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Cardiomyopathy Gene Variants and Polygenic Risk Scores in Atrial Fibrillation

Evidence for an Atrial-First Phenotype

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) is heritable and its complex underlying genetic substrate is gradually being unraveled.

OBJECTIVES We sought to explore the impact of disease-causing cardiomyopathy variants on the risk of AF after adjustment for incident ventricular cardiomyopathy and clinical heart failure in 2 cohort studies (UK Biobank [UKB] and All of Us [AoU]) and evaluate the utility of polygenic risk scores (PRS) to further discern the risk of atrial and ventricular phenotypes in carriers.

METHODS Cox regression was used to evaluate for associations between disease-causing variants within genes for 3 cardiomyopathies (dilated cardiomyopathy [DCM], hypertrophic cardiomyopathy [HCM], and arrhythmogenic right ventricular cardiomyopathy) and AF. Disease-specific PRSs for AF, DCM, and HCM stratified study participants into quintiles. A HR random-effects meta-analysis was performed using the DerSimonian-Laird method. The Kaplan-Meier method was used to ascertain cumulative incidence from birth to 75 years of age.

RESULTS Among 655,796 individuals from UKB and AoU, presence of a disease-causing variant was associated with an increased AF hazard (HR: 1.73; 95% CI: 1.59-1.89; $P < 0.001$), including after adjustment for incident ventricular cardiomyopathy or clinical heart failure (adjusted to HR: 1.55; 95% CI: 1.46-1.64, $P < 0.001$). The cumulative AF risk for study participants with a putative disease-causing rare variant and a PRS_{AF} within the top-risk quintile ranged from 32.5% (UKB) to 32.4% (AoU) relative to 9.8% (UKB) and 11.0% (AoU) for individuals without a putative disease-causing variant and a PRS_{AF} within the lowest-risk quintile. The absolute cumulative cardiomyopathy risk among study participants with both a putative disease-causing variant and a disease-specific PRS within the top-risk quintile ranged from 5.9% (UKB) to 15.2% (AoU) for DCM and from 11.7% (UKB) to 19.1% (AoU) for HCM.

CONCLUSIONS Genetic variants that cause cardiomyopathy also increase the risk of AF, even in individuals without heart failure or overt ventricular disease. Combining disease-specific PRSs with these variants helps identify whether a person is more likely to develop atrial or ventricular disease. Although discovered as causes of cardiomyopathy, these genes often have an equal or greater impact on the risk of AF. (JACC. 2026;87:1279-1299) © 2026 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AoU = All of Us

ARVC = arrhythmogenic right ventricular cardiomyopathy

DCM = dilated cardiomyopathy

HCM = hypertrophic cardiomyopathy

P/LP = pathogenic/likely pathogenic

PRS = polygenic risk score

TTN = *Titin*

UKB = UK Biobank

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is estimated to affect upwards of 59 million people worldwide and 10 million individuals in the United States alone.[1,2] Affected patients experience debilitating symptoms and increased risks of heart failure, stroke, and death.[3] Despite multiple well-established clinical risk factors for the arrhythmia, our insight into its underlying pathophysiology remains incomplete.

An extensive body of literature has established that AF is heritable and the underlying genetic contributors continue to be unraveled.[4-7] The most common perceived "monogenic" AF culprit is *Titin* (*TTN*), which is notable given that *TTN* truncating variants are also the most common genetic cause of dilated cardiomyopathy (DCM).[4,8-12] Heart failure is a potent AF risk factor, which had traditionally been assumed to be secondary to atrial stretch stemming from increased intracardiac filling pressures and a potential adverse impact of an aberrant neurohormonal milieu on atrial electrophysiology.[13] Although a portion of individuals possessing disease causing *TTN* variants develop AF in the presence of preexisting DCM, a majority that manifest with AF do so in the absence of cardiomyopathy.[8] This observation, coupled with the recognition that *TTN* is also highly expressed within atrial tissue, alludes to the notion that pathogenic *TTN* variants may predispose to AF through a direct effect on atrial tissue, potentially through a primary atrial cardiomyopathy.[14-16]

Beyond *TTN*, multiple other ventricular cardiomyopathy genetic culprits have been implicated in AF, however, the concept that these genes may predispose to AF independent of ventricular cardiomyopathy remains modestly explored.[4,7,12,17-19] Choi et al[7] previously reported that *TTN*, *MYBPC3*, *LMNA*, and *PKP2* associated with AF in the absence of cardiomyopathy and clinical heart failure and similar findings for *TTN* and *PKP2* were also observed by Vad et al,[4] however, this concept has yet to be evaluated for the majority of cardiomyopathy genes. Given that all ventricular cardiomyopathy genes have concomitant atrial expression, although these genes were originally discovered as culprits of ventricular cardiomyopathy, it is conceivable that they may confer a greater impact on the risk for AF compared with heart failure among individuals in the general population. In this overall context, development of AF among carriers of a disease-causing cardiomyopathy variant may also increase their risk of ventricular cardiomyopathy, potentially secondary to a clinically perceived tachycardia-induced cardiomyopathy. Factors governing onset of an atrial rather than a ventricular phenotype in the setting of a pathogenic cardiomyopathy variant are unclear. Integrating recently developed polygenic risk scores (PRS) for AF, DCM, and hypertrophic cardiomyopathy (HCM) may provide insight into the chamber-specific disease risks conferred by these variants.[20-22]

Our study endeavored to use the UK Biobank (UKB) and All of Us (AoU), 2 large prospective cohort studies, to further explore these concepts.

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METHODS

STUDY COHORTS. The UK Biobank. The UKB is a large prospective cohort study that recruited approximately 500,000 individuals aged 40 to 69 years from the United Kingdom National Health Services between 2006 and 2010.[23] Detailed phenotypic and genetic data were collected as previously described and all study participants provided informed consent.[23] Methodology used for ancestry ascertainment is described in the Supplemental Methods. Analyses were restricted to individuals that had both whole exome and genome sequencing available. Quality control and filtering steps were applied to arrive at the final cohort as detailed in the Supplemental Methods and Supplemental Figure 1.

All of Us. The AoU Research Program is a large prospective cohort study from the United States enrolling individuals aged ≥18 years.[24] Phenotypic and genetic data were collected as previously described and all study participants provided informed consent.[24] The latest AoU release (Curated Data Repository version 8) includes approximately

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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633,000 individuals, representing participants from all ethnicities. Analyses were restricted to individuals with electronic health records and whole genome sequencing. Details delineating ancestry groupings are provided in the Supplemental Methods. Quality control and filtering steps were applied to arrive at the final cohort as detailed in the Supplemental Methods and Supplemental Figure 2.

The study was performed as part of a research program ("Molecular Determinants of Health and Disease States") approved by the Hamilton Integrated Research Ethics Board (Hamilton, Ontario, Canada).

PHENOTYPE DEFINITIONS. Longitudinal health outcomes were ascertained in the UKB through self-report from medical history interviews, primary care and hospital-reported International Classification of Diseases 10th revision codes, operation codes, and death registry records.[23] In AoU, the longitudinal phenotypic data were captured from electronic health records from each participating hospital and harmonized to the Observational Medical Outcomes Partnership Common Data Model.[24] The primary outcome of incident AF was defined as the date of the first documentation of either AF or atrial flutter. The specific UKB data fields and AoU Observational Medical Outcomes Partnerships used to ascertain a subset of phenotypic exposures and each outcome are provided in Supplemental Table 1.

SEQUENCING, VARIANT ANNOTATION, AND QUALITY CONTROL. Details of whole exome and genome sequencing in UKB and AoU have been previously described.[25-28] Variants were annotated using ANNOVAR in UKB and NIRVANA 3.18 in AoU. Protein-altering variants were defined as truncating if they resulted in a frameshift, stop-gain, start-loss, or involved a canonical splice site. Exome allele frequency was ascertained using the Genome Aggregation Database version 4.1.0 as a reference with hg38 and hg19.[29] The quality control and filtering steps used have been previously described[28,30] and are detailed in the Supplemental Methods and Supplemental Figures 1 and 2.

SELECTION OF VENTRICULAR CARDIOMYOPATHY GENES AND RARE PATHOGENIC/LIKELY PATHOGENIC AND TRUNCATING VARIANTS. Genes implicated in DCM, HCM, and arrhythmogenic right ventricular cardiomyopathy (ARVC) were included in the main analysis if they had been concluded by ClinGen to have "Definitive," "Strong," or "Moderate" levels of evidence for their involvement in disease through an autosomal-dominant inheritance pattern.[31-35] This led to the inclusion of 29 genes (Table 1). All rare variants within these genes annotated as pathogenic/likely pathogenic (P/LP) by ClinVar with a minor allele frequency <0.01% were included with the exception of nontruncating *SCN5A* variants, which frequently predispose to cardiac channelopathies rather than cardiomyopathy.[36] All rare *SCN5A* missense variants annotated by ClinVar as P/LP were curated by G.L.dR. and J.D.R. and only included in the analyses if they had previously been observed in patients with ventricular cardiomyopathy.

TABLE 1 ClinGen-Adjudicated Genes Causative for Ventricular Cardiomyopathy and Their Putative Disease-Causing Variants Included in the Analyses

Definitive/Strong Cardiomyopathy Genes					Moderate Cardiomyopathy Genes	
DCM		HCM		ARVC	DCM	HCM
*BAG3**	*DES*	*ACTC1*	*ACTN2*	*DSC2**	*ACTC1**	*JPH2*
*DSP**	*FLNC**	*ALPK3**	*CSRP3**	*DSG2**	*ACTN2**	
*LMNA**	*MYH7*	*FHOD3*	*FLNC*	*PKP2**	*JPH2**	
*PLN**	*RBM20**	*MYBPC3**	*MYH7*		*NEXN**	
*SCN5A**[a]	*TMEM43*	*MYL2*	*MYL3*		*TNNI3**	
TNNC1	*TNNT2*	*TNNC1*	*TNNI3*		*TPM1**	
*TTN**[b]		*TNNT2*	*TPM1*		*VCL**	

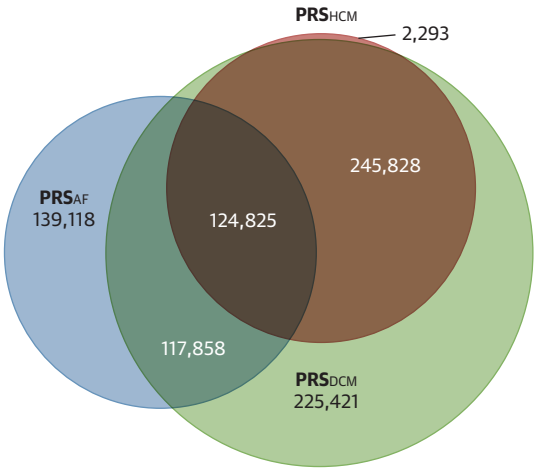
[a]*SCN5A* missense variants were restricted to ClinGen-adjudicated P/LP variants that had previously been implicated in DCM. Truncating variants anticipated to result in nonsense-mediated decay were included for genes marked with an asterisk (*). [b]*TTN* truncating variants were restricted to those within exons with a PSI ratio >90%. All P/LP variants with a minor allele frequency <0.01% within these 29 genes were included in the analyses with the exception of *SCN5A*.

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; P/LP = pathogenic/likely pathogenic; PSI = percent spliced in.

