,20). The estimation of heritability from GWAS data is based on the idea that if genetics underlie the predisposition to disease, individuals with more similar levels of a trait or with a disease will tend to share more alleles than individuals with less similar trait levels or without the disorder (21). For example, estimates of heritability based on GWAS of nonfamilial data range from 55% to 81% for height (19,22), 23% to 51% for body mass index (BMI) (20,23), and 37% to 50% for depression (24,25). The GWAS-based estimates are usually smaller than those estimated from familial data or twin studies, likely because they only capture additive effects from the variant classes included in the estimation (narrow-sense heritability) (26).

The genetic contributions to trait level or disease risk can vary by age or sex (27), and these differences can be assessed by estimating heritability in subgroups of samples. For example, many physical measures, including basal metabolic rate, systolic blood pressure, BMI, and neck pain, appear to be more heritable in younger individuals (28), potentially because trait differences at younger ages are less driven by environmental factors or because the processes that cause trait differences at older ages are different from or more diverse than those at younger ages.

This study was undertaken to estimate the heritability of FM and of a continuous measure of FM severity and to investigate whether heritability differs by patient sex and/or age at assessment. To do this, we measured FM severity using patient-completed 2011 Survey Criteria for FM (29,30) from 26,749 individuals of European ancestry undergoing elective surgery in the Michigan Genomics Initiative. Using GWAS data, we estimated the heritability of a continuous phenotype, FM severity (FM score), across age categories. We also dichotomized FM scores as a case–control phenotype according to 2 different definitions and estimated their heritability across age categories. Further, we estimated the genetic correlation of FM score with several psychiatric, personality, and autoimmune traits using publicly available GWAS summary statistics.

PATIENTS AND METHODS

Patients. Participants were prospectively recruited into the Michigan Genomics Initiative, an institutional biorepository at the University of Michigan. All patients were ≥18 years of age and were scheduled to have an elective surgery on the day of their recruitment. We excluded patients who did not speak English, were unable to provide written informed consent, or were currently imprisoned. We obtained written informed consent from all patients for use of their clinical data and DNA for research purposes. This study was approved by the University of Michigan Institutional Review Board (IRB ID HUM00099605).

Genotyping. We genotyped DNA from blood samples using customized versions of an Illumina HumanCoreExome v12.1 array and applied quality control filters (see Supplementary text, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract). After sample quality control, 37,412 samples remained, with 462,868 polymorphic variants. The average genotyping rate for the samples and variants included was 99.96%.

We projected the genotype data for the 37,412 samples on the principal components of Human Genome Diversity Project data using TRACE (31) to infer the genetic ancestry of the samples. Of these samples, 31,730 (84.8%) were inferred to be from individuals of European ancestry. We estimated the sample kinship (32) and retained 30,431 samples from participants who had less than a second-degree relationship. We next performed principal components analysis on their genotype data. We excluded 33 samples that were outliers based on the first and second principal components, resulting in 30,398 samples with genotype data (Supplementary text and Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract).

Phenotyping. We phenotyped patients preoperatively using a self-administered questionnaire on widespread pain and psychological status, based on the American College of Rheumatology (ACR) Survey Criteria for FM (30). These criteria for FM, conceptualized in 2011, represent a validated self-report measure based on the presence of widespread pain and comorbid symptoms (29,30). To calculate the Widespread Pain Index (WPI), we assessed 19 specific body areas using the Michigan Body Map (range of possible scores 0–19) as described in the ACR Survey Criteria (30). To calculate a Symptom Severity Index (SSI) we used the comorbid Symptom Severity Scale with questions on fatigue, trouble thinking or remembering, waking up tired, pain or cramps in the lower abdomen, depression, and headache (range of possible scores 0–12). Following the method of Wolfe et al (30), we

summed the WPI and SSI to create an FM score (range of possible scores 0–31).

