Supplemental material

Vad et al., Prevalence of deleterious variants in cardiomyopathy genes in early-onset atrial fibrillation

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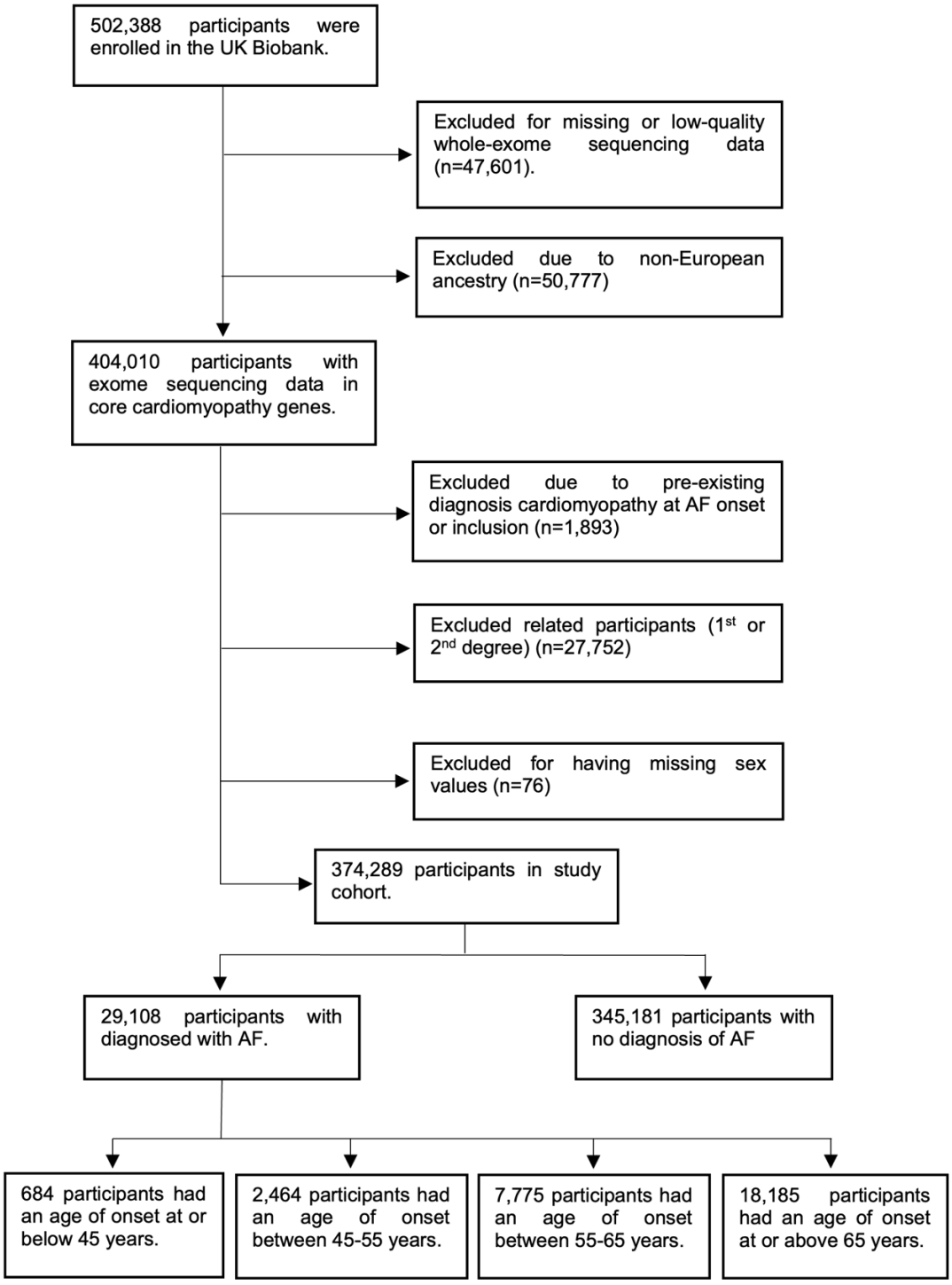
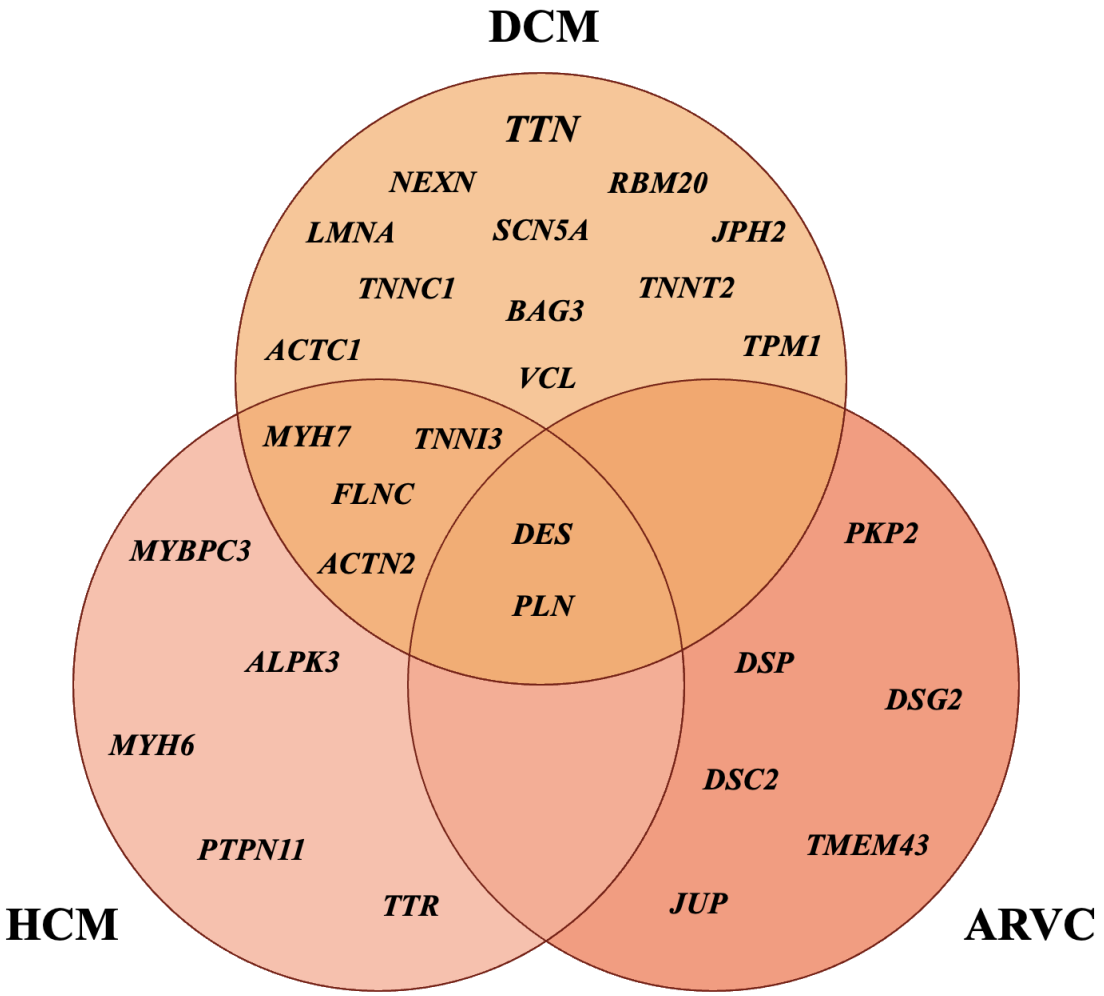
Figure S1. Flowchart of the study design.