Within this overall group of genes, a subset of 21 had been implicated in cardiomyopathy through truncating variants anticipated to result in nonsense mediated decay (Table 1).[33,35] Truncating variants (as defined already in this article) within these 21 genes considered to be "high-confidence" for being loss-of-function according to LOFTEE filters and additional manual curation performed within the Genome Aggregation Database were also included in the analyses.[37] For *TTN* alone, truncating variants were only included if contained within exons anticipated to be present within >90% of cardiac transcripts, defined as a percent spliced in ratio >90%.[38]

POLYGENIC RISK SCORES. The PRSs for AF (PRS_{AF}),[20] DCM (PRS_{DCM}),[21] and HCM (PRS_{HCM})[22] included in the analyses have been previously reported. The PRS_{AF} was generated using results from a meta-analysis of 40 AF genome-wide association studies involving 181,446 AF cases and 1,468,899 controls.[20] The PRS_{DCM} was derived from 14,256 DCM cases and 1,199,156 controls from the HERMES (Heart Failure Molecular Epidemiology for Therapeutic Targets) Consortium.[21,39] The PRS_{HCM} was derived from the largest HCM genome-wide association study involving 5,900 cases and 68,359

FIGURE 1 Venn Diagram Depicting Genetic Variant Overlap Drawn to Scale for the PRS_{AF}, PRS_{DCM}, and PRS_{HCM}



An additional 1,162 variants exclusively overlap between the PRS_{AF} and PRS_{HCM}. AF = atrial fibrillation; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; PRS = polygenic risk score.

controls.[22,40] Each PRS had been derived using a Bayesian regression framework that models linkage disequilibrium with an external linkage disequilibrium reference set and a continuous shrinkage prior on single nucleotide polymorphism effect sizes.[21,22,41] The PRSs were standardized to have a mean of 0 and a SD of 1. None of the cases used to derive the PRSs were derived from UKB or AoU, although PRS_{HCM} involved UKB study participants as controls.

Correlation between the PRS_{AF}, PRS_{DCM}, and PRS_{HCM} was assessed using the Pearson correlation coefficient and scatter plots were used to visualize the distributions (Supplemental Figures 3 to 6). A Venn diagram was used to visualize variant overlap (**Figure 1**).

STATISTICAL ANALYSIS. Normally and non-normally distributed continuous variables are presented as mean ± SD and median (IQR).

The natural history of carriers and noncarriers of putative disease-causing cardiomyopathy rare variants was assessed from birth, when they were assumed to be disease free (healthy), until 75 years of age. Individuals could transition between 3 states: healthy, AF, and a composite of ventricular cardiomyopathy and/or heart failure. Study participants could transition from healthy to another state, however, could not revert to healthy and a diagnosis of AF, ventricular cardiomyopathy, or heart failure was considered permanent. Sankey diagrams (SankeyMATIC software) were used to visualize the trajectories of study participants.

Time-to-event analyses using Cox proportional hazards models were used to evaluate for associations between carrier status of a putative disease-causing rare variant within a ventricular cardiomyopathy gene and incident AF. Time zero was date of birth, which was considered reasonable given that genetic exposures may influence disease risk from conception, coupled with timing of an incident AF or flutter diagnosis being available from birth (prior to UKB and AoU enrollment). Multivariable Cox regression models included covariables for sex and the first 10 principal components (Model 1) and Model 2 additionally included a time-dependent covariable for incident ventricular cardiomyopathy and/or clinical heart failure. Additional analyses were performed that were restricted to putative disease-causing rare variants within: 1) ventricular cardiomyopathy genes excluding *TTN*; ClinGen adjudicated 2) "Strong"/"Definitive" and 3) "Moderate" level of evidence genes; and 4) individual ventricular cardiomyopathy genes. Analyses stratified by ventricular cardiomyopathy subtype (DCM, HCM, and ARVC) were also performed. For genes implicated in >1 form of ventricular cardiomyopathy, all nontruncating P/LP variants were reviewed by G.L.dR. and J.D.R. and adjudicated to the appropriate cardiomyopathy subtype. Subgroup analyses by ancestry were additionally pursued.

Similar Cox regression models were used to evaluate the impact of PRS_{AF} on the hazard of incident AF in the setting of a putative disease-causing rare variant within a ventricular cardiomyopathy gene. Study participants were stratified into PRS quintiles and carrier status of a putative disease-causing rare variant, yielding 10 subgroups. Additional analyses restricted to putative disease-causing rare variants within: 1) ventricular cardiomyopathy genes excluding *TTN*; and 2) ClinGen-adjudicated "Strong"/"Definitive" level of evidence genes were performed. Similar analyses were performed for HCM and DCM. The HCM analyses included the PRS_{HCM} and were restricted to putative disease-causing rare variants within the HCM subgroup of genes (15 genes), whereas the DCM analyses involved the PRS_{DCM} and were restricted to putative disease-causing rare variants within the DCM gene subgroup (20 genes). Covariables in these Cox regression models were consistent with those for Models 1 and 2, as described already in this article.

Cox regression models were additionally used to evaluate for associations between the PRS_{DCM} and PRS_{HCM} for incident AF. Covariables in these Cox regression models were consistent with those for Models 1 and 2, as described already in this article.

The Kaplan-Meier method was used to plot the cumulative incidence of AF from birth to 75 years of age from the 1-survival probability of the Cox regression models adjusted for sex and the first 10 principal components. Analyses were stratified by PRS quintile and putative disease-causing rare variant carrier status for AF, HCM, and DCM, as described already in this article. Given the perceived low penetrance for ClinGen-adjudicated "Moderate" level of evidence genes, more recently discovered HCM genes, and the potential for *SCN5A* truncating variants to predispose to cardiac channelopathies, these analyses were repeated by restricting the list to ClinGen-adjudicated "Definitive"/"Strong" level of evidence DCM and ARVC genes, HCM genes to the 8 primary sarcomeric genes (*MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, and *ACTC1*), and *SCN5A* variants to P/LP missense variants previously implicated in cardiomyopathy. This panel is subsequently referred to as the "Traditional Ventricular Cardiomyopathy Gene Panel." Sensitivity analyses excluding: 1) cases of incident death and ischemic heart disease; and 2) incident ventricular cardiomyopathy and heart failure were additionally performed.

All analyses were initially performed separately in UKB and AoU. A HR random effects meta-analysis was performed to combine results of the UKB and AoU Cox regression analyses using the DerSimonian-Laird method. For each cohort, we extracted the log-transformed HR and its 95% CI from the Cox proportional hazard models. SEs were computed from the reported CIs.

Two-tailed P values <0.05 were considered statistically significant unless otherwise specified. Statistical analyses were performed using R version 4.4 and the *meta* R package version 8.2.1.

RESULTS

STUDY POPULATION. A total of 364,714 and 291,082 study participants from UKB and AoU, respectively, were included. The mean ages, sex and ancestry distributions, and other clinical features of study participants stratified by carrier status of a putative disease-causing rare variant are provided for each cohort in **Table 2**. Within UKB, a total of 31,730 study participants received an AF diagnosis (6,280 prevalent and 25,450 incident cases [relative to the time of enrollment]) in comparison with 19,686 in AoU (13,450 prevalent and 6,236 incident cases). Both cohorts combined included a total of 9,410 carriers of a putative disease-causing rare variant (5,391 in UKB and 4,019 in AoU) (Supplemental Table 2). A minority of these study participants possessed a *TTN* truncating variant (1,262 [23.4%] in UKB and 762 [19.0%] in AoU) (Supplemental Table 2). Subdivided by cardiomyopathy subtype, 2,817, 1,745, and 869 study participants had a putative disease-causing rare variant within a DCM, HCM, or ARVC gene, respectively, within UKB, in comparison with 2,394 (DCM), 1,093 (HCM), and 558 (ARVC) in AoU (Supplemental Table 3).

IMPACT OF PUTATIVE DISEASE-CAUSING RARE VARIANTS WITHIN VENTRICULAR CARDIOMYOPATHY GENES ON THE RISK OF AF. The natural history of carriers and noncarriers of a putative disease-causing rare variant within ventricular cardiomyopathy genes for the outcomes of AF and the composite of ventricular cardiomyopathy or clinical heart failure in UKB and AoU are shown in **Figure 2** and Supplemental Table 4. Being a carrier of a putative disease-causing rare variant within a ventricular cardiomyopathy gene was associated with an increased hazard of AF within UKB (HR: 1.80; 95% CI: 1.67-1.93; $P < 0.001$), AoU (1.65; 95% CI: 1.49-1.82), and within both cohorts combined (1.73; 95% CI: 1.59-1.89; $P < 0.001$) (**Figure 3**). These associations persisted when the analyses included a time-dependent covariable for incident ventricular cardiomyopathy and/or clinical heart failure (**Figure 3**). When *TTN* truncating variants were excluded, carriers of a putative disease-causing rare variant within the remaining ventricular cardiomyopathy genes remained at an increased hazard of an AF diagnosis (**Figure 3**) and this association persisted within UKB and both cohorts combined after adjustment with a time-dependent covariable for incident ventricular cardiomyopathy and/or clinical heart failure (**Figure 3**). Subgroup analyses by ancestry revealed comparable findings among White European and African ancestries (Supplemental Tables 5 and 6).

Subdivided by cardiomyopathy gene subtype, carriers of a putative disease-causing rare variant within DCM, HCM, and ARVC genes all had statistically significant increased hazards of AF (**Figure 4**). The hazard for incident AF for DCM genes within the combined data set remained significant when *TTN*-truncating variants were excluded (**Figure 4C**). Analyses adjusted for incident ventricular cardiomyopathy and/or clinical heart failure also yielded statistically significant associations with AF for genes

TABLE 2 Clinical Characteristics of Carriers and Noncarriers of a Putative Disease-Causing Rare Variant Within a Cardiomyopathy Gene at Enrollment in the UKB and AoU