To dichotomize patients as FM cases or controls based on the FM score and its components, we used the following 2 definitions: 1) any individual with an FM score of ≥13 was defined as a case according to the 2011 criteria for FM; and 2) any individual with pain in 4 of the 5 main body regions, a WPI score of ≥7, and an SSI score of ≥5, or with pain in 4 of the 5 main body regions, a WPI score of 4–6, and an SSI score of ≥9 was defined as a case according to the modified 2016 criteria for FM. The modified 2016 criteria is a modified version of the criteria outlined by Wolfe et al (33) in 2016, adapted to our study according to the availability of data. (For details, see Supplementary text, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract.) All individuals who were not classified as cases according to the definitions described above were classified as controls. Of the 30,398 individuals of European ancestry with genotype data, 3,649 (12.0%) did not have an FM score (WPI was missing for 2,708 [8.9%] and SSI was missing for 3,494 [11.5%]), leaving 26,749 individuals for analysis.

Log transformation of FM score, WPI, and SSI. Since the distribution of the FM score was highly skewed, we added a small constant (0.1) to the FM score to retain individuals with a value of 0 in the analysis, and log transformed the adjusted score. We regressed the log-transformed FM score (log FM) on age, age squared, and sex using a linear regression model and inverse normalized the residuals (inverse normalized FM score). The same transformations were applied to the WPI and SSI.

Estimation of heritability and genetic correlation. The genetic contribution to a phenotype can be measured by heritability, the fraction of trait variation explained by genetic variation. We estimated the heritability of the FM score, WPI, and SSI using a linear mixed-effects model (34) defined as:

$$y = X\beta_y + g_y + \varepsilon_y$$

where y is the vector of phenotype values for n individuals, in this case the inverse normalized FM score (or inverse normalized WPI/SSI score); X is a matrix of nongenetic covariates containing the top 10 genetic principal components and a binary variable with levels 0 and 1 indicating the genotype array (UM_HUNT_Biobank or UM_HUNT_Biobank_v1-1); β_y is the vector of corresponding fixed effects; g_y is a random vector of genetic contributions to the phenotypes, random effects, with $g_y \sim N(0,\sigma_y^2 K)$, where K is the genetic relatedness matrix (GRM) between the pairs of individuals (see Supplementary text for the construction of the GRM) and σ_y^2 is the genetic variability contributed by the genetic relatedness of the samples; and $\varepsilon_y \sim N(0,\sigma_{ey}^2 I)$, where σ_{ey}^2 is the residual variance of the model.

The heritability of the phenotype y is estimated as $h^2 = \sigma_y^2/(\sigma_y^2 + \sigma_{ey}^2)$. We used genome-wide complex trait analysis (35) to fit this model and estimate the heritabilities. We used a likelihood ratio test to evaluate the significance of the estimated heritability. We note that h^2 used here is a narrow-sense heritability measure. Thus, h^2 only measures the fraction of trait variability explained by the additive effects of the variants in the array, which is lower than the total trait heritability. For a case–control phenotype (binary), we used the same linear mixed-effects model but with a liability scale, adjusting for ascertainment probabilities of the cases by the population prevalence (36). We used 2 different ways to dichotomize individuals into cases and controls based on FM score. For both case–control definitions we used a population prevalence of 2% to estimate the heritability of FM as a case–control phenotype (37).

The genetic overlap between 2 phenotypes y and w can be measured by the genetic correlation (20). We estimated the genetic correlation among the FM score, SSI, and WPI using a multiple linear mixed-effects model. For phenotype w, we used the same linear mixed-effects model as for y:

$$w = X\beta_w + g_w + \varepsilon_w;\ g_w \sim N(0,\sigma_w^2 K);\ \varepsilon_w \sim N(0,\sigma_{ew}^2 I)$$

with the additional assumption $cov(g_y,g_w) = \sigma_{yw}K$, where σ_{yw} is defined as the coheritability of the phenotypes y and w. The genetic correlation between the phenotypes is then defined as $r_{yw} = \sigma_{yw}/\sigma_y\sigma_w$. We used Phenix (38) to fit the model and calculate the coheritability and subsequently estimated the genetic correlations. Further, we estimated the genetic correlation of FM score with selected traits using publicly available summary statistics from existing genetic association studies using linkage disequilibrium score regression (39–41).