AF: Atrial Fibrillation

Figure S2. Venn diagram illustrating the distribution of Cardiomyopathy-associated genes examined in the study.



Distribution of genes by their association with either hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Figure S3. Percentage and odds ratio of participants carrying missense variants in cardiomyopathy genes based on age at AF diagnosis.

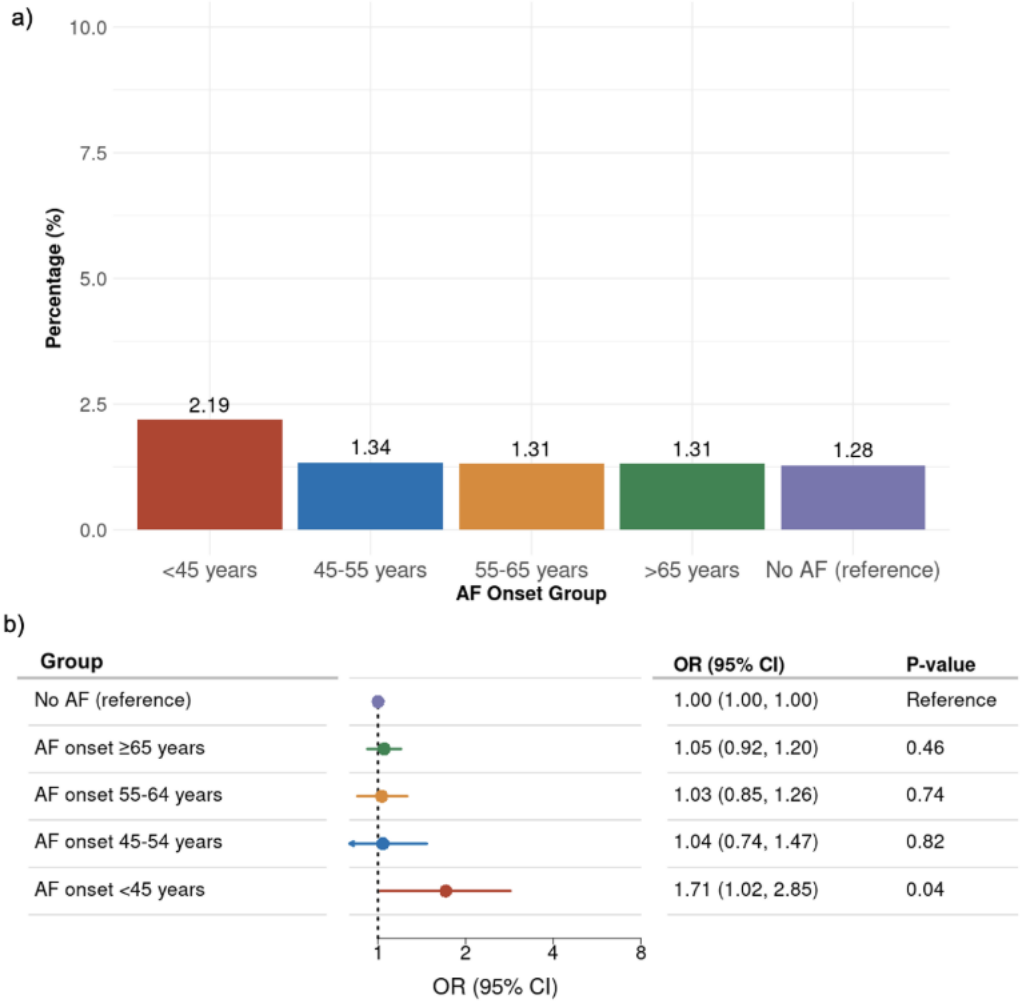
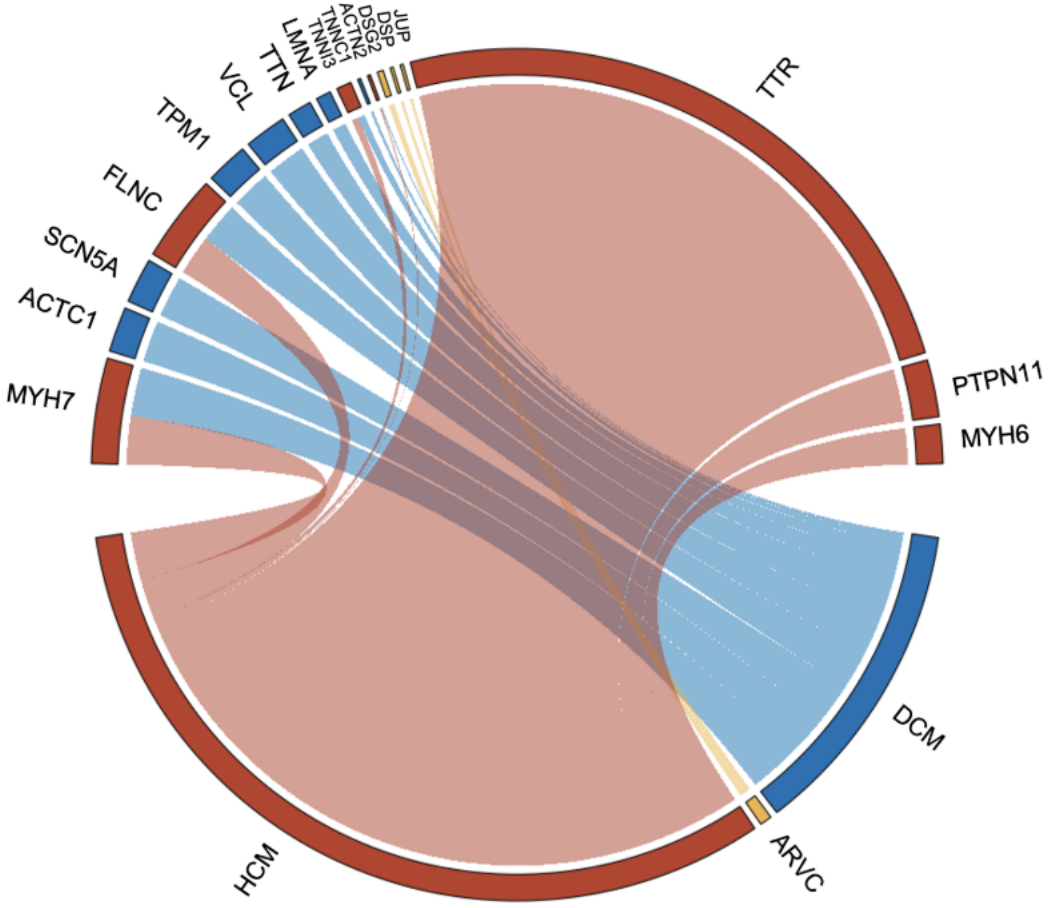