	UKB			AoU		
	Noncarrier (n = 359,323)	Carrier (n = 5,391)	*P* value	Noncarrier (n = 287,063)	Carrier (n = 4,019)	*P* value
Age, y	56.7 ± 8.1	56.6 ± 8.1	0.72	55.6 ± 17.0	54.6 ± 16.8	0.004
Male	165,748 (46.1)	2,474 (45.9)	0.73	113,371 (39.5)	1,588 (39.5)	0.99
Ancestry			0.60			0.08
European	350,488 (97.5)	5,246 (97.3)		168,683 (58.8)	2,328 (57.9)	
African	6,493 (1.8)	106 (2.0)		56,041 (19.5)	754 (18.8)	
Admixed American	-	-		51,042 (17.8)	753 (18.7)	
Mixed	1,111 (0.3)	16 (0.3)		-	-	
Other	1,226 (0.3)	23 (0.4)		-	-	
South Asian	4 (0.0)	0 (0.0)		3,637 (1.3)	66 (1.6)	
East Asian	1 (0.0)	0 (0.0)		6,554 (2.3)	104 (2.6)	
Middle Eastern	-	-		1,106 (0.4)	14 (0.3)	
Body mass index, kg/m^2	27.4 ± 4.8	27.4 ± 4.9	0.80	29.9 ± 7.6	30.0 ± 7.7	0.57
Hypertension	96,233 (26.8)	1,440 (26.7)	0.91	100,761 (35.1)	1,399 (34.8)	0.71
Type 2 diabetes mellitus	9,214 (2.6)	125 (2.3)	0.28	46,549 (16.2)	662 (16.5)	0.68
Alcohol			0.35			0.80
>Twice per week	161,383 (45.0)	2,408 (44.7)		67,914 (26.8)	928 (26.1)	
≤Twice per week	197,643 (55.0)	2,980 (55.3)		185,289 (73.2)	2,632 (73.9)	
Smoking			0.40			0.38
Never	194,832 (54.4)	2,946 (54.9)		144,495 (72.6)	2,089 (73.2)	
Previous	125,837 (35.2)	1,892 (35.2)		46,617 (23.4)	665 (23.3)	
Current	37,372 (10.4)	530 (9.9)		8,052 (4.0)	101 (3.5)	
Ischemic heart disease	19,060 (5.3)	338 (6.3)	0.002	19,988 (7.0)	357 (8.9)	<0.001
AF	6,077 (1.7)	203 (3.8)	<0.001	13,153 (4.6)	297 (7.4)	<0.001
DCM	866 (0.2)	96 (1.8)	<0.001	1,244 (0.4)	59 (1.5)	<0.001
HCM	434 (0.1)	90 (1.6)	<0.001	728 (0.3)	69 (1.7)	<0.001
Other/unspecified cardiomyopathy	1,057 (0.3)	111 (1.8)	<0.001	5,314 (1.9)	149 (3.7)	<0.001
Heart failure	1,926 (0.5)	75 (1.4)	<0.001	15,510 (5.4)	350 (8.7)	<0.001

Values are mean ± SD or n (%).
AF = atrial fibrillation; AoU = All of Us; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; UKB = UK Biobank.

implicated in DCM and ARVC, but not HCM, when both cohorts were combined (Figure 4).

Single-gene analyses within the combined cohorts revealed that carriers of a *TTN*-truncating variant had an increased hazard of AF (HR: 2.79; 95% CI: 2.18-3.56; $P < 0.001$), including after adjustment for incident ventricular cardiomyopathy and/or clinical heart failure (HR: 2.33; 95% CI: 2.11-2.57; $P < 0.001$) (Figures 3 and 5). Among the additional ClinGen-adjudicated "Strong"/"Definitive" level of evidence genes, carriers of a putative disease-causing rare variant in 7 DCM genes (*BAG3*, *FLNC*, *LMNA*, *MYH7*, *PLN*, *RBM20*, and *SCN5A*), 4 HCM genes (*MYBPC3*, *MYH7*, *TNNT2*, and *TPM1*), and 1 ARVC gene (*PKP2*) had statistically significant increased hazards of AF (Figure 5, Supplemental Figure 7). The associations for *BAG3*, *FLNC*, *LMNA*, *RBM20*, *SCN5A*, *MYH7* (HCM), *TPM1*, and *PKP2* remained statistically significant after adjustment for incident ventricular cardiomyopathy and/or heart failure (Figure 5). Among ClinGen-adjudicated "Moderate" level of evidence genes, statistically significant associations were observed for *ACTC1* and *ACTN2* (Figure 5, Supplemental Figure 8).

IMPACT OF PRSs ON THE RISK OF ATRIAL AND VENTRICULAR PHENOTYPES IN THE SETTING OF A PUTATIVE DISEASE-CAUSING RARE VARIANT WITHIN A VENTRICULAR CARDIOMYOPATHY GENE.

To evaluate the impact of disease-specific PRSs on the risk of developing an atrial or ventricular phenotype in the setting of a putative disease-causing rare variant within a ventricular cardiomyopathy gene, study participants were stratified into PRS quintiles and the presence or absence of a putative disease-causing rare variant.

Atrial fibrillation. Increasing PRS_{AF} quintiles were associated with progressively increased hazards of

AF and, within each quintile, presence of a putative disease-causing rare variant further increased the magnitude of the HR (**Figure 6** [UKB and AoU combined], Supplemental Figure 9 [UKB] and Supplemental Figure 10 [AoU], and Supplemental Table 7). Within UKB and AoU combined, relative to study participants within the lowest PRS_{AF} quintile that did not have a putative disease-causing rare variant, study participants in the top PRS_{AF} quintile with a putative disease-causing rare variant had a 3.45-fold increased hazard of AF (95% CI: 3.05-3.89; P < 0.001) (**Figure 6A**, Supplemental Table 7). A statistical test for interaction between rare variant carrier status and PRS_{AF} treated as a continuous variable for the meta-analyzed results was not significant ($P = 0.63$). Similar results were observed when *TTN* putative disease-causing rare variants were excluded from the analyses (**Figure 6B** [UKB and AoU combined] and Supplemental Figure 9 [UKB] and Supplemental Figure 10 [AoU]), after adjustment for incident ventricular cardiomyopathy and/or heart failure (Supplemental Figure 11 [UKB and AoU combined] and Supplemental Figure 12 [UKB] and Supplemental Figure 13 [AoU]), and when the analyses were restricted to ClinGen-adjudicated "Definitive"/"Strong" level of evidence genes (Supplemental Figure 14 [UKB and AoU combined] and Supplemental Figure 15 [UKB] and Supplemental Figure 16 [AoU]).

HCM and DCM. Using this approach for HCM and DCM, similar patterns were observed, although the magnitudes of the measures of association were larger (**Figure 7**, Supplemental Figures 17 to 20). Analyses for HCM were restricted to the 15 genes implicated in HCM and a similar approach was used for DCM, which involved 20 genes.

For HCM within UKB and AoU combined, relative to study participants within the lowest PRS_{HCM} quintile that did not possess a putative disease-causing rare variant, study participants in the top PRS_{HCM} quintile with a putative disease-causing rare variant had a 74-fold increased hazard of HCM (95% CI: 15-350; $P < 0.001$) (**Figure 7A**, Supplemental Table 8). For DCM within UKB and AoU combined, relative to study participants within the lowest quintile PRS_{DCM} that did not have a putative disease-causing rare variant, study participants in the top PRS_{DCM} quintile with a putative disease-causing rare variant had a 22.3-fold increased hazard of a DCM diagnosis (95% CI: 14.2-35.2; $P < 0.001$) (**Figure 7B**, Supplemental Table 8).

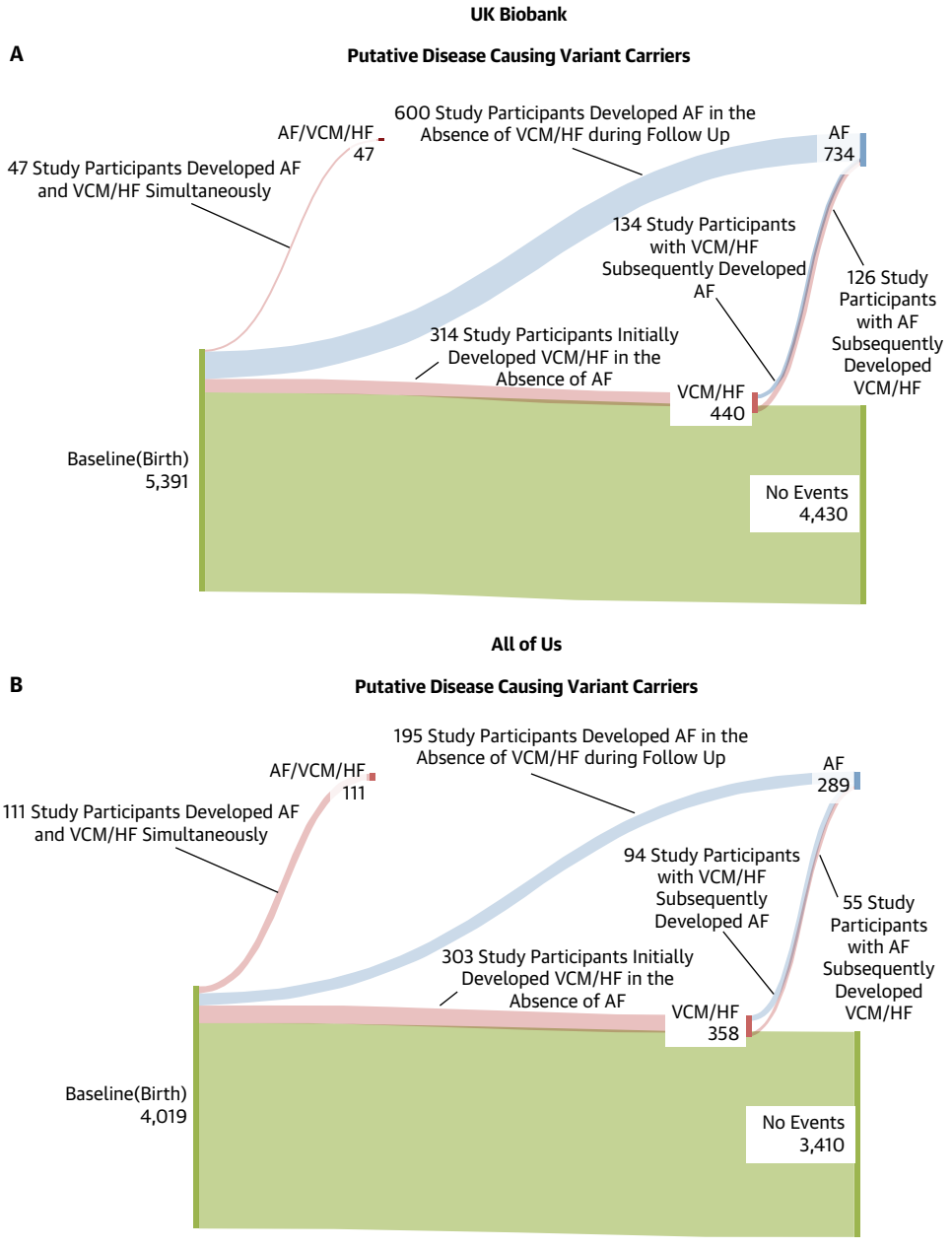
IMPACT OF THE PRS_{DCM} AND PRS_{HCM} ON THE RISK OF AF. The PRS_{DCM} was found to be associated with increased hazards (for 1 SD increase) for AF in both UKB (HR: 1.05; 95% CI: 1.03-1.06; $P < 0.001$) and AoU (1.09: 95% CI: 1.07-1.11; $P < 0.001$), including when the analyses were adjusted for incident ventricular cardiomyopathy and/or clinical heart failure ([UKB] HR: 1.06; 95% CI: 1.05-1.07; $P < 0.001$; [AoU] HR: 1.09; 95% CI: 1.08-1.11; $P < 0.001$). In contrast, a statistically significant association was only observed for the PRS_{HCM} in AoU (UKB analyses were nonsignificant) after adjustment for incident ventricular cardiomyopathy and/or clinical heart failure (HR: 1.02; 95% CI: 1.00-1.03; $P = 0.023$) (Supplemental Table 9).

CUMULATIVE RISK OF INCIDENT ATRIAL AND VENTRICULAR PHENOTYPES. For cumulative risk analyses, date of birth was considered time zero and study participants were censored after an AF diagnosis, death, loss to follow-up, or on reaching 75 years of age. The median follow-up times were 66 (IQR: 59.2-72.2; UKB) and 58 years (IQR: 41.0-69.0; AoU) and the total number of AF cases were 24,556 and 16,064, respectively.