RESULTS

Our analysis included 26,749 patients of European ancestry who were scheduled for elective surgery. Their mean ± SD age was 54.2 ± 15.9 years, and 53.2% were women. The distribution of the FM scores for the 26,749 individuals is shown in Figure 1. For 10.8% of the samples, the FM score was 0 (both the WPI and SSI scores were 0). (See Supplementary Figure 2, available on the

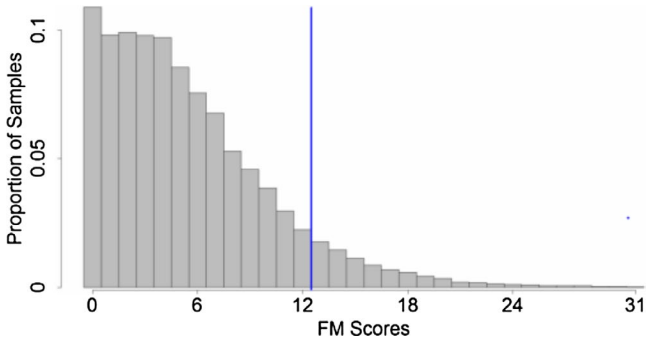

Figure 1. Distribution of fibromyalgia (FM) scores in the sample included for analysis. The range of possible scores is 0–31. Vertical line indicates the cutoff for considering an individual an FM patient (FM score ≥13). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract.

Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract, for WPI and SSI distributions.)

FM scores by age categories and sex are shown in Figure 2. When divided into age subcategories of 10 years, individuals who were 40–50 years old and those who were 50–60 years old had significantly higher FM scores than those who were ≤40 years old. Individuals who were 60–70 years old, those who were 70–80 years old, and those who were 80–90 years old had lower FM scores than those who were ≤40 years old (Figure 2). This pattern was consistent for women and men (Figure 2) (for regression estimates see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract). In the total sample, the mean ± SD FM score was higher in women than in men (6.2 ± 4.9 versus 4.6 ± 4.2, respectively; mean score in women/mean score in men = 1.34). (See Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract, for the FM scores for patients dichotomized into 2 groups by age [≤50 years or >50 years].)

We investigated whether the components of the FM score, measurements of pain at different sites of the body (WPI), and symptoms of pain (SSI) had consistent trends across age and sex (Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract). Younger individuals (age ≤50 years) had a lower WPI score than older individuals (age >50 years) (mean ± SD 1.8 ± 2.6 versus 2.0 ± 2.6, respectively). In contrast, younger individuals had a higher SSI score than older individuals (mean ± SD 3.8 ± 2.9 versus 3.4 ± 2.8) (Supplementary Table 3). Women had higher WPI and SSI scores than men (2.1 ± 2.8 versus 1.6 ± 2.3 for WPI and 4.1 ± 2.9 versus 3.0 ± 2.6 for SSI).

To evaluate the significance of the effects of age and sex on FM score–related measures, we used a multiple linear regression model simultaneously adjusted for age, age squared, and sex. We found that age, age squared, and sex were significantly associated with the FM score, WPI, and SSI ($P < 0.05$) (Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract). To determine if the effect of age category (younger or older) on FM score varied by sex or if the effect of sex on FM score varied by age category (younger or older), we tested for an interaction between age category and sex. We did not find significant