Within UKB, the absolute cumulative risk of AF among study participants without a putative disease-causing rare variant and having a PRS_{AF} within the first quintile was 9.8% (95% CI: 9.5-10.1%) (**Figures 8A and 9A**, Supplemental Table 10). In contrast, the cumulative AF risk for study participants with a putative disease-causing rare variant and a PRS_{AF} within the top quintile was 32.5% (95% CI: 28.2.3-36.5%), corresponding to an absolute risk increase of 22.7% (95% CI: 19.9-25.5%) (**Figures 8A and 9A**, Supplemental Table 10). Sensitivity analyses excluding study participants with any cause of death or ischemic heart disease revealed a comparable absolute risk increase for AF (UKB 18.7%; 95% CI: 15.4-22.0%) (Supplemental Table 11). Similar results were observed when the analyses were restricted to individuals without incident ventricular cardiomyopathy or heart failure (Supplemental Table 12 UKB). When the analysis was performed using the Traditional Ventricular Cardiomyopathy Gene panel, the cumulative AF risk for study participants with a putative disease-causing rare variant and a PRS_{AF} within the top quintile increased to 36.8% (95% CI: 31.4-41.9%) (**Figure 9C**, Supplemental Figure 21A, Supplemental Table 13). Corresponding results for AoU are provided in **Figures 8B, 9B, and 9D**, Supplemental Figure 21B, and Supplemental Tables 14 to 17.

Within UKB, the absolute cumulative risk of DCM among study participants having a PRS_{DCM} within the lowest-risk quintile and without a putative disease-causing rare variant in a DCM gene was 0.2%

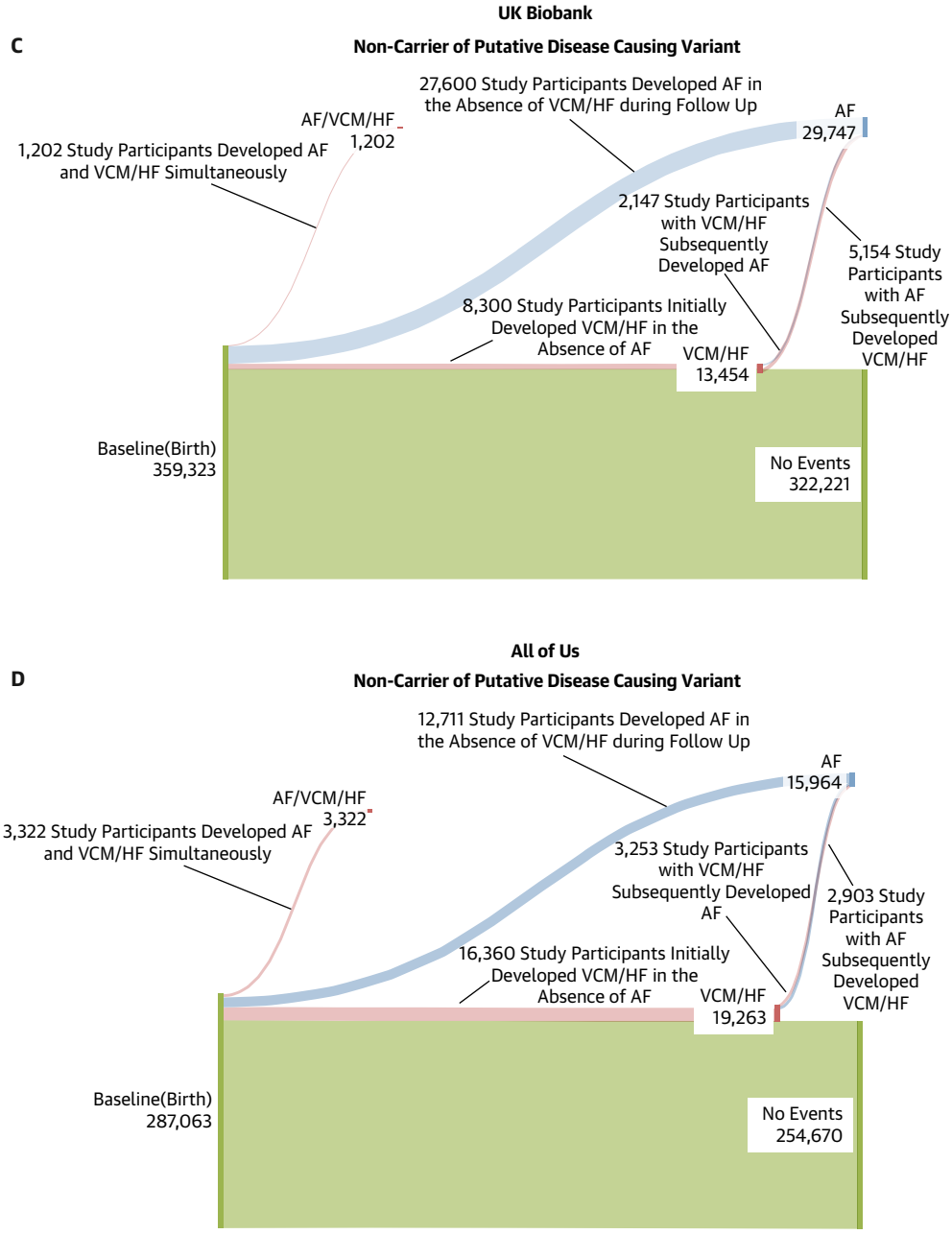
FIGURE 2 **Sankey Diagrams Depicting the Natural History of Carriers and Noncarriers of Putative Disease-Causing Rare Variants Within Cardiomyopathy Genes for Incident Atrial Fibrillation and Ventricular Cardiomyopathy/Clinical Heart Failure**



Carriers (A) (UK Biobank) and (B) (All of Us) and noncarriers (C) (UK Biobank) and (D) (All of Us) of putative disease-causing rare variants within cardiomyopathy genes. The width of lines/curves corresponds to the proportion of study participants transitioning to an outcome (and the specific number of study participants is additionally provided). AF = atrial fibrillation; VCM/HF = any form of ventricular cardiomyopathy or clinical heart failure; other abbreviations as in Figure 1.

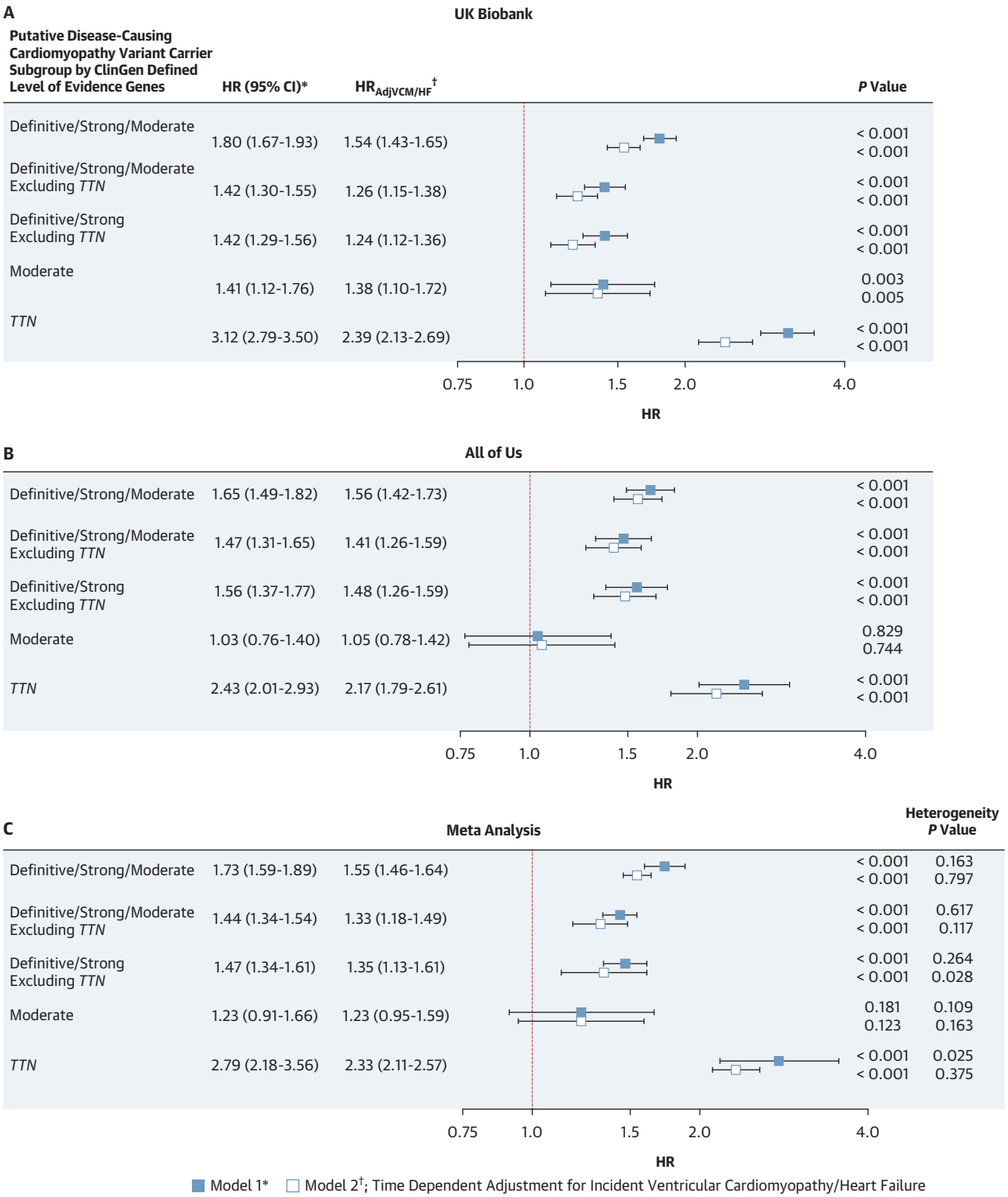
Continued on the next page

FIGURE 2 Continued



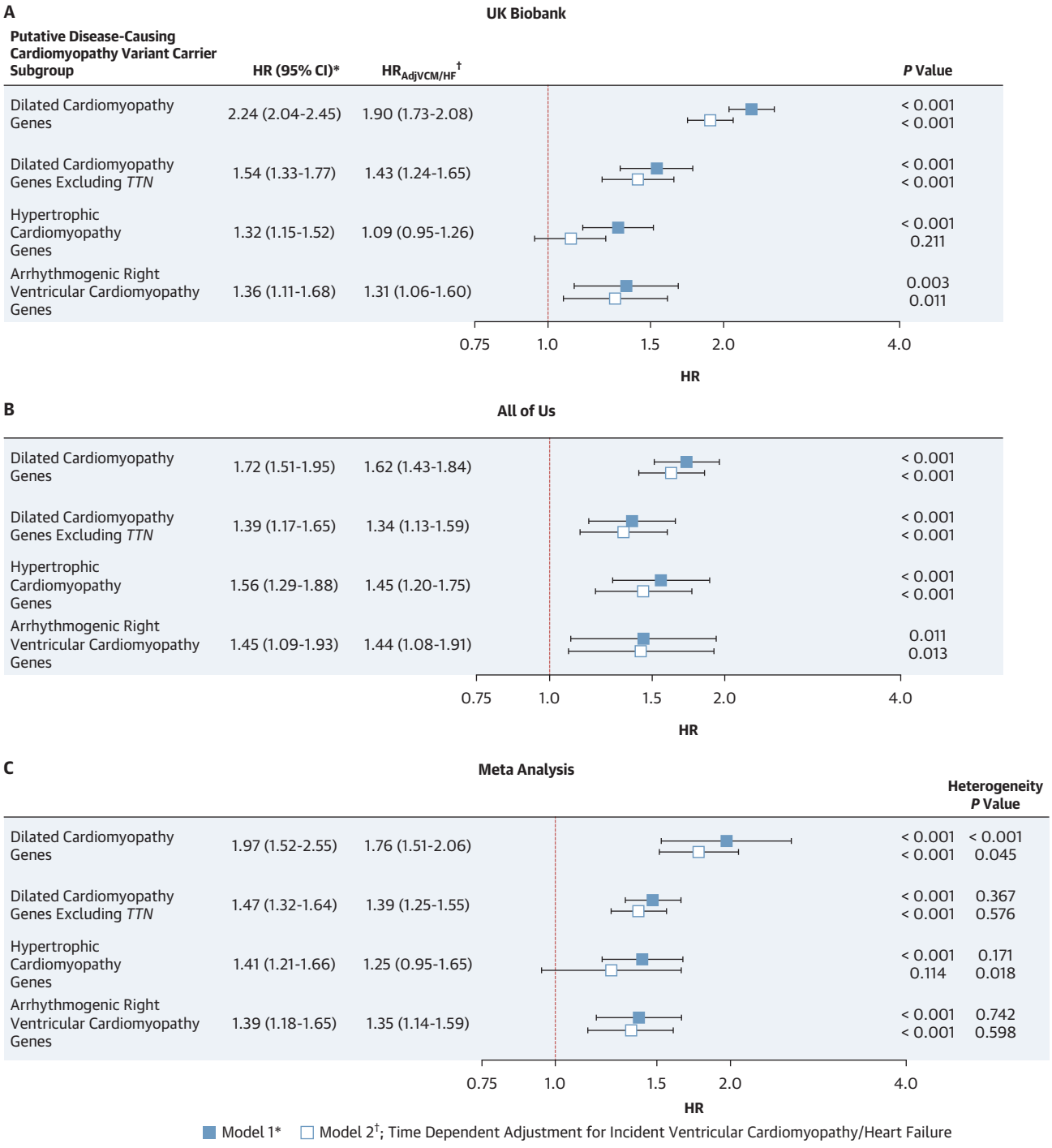
(95% CI: 0.2-0.3%) (**Figures 8C and 9A**, Supplemental Table 10). In contrast, the cumulative risk for DCM among study participants with a putative disease-causing rare variant in a DCM gene and a PRS_{DCM} within the top quintile was 5.9% (95% CI: 3.7-8.1%), corresponding to an absolute risk increase of 5.7% (95% CI: 3.8-7.6%) (**Figures 8C and 9A**, Supplemental Table 10). Sensitivity analyses excluding study participants with incident death or ischemic heart disease revealed a comparable absolute risk increase (UKB 3.4%; 95% CI: 1.6-5.2) (Supplemental Table 11). When the analysis was restricted to the DCM portion of the Traditional Ventricular Cardiomyopathy Gene panel, the cumulative risk for DCM among study participants with a putative disease-causing rare variant and a PRS_{DCM} within the top quintile

FIGURE 3 Association of Carrier Status of a Putative Disease-Causing Cardiomyopathy Rare Variant on the Hazard of Incident AF in the UKB and AoU



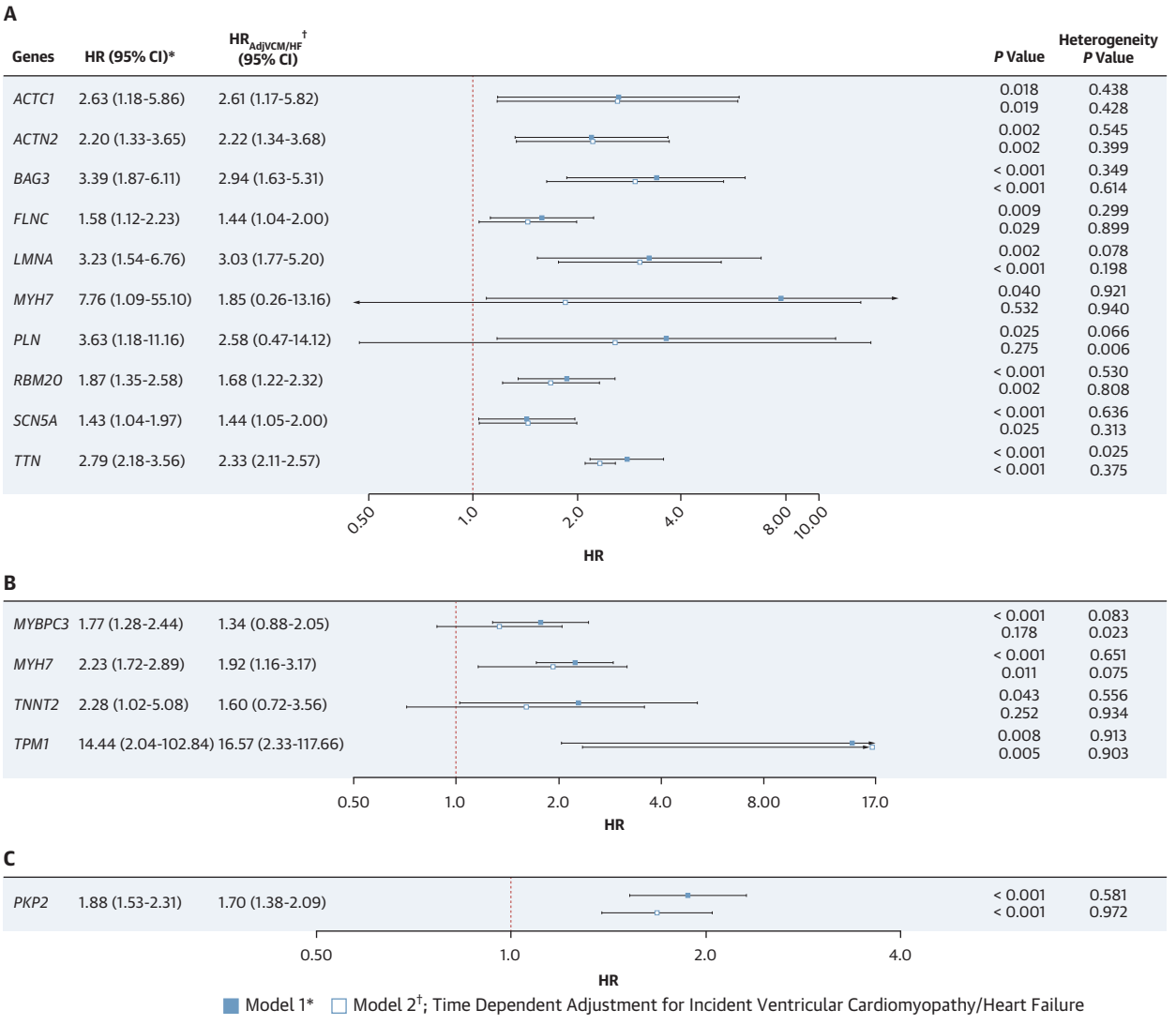
*Model 1 analyses are adjusted for sex and the first 10 principal components. †Model 2 analyses are additionally adjusted with a time-dependent covariable for incident ventricular cardiomyopathy and/or heart failure. Pooled effect size from meta-analysis between UKB and AoU. Error bars represent 95% CIs. Abbreviations as in Figure 2.

FIGURE 4 Association of Carrier Status of a Putative Disease-Causing Cardiomyopathy Rare Variant on the Hazard of Incident AF by Ventricular Cardiomyopathy Subtype in the UKB and AoU



*Model 1 analyses are adjusted for sex and the first 10 principal components. †Model 2 analyses are additionally adjusted with a time-dependent covariable for incident ventricular cardiomyopathy and/or heart failure. Pooled effect size from meta-analysis between UKB and AoU. Abbreviations as in Figures 1 and 2. Error bars represent 95% CIs.

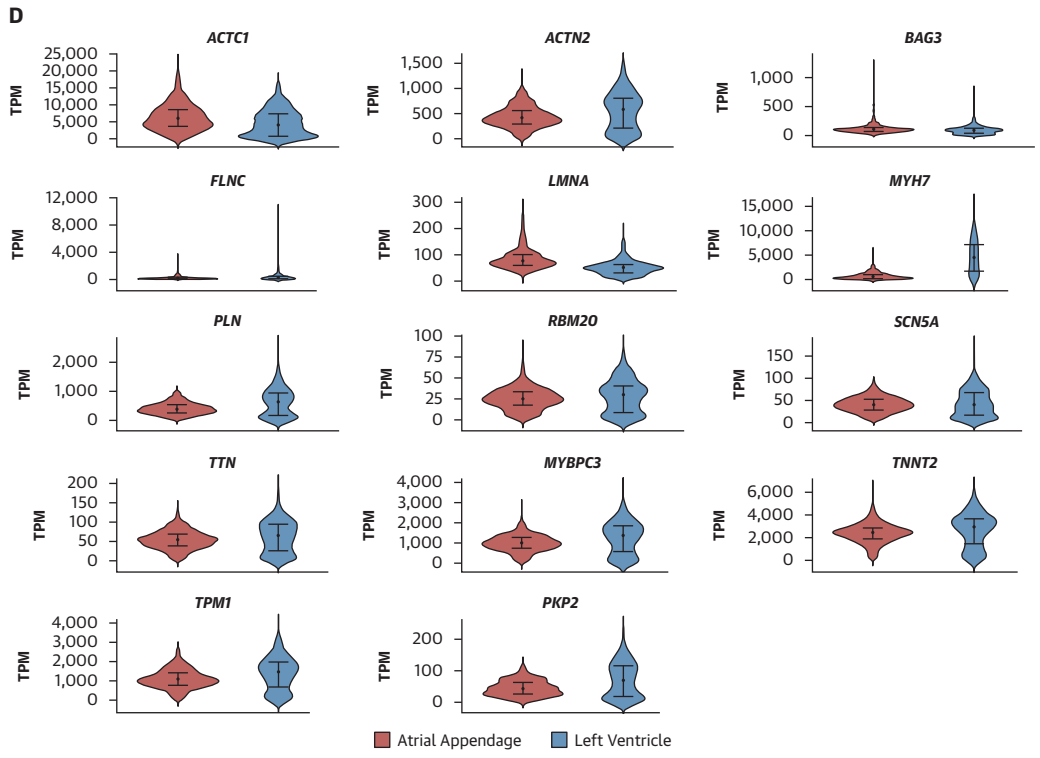
FIGURE 5 **Association of Carrier Status of a Putative Disease-Causing Rare Cardiomyopathy Variant on the Hazard of Incident Atrial Fibrillation Within Statistically Significant Cardiomyopathy Genes and their Expression Levels in Atrial Appendage and Left Ventricular Tissue**



(A) Dilated cardiomyopathy; (B) hypertrophic cardiomyopathy, and (C) arrhythmogenic right ventricular cardiomyopathy. (D) Gene expression levels as measured by RNA sequencing (transcripts per million) in atrial appendage and left ventricular tissue from the adult Genotype-Tissue Expression (GTEx) Repository for these statistically significant cardiomyopathy genes. All analyses are adjusted for sex and the first 10 principal components. †Analyses are additionally adjusted with a time-dependent covariable for incident ventricular cardiomyopathy and/or heart failure. Pooled effect size from meta-analysis between UK Biobank and All of Us. Error bars represent 95% confidence intervals. TPM = Transcripts per million; other abbreviations as in Figures 1 and 2.