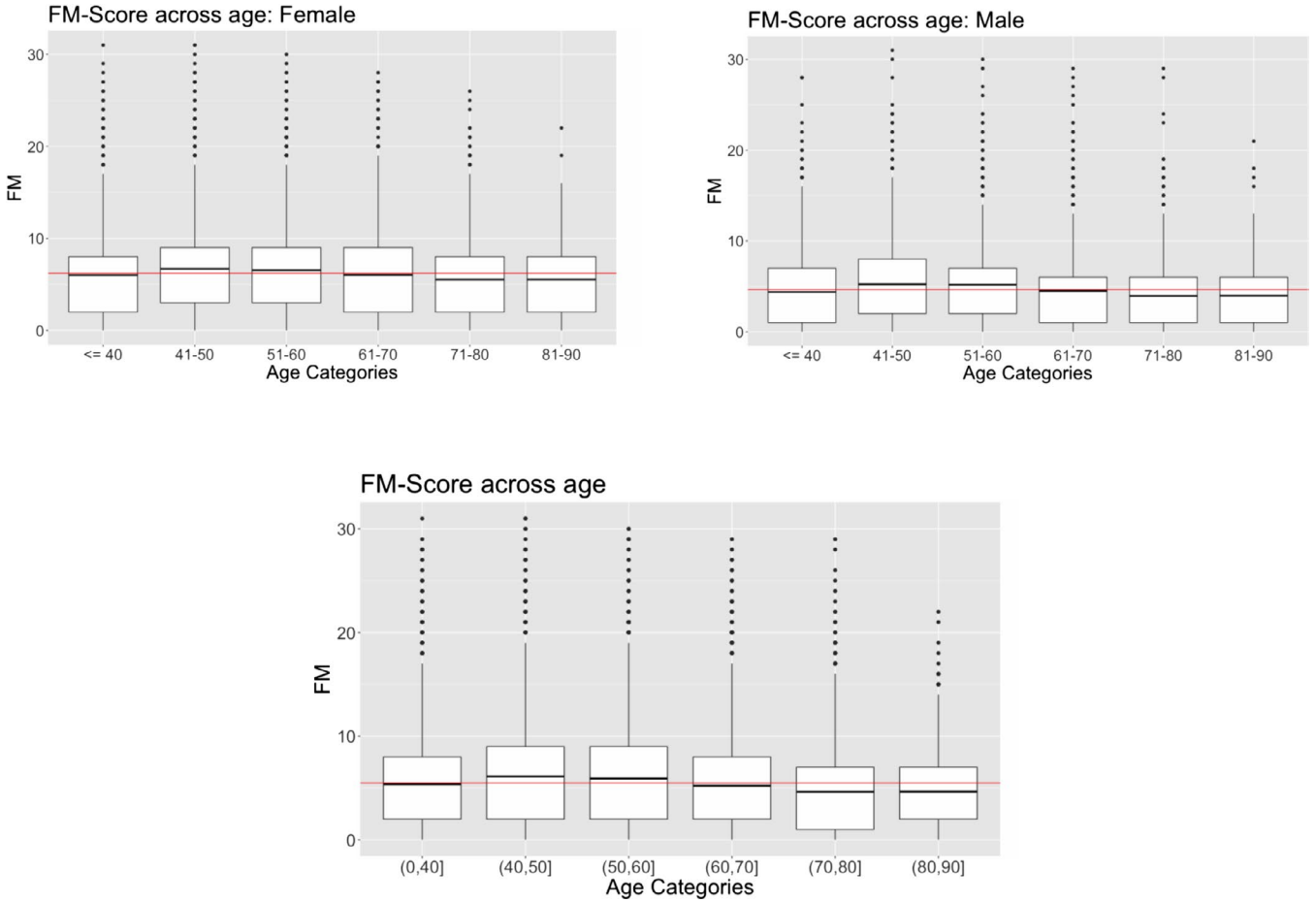

Figure 2. Distribution of fibromyalgia (FM) scores in women, men, and the entire sample, divided into 10-year age categories. Data are shown as box plots, where the boxes represent the 25th to 75th percentiles, the lines within the boxes represent the median, and the lines outside the boxes represent the 10th and 90th percentiles. Circles indicate outliers. Red lines indicate the mean FM score across all age categories.

evidence that the effect of sex varied between older and younger individuals or that the effect of age varied by sex.

To estimate the genetic contribution to FM score, we calculated the genotype-based heritability of the inverse normalized FM score. We constructed the GRM using the common variants (minor allele frequency >5%) and fit a linear mixed-effects model (see Patients and Methods). The estimated heritability of FM was 13.9% (SE 2.9%) ($P = 1.6 \times 10^{-7}$). To examine if heritability differed by age, we divided the sample into 10-year age categories. Patients ≤40 years old had the highest heritability, estimated at 22.8% (SE 13.4%), and those 60–70 years old had the lowest heritability, estimated at 3%, although no age category was significantly heritable on its own. We saw similar trends for WPI and SSI (Figure 3).

To obtain larger age subgroups, we dichotomized patients by age cutoffs and estimated the heritability in the corresponding age groups (Table 1). For each age cutoff we observed that younger individuals consistently had higher heritability of FM than older individuals. For example, individuals age ≤50 years had an estimated heritability of 23.5% (SE 7.9%) ($P = 3.0 \times 10^{-4}$) and those age >50 years had an estimated heritability of 8.6% (SE 5.6%) ($P = 0.12$). This means that the estimated heritability of FM for individuals ≤50 years old is significantly higher than 0. Conversely, the heritability for individuals >50 years old is low and could not be distinguished from 0 in this sample.

When we repeated the analysis by age category for men and women separately, we found that women had slightly higher estimated heritabilities than men in almost all age categories. However, we found no evidence of a significant difference in the estimated heritabilities between men and women (Supplementary text and Supplementary Table 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract).

To assess the heritability in individuals more likely to have FM we used the 2 definitions of FM cases described above. Any individual with an FM score of ≥13 was defined as a case according to the 2011 FM criteria (22) (n = 2,304; sample prevalence 8.6%).

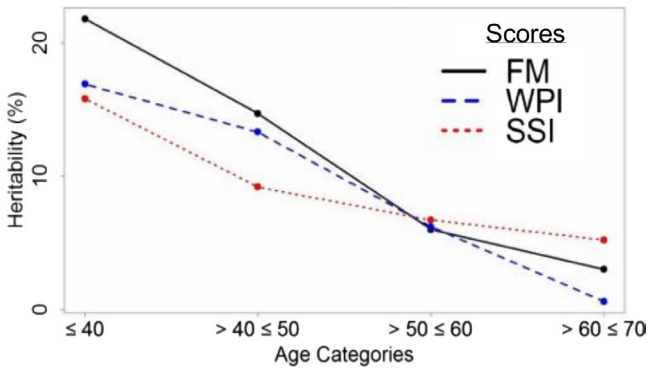

Figure 3. Heritability of fibromyalgia (FM) score, Widespread Pain Index (WPI), and Symptom Severity Index (SSI) scores by 10-year age category.

Table 1. Heritability of inverse normalized fibromyalgia score by age

Age, years	n	Heritability estimate, %	SE	*P*
≤40	5,693	22.8	13.4	0.09
>40	21,056	8.1	4.9	0.06
≤50	10,201	23.5	7.9	3.0×10^{-4}
>50	16,548	8.6	5.6	0.12
≤60	16,687	12.4	5.5	0.01
>60	10,062	7.5	8.1	0.41
All	26,749	13.9	2.9	1.6×10^{-7}

Any individual with pain in 4 of the 5 main body regions, a WPI score of ≥7, and an SSI score of ≥5, or with pain in 4 of the 5 main body regions, a WPI score of 4–6, and an SSI score of ≥9 was defined as a case according to the modified 2016 criteria (adapted from Wolfe et al [33]) (n = 1,319; sample prevalence 4.9%). All individuals not defined as a case were defined as controls. All but 48 of the participants who met the modified 2016 criteria also met the 2011 criteria. We estimated heritabilities as 8.6% ($P = 0.005$) for those who met the 2011 criteria and 7.9% ($P = 0.41$) for those who met the modified 2016 criteria. When participants were divided into age categories, we observed higher estimated heritability for younger individuals than for older individuals, suggesting that the overall trends by age were consistent in the data across varying levels of FM severity measured by different criteria (Supplementary Table 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract).

To understand the contributions of the WPI and SSI to the age-based heritability trends for FM score, we estimated the genetic correlations of FM score with WPI and SSI by 10-year age categories (Figure 4). The estimated genetic correlation between the FM score and WPI score varied from 38% for younger individuals (age ≤40 years), to 56% for individuals ages >40 and ≤50 years and those ages >50 and ≤60 years and 30% for the group of older individuals (ages >60 and ≤70 years). The genetic correlation between the FM score and SSI varied from 57% in individuals age ≤40 years to 88% in individuals ages >60 years and ≤70 years. The estimated genetic correlation between WPI and SSI varied between 55% for individuals ages >40 years and ≤50 years and 6% for older individuals (ages >60 years and ≤70 years). These genetic correlation estimates show that for younger individuals, both WPI and SSI contribute substantially toward the genetic components of FM, while in older individuals SSI appears to be the dominant component. Further, our estimates show that, for younger individuals, WPI and SSI have a substantial shared genetic component, while in older individuals, they have a low genetic correlation. Using the definitions based on the 2011 criteria for FM and the modified 2016 criteria for FM to dichotomize individuals as cases and controls, we found similar patterns of genetic correlations across age categories (Supplementary Figure 3,