Continued on the next page

FIGURE 5 Continued



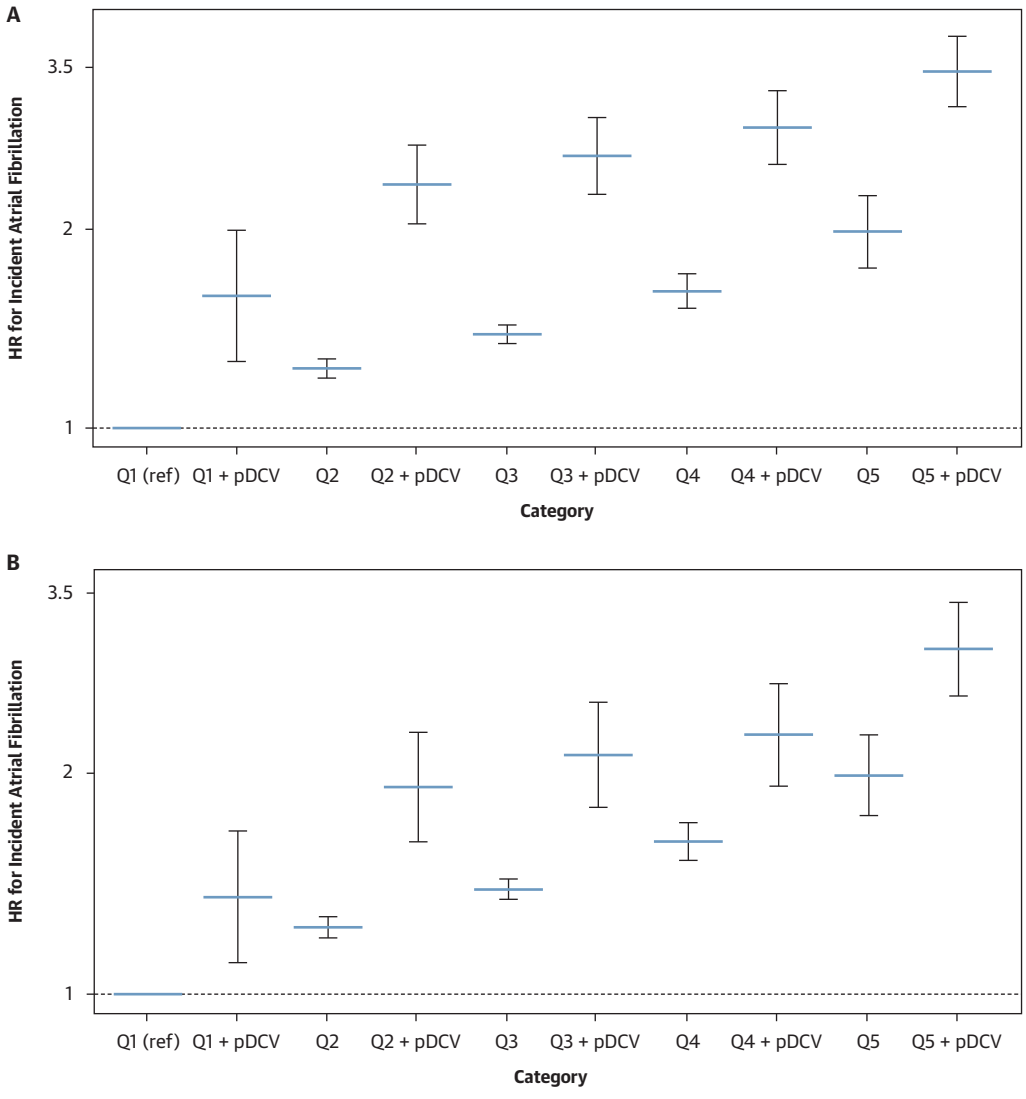
increased to 8.3% (95% CI: 5.1-11.0%) (**Figure 9C**, Supplemental Figure 21C, Supplemental Table 13). Corresponding results for AoU were similar and are provided in **Figures 8D, 9B, and 9D**, Supplemental Figure 21D, and Supplemental Tables 14, 15, and 17.

Within UKB, the absolute cumulative risk of HCM among study participants without a putative disease-causing rare variant in a HCM gene and having a PRS_{HCM} within the lowest-risk quintile was 0.08% (95% CI: 0.05-0.1%) (**Figures 8E and 9A**, Supplemental Table 10). In contrast, the cumulative HCM risk for study participants with a putative disease-causing rare variant in a HCM gene and a PRS_{HCM} within the top quintile was 11.7% (95% CI: 7.5-15.8%), corresponding to an absolute risk increase of 11.6% (95% CI: 8.0-15.2%) (**Figures 8E and 9A**, Supplemental Table 10). When the analysis was restricted to the HCM portion of the Traditional Ventricular Cardiomyopathy Gene panel, the cumulative risk for HCM among study participants with a putative disease-causing rare variant and a PRS_{HCM} within the top quintile increased to 21.8% (95% CI: 13.6-29.2%) (**Figure 9C**, Supplemental Figure 21E, Supplemental Table 13). Corresponding results for AoU were similar and are provided in **Figures 8F, 9B, and 9D**, Supplemental Figure 21F, and Supplemental Tables 14, 15, and 17.

DISCUSSION

Our study involving 655,796 individuals from UKB and AoU found that presence of a putative disease-causing rare variant within the full complement of ClinGen-adjudicated genes with at least moderate level of evidence for ventricular cardiomyopathy was associated with an increased risk of incident AF. Importantly, the associations persisted in analyses adjusted for incident ventricular cardiomyopathy and/or clinical evidence of heart failure. These findings allude to the possibility that rare variants known to be causative for ventricular cardiomyopathy may simultaneously predispose to AF via a direct impact on atrial tissue (**Central Illustration**), although we acknowledge that other explanations remain

FIGURE 6 Combined Impact of a Putative Disease-Causing Cardiomyopathy Rare Variant and Quintile Status of a Polygenic Risk Score for Atrial Fibrillation on the Risk of Incident Atrial Fibrillation

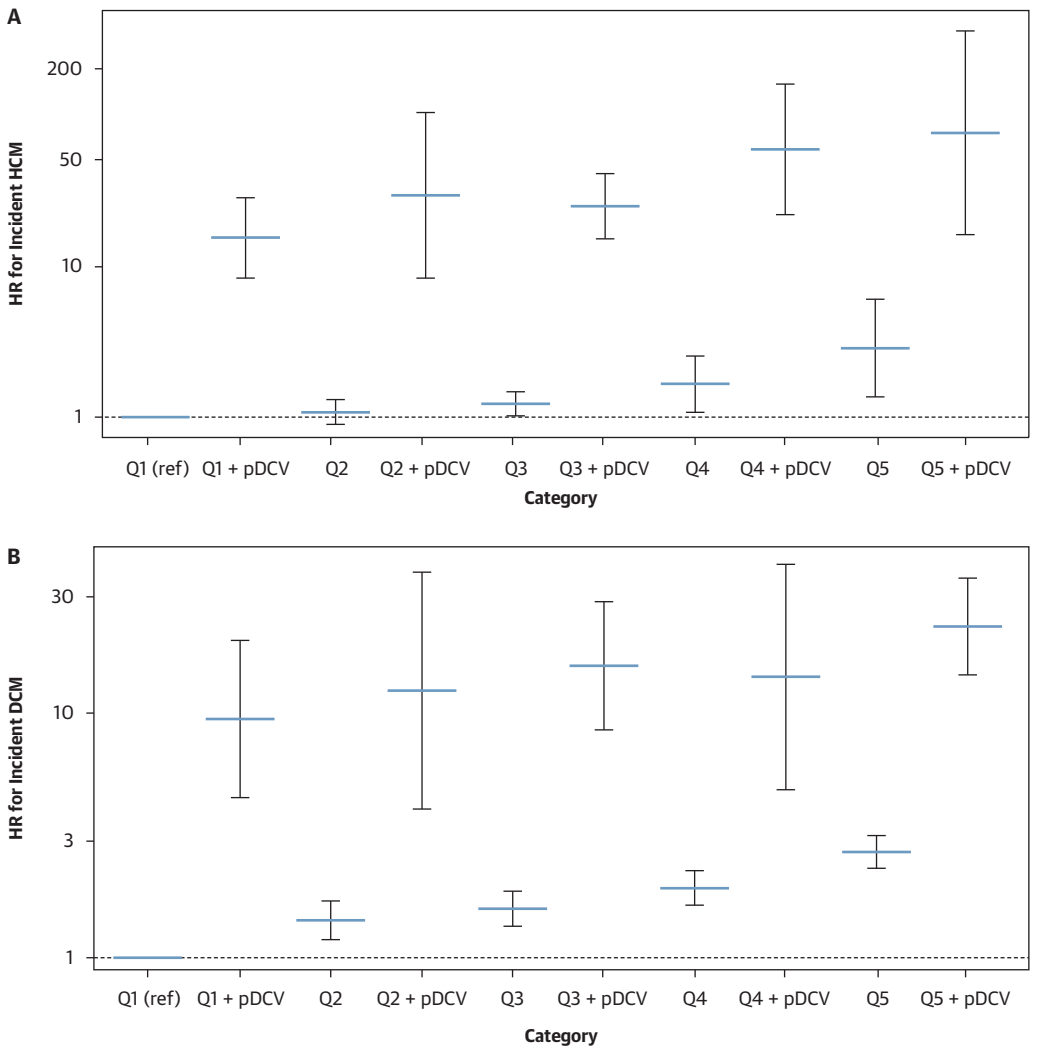


ClinGen adjudicated "Definitive"/"Strong"/"Moderate" level of evidence genes with (A) and without (B) *TTN*. Analyses adjusted for sex and the first 10 principal components. Pooled effect size from meta-analysis between UKB and All of Us. Study participants are stratified into 10 groups on the basis of PRS_{AF} quintile and carrier status of a putative disease-causing cardiomyopathy rare variant. The reference group for the analysis is individuals in the lowest risk PRS_{AF} quintile (Q1) that do not possess a putative disease-causing cardiomyopathy rare variant. QX = PRS_{AF}quintile wherein X ranges from 1 to 5 (1 being the lowest and 5 being the highest risk quintile). + pDCV = carrier of a putative disease-causing cardiomyopathy rare variant. Error bars represent 95% confidence intervals.

plausible. This contrasts with the traditional view that the increased risk of AF observed for genetic forms of ventricular cardiomyopathy arises secondary to increased intracardiac filling pressures and the neurohormonal consequences of heart failure.[42]

Given the recognition that pathogenic ventricular cardiomyopathy variants may give rise to either AF or ventricular cardiomyopathy (or both), we explored the impact of disease-specific PRSs to further discern vulnerability to atrial and ventricular phenotypes in

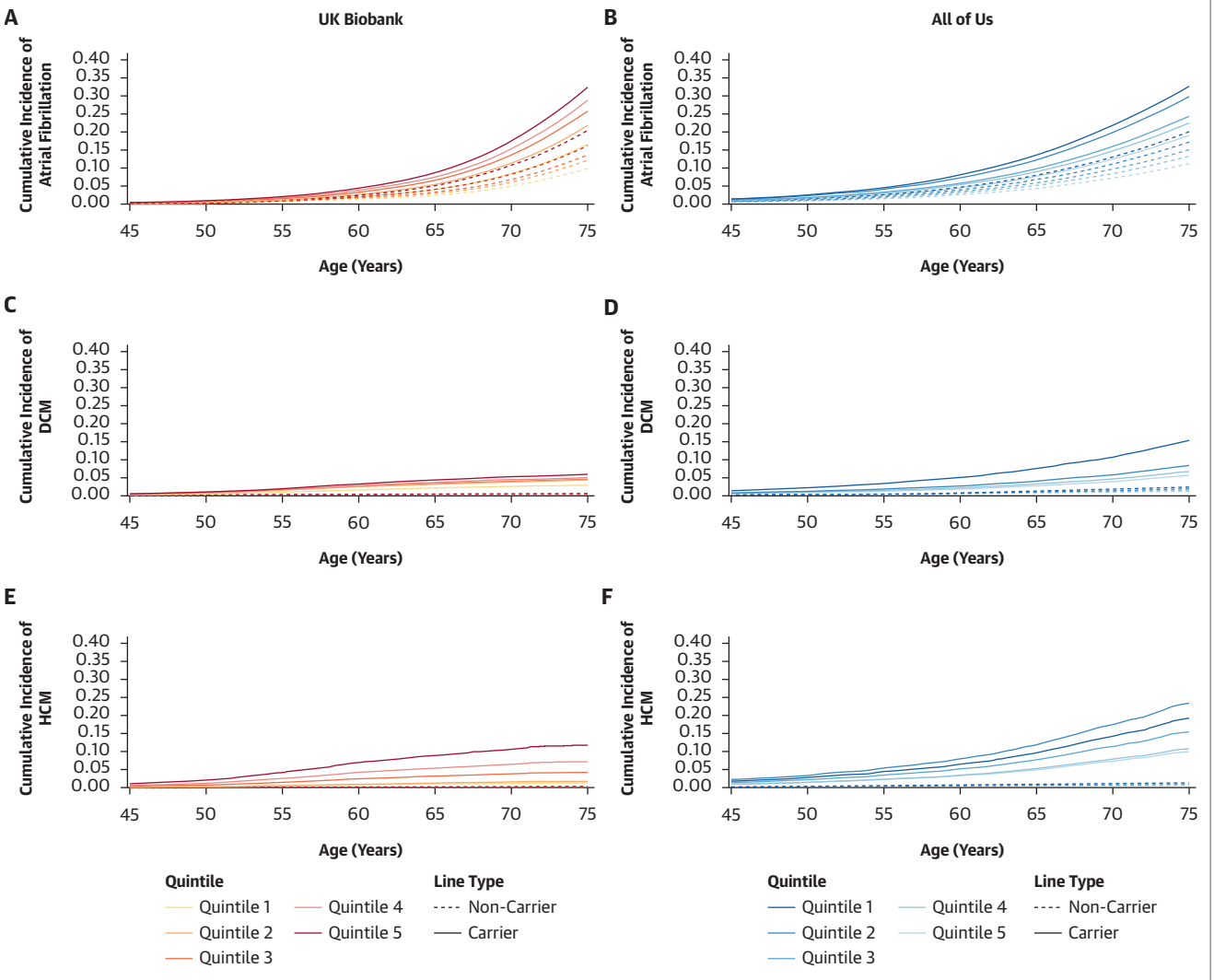
FIGURE 7 Combined Impact of a Putative Disease-Causing Rare Cardiomyopathy Variant and Quintile Status of a Polygenic Risk Score on the Risk on Incident Hypertrophic and Dilated Cardiomyopathy



Analyses adjusted for sex and the first 10 principal components. Study participants are stratified into 10 groups on the basis of: PRS_{HCM} quintile and carrier status of a putative disease-causing rare cardiomyopathy variant within an HCM gene (A) or PRS_{DCM} quintile and carrier status of a putative disease-causing rare cardiomyopathy variant within a DCM gene (B). Genes included were the ClinGen adjudicated "Definitive"/"Strong"/"Moderate" level of evidence genes. Pooled effect size from meta-analysis between UKB and All of Us. The reference groups for the analyses are individuals in the first PRS quintile (Q1) that do not possess a putative disease-causing rare cardiomyopathy variant. QX = PRS_{HCM} or PRS_{DCM} quintile wherein X ranges from 1 to 5 (1 being the lowest and 5 being the highest risk quintile). + pDCV = carrier of a putative disease-causing rare cardiomyopathy variant. Error bars represent 95% confidence intervals. Abbreviations as in Figures 1, 2, and 5.

the presence of these disease-causing rare variants. Stratifying carrier status of putative disease-causing rare variants by disease-specific PRS quintile status dramatically improved the ability to discern the risk of onset of AF, DCM, and HCM and appears to provide important insight into chamber-specific risk. Perhaps equally striking, despite the much larger relative hazards for DCM and HCM, putative disease-causing rare cardiomyopathy variants imparted an at least comparable and often greater impact on the absolute risk of AF relative to these ventricular cardiomyopathies in these study cohorts, as highlighted in Figures 8 and 9. Although these genes were originally identified as causes of ventricular cardiomyopathy,

FIGURE 8 Cumulative Incidence of Atrial Fibrillation, Dilated Cardiomyopathy, and Hypertrophic Cardiomyopathy From Birth to 75 Years Stratified by Carrier Status of a Putative Disease-Causing Cardiomyopathy Rare Variant* and Risk Quintiles of a Disease Specific Polygenic Risk Score

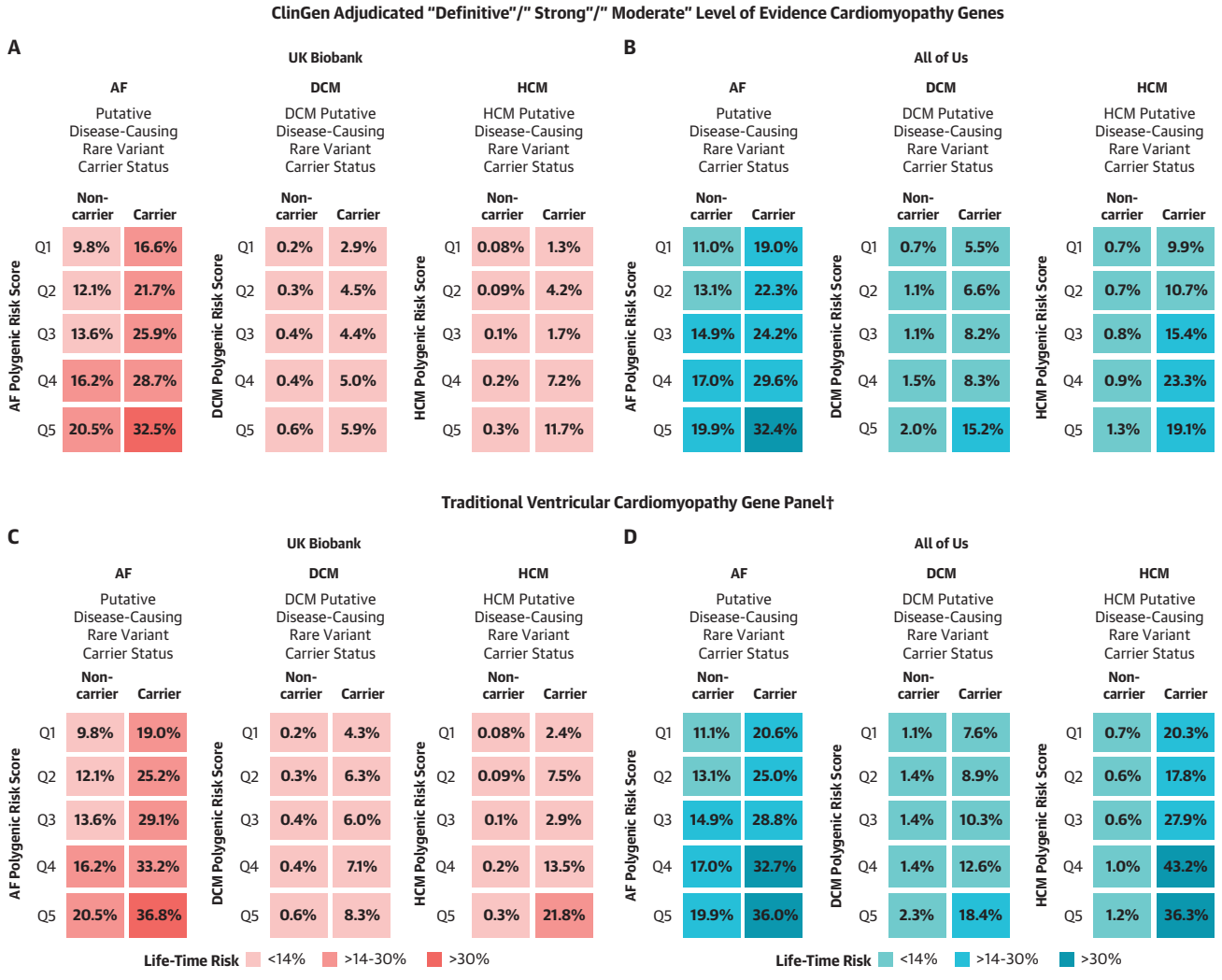


Atrial fibrillation (A) (UK Biobank) and B (All of Us), dilated cardiomyopathy (C) (UK Biobank) and D (All of Us), and hypertrophic cardiomyopathy (E) (UK Biobank)and F (All of Us). *Putative disease-causing cardiomyopathy rare variant status for atrial fibrillation is inclusive of all 28 cardiomyopathy genes with at least one carrier, whereas for DCM and HCM it is restricted to their 19 and 11 disease-specific genes with at least one carrier, respectively. PRS quintiles range from lowest (1) to highest (5) risk. DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy.

their greatest impact on the risk of incident disease within the general population may be as predisposing factors for AF.