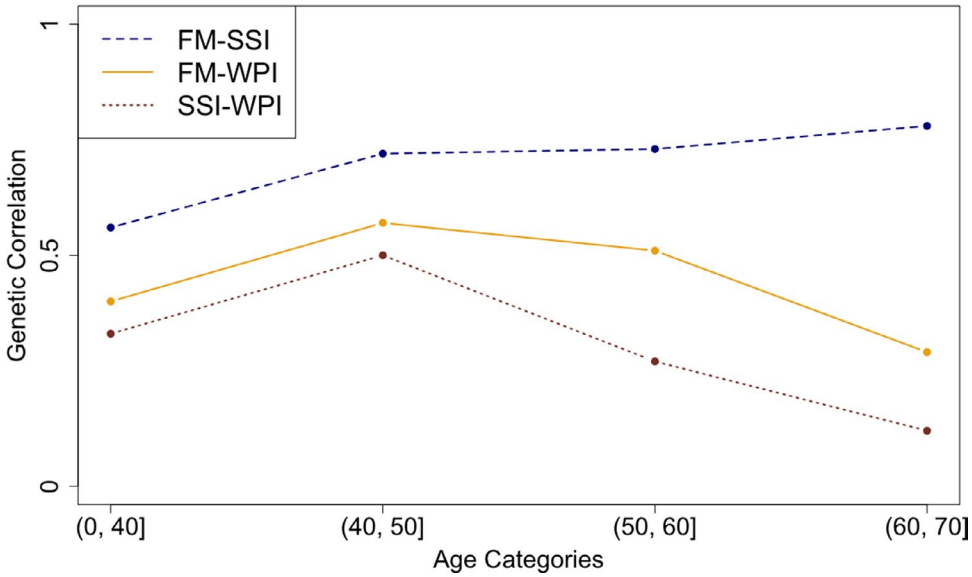

Figure 4. Estimated genetic correlation between the fibromyalgia (FM) score and Symptom Severity Index (SSI), between the FM score and Widespread Pain Index (WPI), and between SSI and WPI, by 10-year age categories.

available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41171/abstract).

We next tested for coheritability of FM score with traits that might a priori be expected to be correlated with FM score or were found to be significant in the UK Biobank study of MCP. FM score had a significant genetic correlation with psychiatric disorders such as attention deficit hyperactivity disorder (ADHD), neuroticism, major depressive symptoms, subjective well-being, and depressive symptoms (–0.26 to 0.78) (Table 2). We also found significant genetic correlation of FM score with immune and autoimmune diseases such as asthma and rheumatoid arthritis (RA) (0.31 to 0.35) (Table 2). To understand the contribution of SSI and WPI to the genetic correlations of FM score, we estimated their genetic correlations with the same traits separately. For almost all traits tested, SSI had similar estimated genetic correlations as FM score. WPI had similar estimated genetic correlations as FM score for asthma and RA, and of the traits tested, these were the most strongly genetically correlated with WPI. In contrast, WPI showed much

Table 2. Genetic correlation of FM score, WPI, and SSI with selected traits for the overall sample and by age*

Trait	PubMed ID	All			Age ≤50 years			Age >50 years			Genetic correlation in UK Biobank (MCP)
		FM	WPI	SSI	FM	WPI	SSI	FM	WPI	SSI	
Depressive symptoms†	27089181	0.53‡	0.11	0.49‡	0.63‡	0.12	0.59‡	0.49‡	0.07	0.44‡	0.59‡
Major depressive disorder†	29700475	0.40‡	0.08	0.43‡	0.48‡	0.07	0.50‡	0.36‡	0.09	0.37‡	0.53‡
Bipolar disorder†	21926972	0.08	0.03	0.09	0.13	0.04	0.14‡	0.06	0.04	0.07	0.02
ADHD†	27663945	0.78‡	0.19‡	0.66‡	0.81‡	0.20‡	0.80‡	0.53‡	0.15	0.54‡	NR
Subjective well-being†	27089181	−0.26‡	−0.12	−0.28‡	−0.25‡	−0.11	−0.23‡	−0.21‡	−0.14	−0.22‡	NR
PGC cross-disorder analysis†	24353885	0.28‡	0.15	0.33‡	0.32‡	0.13	0.34‡	0.25‡	0.11	0.30‡	0.13‡
Autism spectrum disorder†	30804558	0.04	−0.01	0.05	−0.01	−0.02	0.04	0.05	0.01	0.07	−0.10‡
Anorexia nervosa†	24514567	−0.09	−0.06	−0.12	−0.13	−0.07	−0.17‡	−0.07	−0.06	−0.10	−0.06‡
RA§	24390342	0.35‡	0.38‡	0.26‡	0.38‡	0.39‡	0.25‡	0.31‡	0.32‡	0.19‡	0.16‡
Asthma§	17611496	0.31‡	0.33‡	0.30‡	0.40‡	0.45‡	0.39‡	0.28‡	0.30‡	0.22	0.22‡
Primary biliary cirrhosis§	26394269	0.13	0.16	0.12	0.15	0.16	0.09	0.11	0.13	0.06	0.10‡
Neuroticism¶	27089181	0.39‡	0.16	0.35‡	0.45‡	0.17‡	0.41‡	0.37‡	0.13	0.38‡	0.40‡
Sleep duration#	27494321	−0.03	0.05	−0.11	−0.02	0.01	−0.08	−0.03	0.02	−0.08	NR
MCP	31194737	0.46‡	0.38‡	0.29‡	0.49‡	0.43‡	0.31‡	0.41‡	0.37‡	0.21‡	–

* FM = fibromyalgia; WPI = Widespread Pain Index; SSI = Symptom Severity Index; MCP = multisite chronic pain; ADHD = attention deficit hyperactivity disorder; NR = not reported; PGC = Psychiatric Genomic Consortium; RA = rheumatoid arthritis.
† Psychiatric trait.
‡ Significant estimate ($P < 0.05$).
§ Immune/autoimmune trait.
¶ Personality trait.
# Sleeping trait.

lower genetic correlation with psychiatric traits (–0.12 to 0.19) than we found for FM score or SSI, although genetic correlation of WPI with ADHD and neuroticism was nominally significant in younger individuals. Multiple phenotypes that were reported to have significant genetic correlation with MCP in the UK Biobank study (18) did not have significant genetic correlation with FM score, WPI, or SSI. However, the directions of genetic correlations for these traits were highly consistent between the UK Biobank and our sample (9 of the 10 reported traits in Table 2 had the same direction of effects). Further, the estimated genetic correlations for these traits were highly correlated with those estimated in the UK Biobank sample for MCP ($r > 0.9$).

We also estimated the genetic correlation of FM score, WPI, and SSI with the UK Biobank MCP. We found significant genetic correlations of MCP with FM score (0.46), WPI (0.38), and SSI (0.29). For younger individuals the genetic correlations were slightly higher than those estimated for older individuals (Table 2).

DISCUSSION

The present study is the largest to date to examine genetic contributions to the FM score (a composite measure of WPI and SSI). We found that the FM score was more heritable in younger individuals than in older individuals in this hospital-based sample. Thus, the variability in FM score for younger individuals, who are potentially more likely to have primary FM, appears to be driven by genetic factors shared across individuals to a greater degree than the variability in FM score in older individuals. Older individuals may have a greater contribution of environmental factors to pain, a greater diversity of conditions that increase pain, and/or more susceptibility towards nociceptive pain.