Given the now firmly established association between *TTN* and AF, we sought to explore associations between disease-causing rare variants in other cardiomyopathy genes and AF. Consistent with *TTN,* other cardiomyopathy genes are expressed at similar levels in the atria and ventricles, as evidenced from RNA-Seq data available from the Adult Genotype-Tissue Expression project (**Figure 5D**, Supplemental Figure 22).[43] The notion that these genes have high levels of atrial expression and could give rise to an atrial cardiomyopathy that manifests clinically as AF aligned with the possibility that they could predispose to AF in isolation. Consistent with prior findings for *TTN* and a small number of other cardiomyopathy genes,[4,7,8] our study found that the full complement of ClinGen-validated cardiomyopathy genes collectively exhibited a robust association with AF in analyses adjusted for incident ventricular cardiomyopathy and/or heart failure. Among cardiomyopathy subtypes, statistically significant adjusted associations were observed for DCM and ARVC. No

FIGURE 9 **Cumulative Lifetime Risk From Birth to 75 years of Age for Atrial Fibrillation, Dilated Cardiomyopathy, and Hypertrophic Cardiomyopathy Stratified by Disease-Specific Polygenic Risk Score Quintiles and Carrier Status of a Putative Disease-Causing Cardiomyopathy Rare Variant**

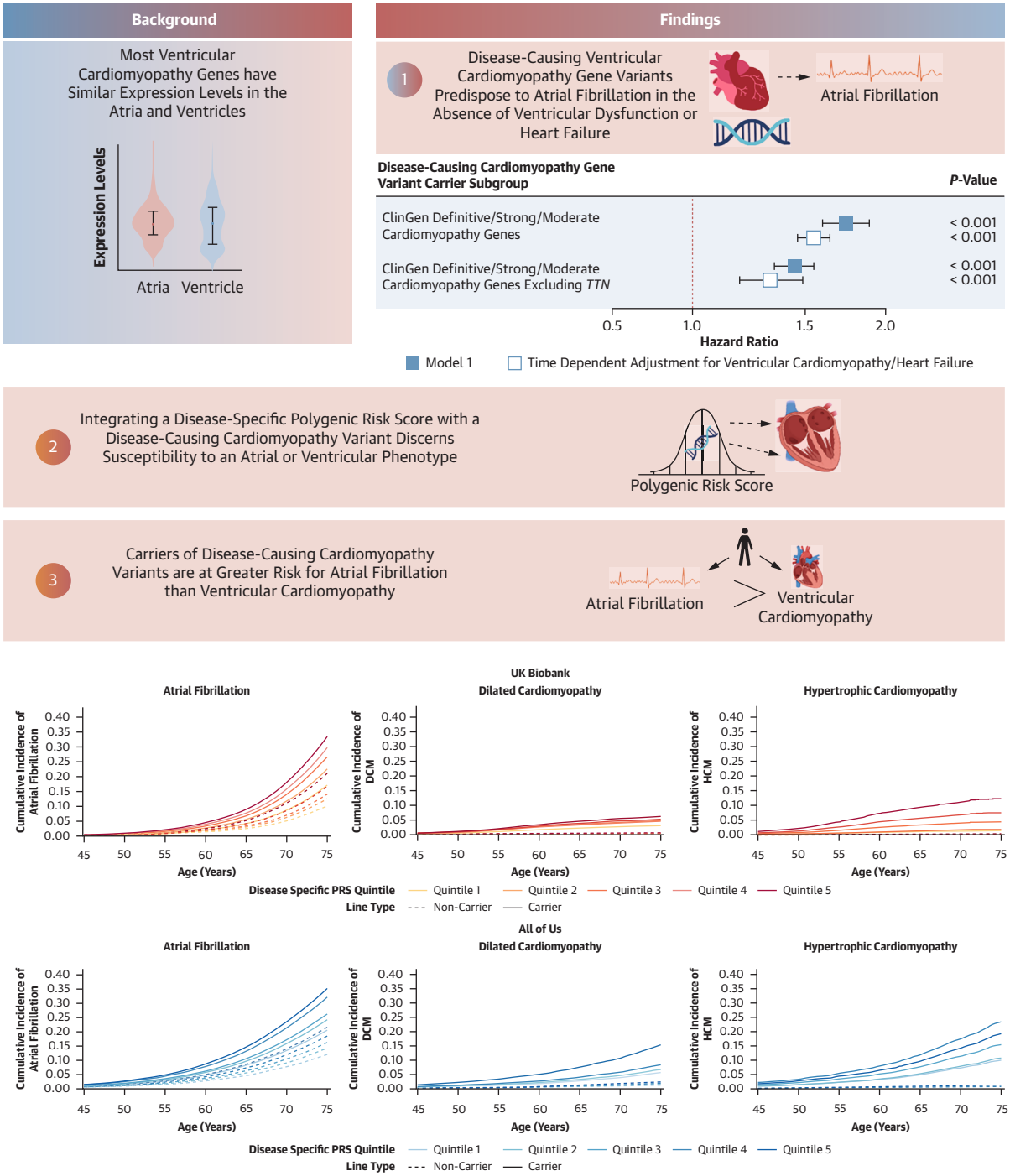


ClinGen adjudicated "Definitive"/"Strong"/"Moderate" level of evidence cardiomyopathy genes (A) (UK Biobank) and (B) (All of Us) and the Traditional Ventricular Cardiomyopathy Gene panel†(C) (UK Biobank) and (D) (All of Us). †The Traditional Ventricular Cardiomyopathy Gene panel consists of ClinGen adjudicated "Definitive"/"Strong" level of evidence DCM and ARVC genes, the 8 primary sarcomeric genes for HCM, and *SCN5A* variants were restricted to ClinGen adjudicated pathogenic/likely pathogenic missense variants that had previously been implicated in DCM. *Putative disease-causing cardiomyopathy rare variant status for AF is inclusive of all cardiomyopathy genes, whereas for DCM and HCM it is restricted to their disease-specific genes. QX = PRS quintile wherein X ranges from 1 to 5 (1 being the lowest and 5 being the highest risk quintile). PRS quintiles range from lowest (1) to highest (5) risk. DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; other abbreviations as in Figures 1 and 2.

detectable association was observed for genes implicated in HCM following adjustment for incident ventricular cardiomyopathy and/or heart failure, however this may have been secondary to inadequate statistical power. Although our findings are compatible with AF in variant carriers arising secondary to atrial cardiomyopathy, it is important to acknowledge that other alternative explanations are plausible, including subclinical forms of ventricular cardiomyopathy and diastolic dysfunction, or unascertained hemodynamic alterations.

Given that pathogenic cardiomyopathy variants may manifest with AF or ventricular cardiomyopathy, clarification of factors that differentially predispose to an atrial or ventricular phenotype is crucial. Guided by prior work that combined common and rare variants to discern disease risk, including in the context of AF,[4] DCM,[21] and HCM,[22] we paired disease-specific PRSs

CENTRAL ILLUSTRATION Disease-Causing Cardiomyopathy Variants Increase the Risk of Atrial Fibrillation in the Absence of Ventricular Cardiomyopathy or Heart Failure and Pairing Polygenic Risk Scores With Cardiomyopathy Variants Informs the Likelihood of Developing Atrial and/or Ventricular Disease



da Rocha GL, et al. JACC. 2026;87(10):1279–1299.

Disease-causing cardiomyopathy variants increase the risk of AF in the absence of ventricular cardiomyopathy or heart failure. Pairing PRS with cardiomyopathy variants informs the likelihood of developing atrial and/or ventricular disease. Although discovered as causes of cardiomyopathy, these genes often have an equal or greater impact on the risk of AF. AF = atrial fibrillation; PRS = polygenic risk score.

with carrier status of a disease-causing cardiomyopathy rare variant. For each of AF, DCM, and HCM, addition of the disease-specific PRS resulted in a dramatic improvement in stratification of chamber-specific risk. Although concerns persist regarding the utility of PRSs and their integration into the clinical setting has been limited to date,[44,45] we believe that their use to determine likelihood of onset of an atrial and/or ventricular phenotype in the setting of a cardiomyopathy variant that could manifest with either or both highlights a potentially powerful clinical use case.

The HRs for incident HCM and DCM among carriers of a putative disease-causing rare variant that were within the highest risk PRS quintiles were much larger relative to the corresponding HRs for incident AF. Although this highlights the critical importance of genetic contributors to developing these ventricular cardiomyopathies, it is not reflective of the absolute risk of these phenotypes in the setting of these genetic substrates. Despite the dramatic measures of association for HCM and DCM, individuals with a putative disease-causing rare cardiomyopathy variant that were within the highest risk AF PRS quintile had comparable and often greater risk and absolute risk increases relative to noncarriers in the lowest PRS quintile for developing AF by 75 years of age relative to the absolute risk and absolute risk increases of developing ventricular cardiomyopathy among the corresponding highest- and lowest-risk individuals for both DCM and HCM. Although development of a ventricular cardiomyopathy may be more severe and clinically impactful, given an often greater impact on the absolute risk for developing AF, appropriate emphasis and counseling on AF vulnerability is likely important. This is viewed as particularly relevant given the broad array of modifiable risk factors that can be optimized to reduce the risk of arrhythmia onset,[3] although we acknowledge that it remains unknown if optimization of risk factors reduces AF vulnerability among carriers of a disease-causing cardiomyopathy variant.

Although presence of a putative disease-causing rare cardiomyopathy variant in UKB and AoU was often associated with a greater impact on risk for AF relative to the ventricular cardiomyopathies that led to their discovery, it should be emphasized that this may not be operative for HCM and DCM families. As shown in the analyses involving PRSs, genomic background is a crucial determinant for risk of manifesting a clinical phenotype. Beyond having a pathogenic and previously presumed "monogenic" culprit for ventricular cardiomyopathy, HCM and DCM families with multiple affected members are anticipated to simultaneously harbor a genomic background that has rendered family members vulnerable to ventricular cardiomyopathy. In this context, their familial risk of ventricular cardiomyopathy may exceed their vulnerability to AF.

STUDY LIMITATIONS. Our study provides important insight into AF vulnerability in the setting of putative disease-causing cardiomyopathy rare variants, however, it has important limitations. Although our approach for ascertaining clinical variables and the outcomes of AF, DCM, and HCM in UKB and AoU is consistent with other studies, incorrect ascertainment is possible. In our genetic analyses, the only true confounder should be population stratification. Confounding bias secondary to population stratification should be minimized through adjustment for principal components. In this overall context, misclassification of the outcomes should be nondifferential and anticipated to result in bias toward the null rather than leading to spurious associations. Although our study was large, the number of carriers of a putative disease-causing rare variant was limited for many of the genes evaluated and hence the lack of associations for individual genes may be secondary to inadequate statistical power.

CONCLUSIONS

This study provides strong evidence that putative disease-causing rare variants within ventricular cardiomyopathy genes are associated with an increased risk of AF, aligning with prior work.[4,7,8,12,19] Importantly, these associations persisted after adjustment for incident ventricular cardiomyopathy and/or clinical heart failure, suggesting they may be secondary to a direct impact on atrial tissue and perhaps a primary atrial cardiomyopathy. Combining carrier status of a putative disease-causing rare variant with disease-specific PRSs for AF, HCM, and DCM substantially improved the ability to predict vulnerability to incident atrial and ventricular phenotypes. Despite these genes having been originally identified as culprits for ventricular cardiomyopathy, their impact on the absolute risk and risk increase for AF appears comparable and often larger relative to those for developing HCM and DCM within the general population. These findings have important implications for the counseling and clinical management of individuals identified to have these variants, particularly when they are identified incidentally (Clinical Implications Box). Among phenotype-negative patients, beyond appropriate counseling

CLINICAL IMPLICATIONS BOX

- Cardiomyopathy genes are expressed in both the atria and ventricles and may give rise to either AF, ventricular cardiomyopathy, or both.
- Pairing disease-specific PRS with cardiomyopathy variants informs the likelihood of developing atrial or ventricular disease.
- Recognition of the relative risks of developing AF and ventricular cardiomyopathy can guide genetic counseling and enable tailoring of clinical monitoring, prevention, and treatment strategies.
  - Examples include:
    - Individuals at high risk of developing AF may benefit from more intensive optimization of modifiable risk factors and monitoring for arrhythmia development
    - Patients with AF and increased vulnerability to DCM may derive increased benefit from a rhythm control approach

and monitoring for onset of ventricular cardiomyopathy, intermittent screening for AF and preventive measures, including optimization of risk factors, may be advisable.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.