We found that there was a substantial genetic correlation of FM with both WPI and SSI for younger individuals, indicating that both the pain component (WPI) and the comorbid symptoms component (SSI) jointly contributed to the genetic architecture of FM in the younger individuals. In contrast, for the older individuals, the heritability of FM was more highly correlated with the comorbidity component (SSI) than with the pain component (WPI). Overall, our results suggest that genetic studies of FM might have differing results depending on the age of the participants.

If FM in younger individuals stayed constant throughout their lives, one would expect FM measures to slowly increase with age as pain from chronic diseases increases, but in this study, the mean FM score (in individuals undergoing elective surgery) was slightly lower in older individuals. Other studies have shown that the incidence and prevalence of FM wanes over time. Wolfe et al (37) showed that the prevalence of chronic widespread pain in Kansas peaked at ages 60–69 and then decreased in older individuals. Vincent et al (42) used the 2011 FM Survey Criteria to show that the prevalence of FM in the general Minnesota population was 8.4% for individuals ages 21–39 years, 6.0% for individuals ages 40–59 years, and 3.8% for individuals >60 years of age (27).

Given that an individual's genetic information is constant from birth until death (notwithstanding epigenetic modifications), our results suggest that, for a set number of FM cases, inclusion of younger individuals might increase the power to detect primary FM. All previous GWAS or large candidate gene studies in FM either included many individuals >50 years of age or did not report age (15,21,43). Thus, all of the large-scale genetic studies performed to date in FM have included sizable numbers of older individuals, where the genetic contributions to FM or FM symptoms might have been lower or different than in younger cohorts.

Differentiating individuals with primary FM from those with pain from an identifiable source, in a hospital or electronic health record (EHR)–based cohort, is difficult, even with the potentially large arrays of phenotype data. Although EHR-based studies can reduce diagnosis/reporting misclassifications and recall bias compared to cohort studies, ongoing sources of nociceptive pain might still be present without a diagnosis and hence not identified in an EHR-based study. In particular, nociceptive pain might be relatively more common in the population we have considered in this study, which consists of patients undergoing elective surgery. How to distinguish between pain with and pain without identifiable causes in such an EHR-based study remains a largely unanswered question. This in turn impedes the ability of our study and other EHR-based studies to isolate the patients with primary FM. In their UK Biobank–based study of MCP, Johnston et al (18) did not report whether individuals had identifiable or nonidentifiable sources of pain. Given our current measures of FM, we cannot definitively say if the older individuals we classified as being FM cases in this study had primary FM or had pain from an identifiable source. Thus, we do not have data to evaluate whether primary FM has a smaller genetic component in older individuals than it does in younger individuals.

Although women had higher FM scores than men across age categories, we did not find evidence that heritability varies by sex. This is possible because women can have a higher mean FM score value than men, for example, because sex-related factors cause higher FM score values in women, but still have the same amount of FM score *variability* explained by genetic variation. We can interpret this as follows: although the average FM scores in women are higher than those in men, the genetic contributions to FM score variability did not differ significantly by sex in this sample size.

FM co-occurs with multiple diseases, suggesting there are shared genetic factors underlying these diseases. We found that FM score and SSI have a strong genetic correlation with several psychiatric and personality syndromes, indicating a substantial genetic overlap between them, potentially because psychological measures are part of the FM score. However, our genetic correlation findings for FM score are consistent with results from a UK Biobank study (n = 387,649) by Johnston et al (18) that found a

genetic overlap between MCP and several psychiatric conditions. FM score and WPI were more strongly positively genetically correlated with asthma and RA than was MCP from the UK Biobank. For RA this may be due to an enrichment of individuals with RA in our surgical patient population compared to the more general UK Biobank population.

One limitation of our study is that our sample is not population based. Individuals who were scheduled to have surgery were eligible for recruitment in the study and are more likely to suffer from pain and to be enriched for particular FM-related disorders. Additionally, we used quantile-based inverse normalization of the FM score, which can affect the power to detect heritability.

Overall, this study highlights the importance of considering the age distribution of individuals when designing a genetic association study of FM. These data support the notion that there are (at least) 2 different forms of FM: one that occurs in younger individuals and is strongly genetically driven and one that occurs in older individuals and can be driven by a variety of nongenetic factors and other conditions that cause pain.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Scott had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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