Figure S3a: UK Biobank data showing rare missense variant carrier percentage, specifically for MTR below the 5th percentile, stratified by age at AF onset. The highest prevalence of carriers is observed among individuals with AF onset before 45 years (red), while the lowest is seen in individuals with onset of AF at or after 65 years of age (green) or no diagnosis (purple).

Figure S3b: Forest plot displaying odds ratios (ORs), confidence intervals (CI) and p-values for missense MTR below the 5th percentile carriers in the UK Biobank.

Figure S4. Distribution of rare missense variants in individuals diagnosed with AF according to genes and their association with different cardiomyopathies.



The blue segments represent variants in genes associated with dilated cardiomyopathy (DCM), the red segments correspond to variants in hypertrophic cardiomyopathy (HCM)-associated genes, and the yellow segments indicate variants in genes associated with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Table S1. Phenotype definitions according to the *International Classification of Diseases, 10th revision* (ICD-10).

Phenotypes	UK Biobank data field	ICD-10 code
Sex	31, 22001	–
Ethnic background	21000	–
Body Mass Index	21001	–
Diabetes	130706, 130708, 130714	E10, E11, E14
Atrial Fibrillation	131350	I48
Cardiomyopathy	131338	I42
Heart Failure	131354	I50
Diastolic Blood pressure	4079	–
Systolic Blood Pressure	4080	–
Hypertension	131286	I10
Principal Components, 1 to 10	22009	–

Table S2. Prevalence of predicted Loss-of-Function variants in *TTN* in the Danish early-onset AF cohort.

Gene	Mutation Type	Variant ID	Clinical Significance	Allele Count
TTN	Frameshift	chr2:179398385 TG>T	VUS	1
TTN	Frameshift	chr2:179398541 C>CT	VUS	2
TTN	Nonsense	chr2:179398832 C>T	P/LP	1
TTN	Frameshift	chr2:179404492 CT>C	P/LP	1
TTN	Nonsense	chr2:179416407 AG>A	LP	1
TTN	Splice donor variant	chr2:179418639 A>C	P	2
TTN	Nonsense	chr2:179425041 A>T	P	1
TTN	Nonsense	chr2:179431758 A>T	VUS	1
TTN	Frameshift	chr2:179437869 TG>T	VUS	1
TTN	Frameshift	chr2:179459103 C>CA	P/LP	2
TTN	Nonsense	chr2:179460360 G>A	VUS	1
TTN	Nonsense	rs72646828	P/LP	1
TTN	Splice donor variant	chr2:179474814 T>TA	VUS	1
TTN	Nonsense	chr2:179477082 G>A	P/LP	2
TTN	Nonsense	rs140743001	P/LP	1
TTN	Nonsense	chr2:179495596 C>A	VUS	1
TTN	Frameshift	chr2:179501177 AAC>A	VUS	1
TTN	Splice donor variant	rs546105899	VUS	1
TTN	Frameshift	chr2:179569604 CTCTG>C	VUS	1
TTN	Nonsense	chr2:179605689 G>A	VUS	1
TTN	Nonsense	chr2:179606008 G>T	VUS	1
TTN	Frameshift	chr2:179606444 AGTGTAGCCACATCCCCCAT>A	VUS	1
TTN	Frameshift	rs781363456	VUS	1
TTN	Frameshift	chr2:179632504 AC>A	VUS	1
TTN	Frameshift	chr2:179665309 TG>T	VUS	1

AF: Atrial Fibrillation

P: Pathogenic

LP: Likely pathogenic

VUS: Variant of uncertain significance

TTN: TTN PSI>90

Table S3. Prevalence of predicted Loss-of-Function variants in non-*TTN* genes in the Danish early-onset AF cohort.

Gene	Mutation Type	Variant ID	Clinical Significance	Allele Count
LMNA	Splice acceptor variant	rs775312747	VUS	1
LMNA	Frameshift	rs863225024	P	1
LMNA	Frameshift	rs941656503	VUS	1
SCN5A	Nonsense	chr3:38595811 C>T	P	1
RBM20	Frameshift	chr10:112572320 A>AGTTGGAC	VUS	1
RBM20	Nonsense	chr10:112572514 G>T	VUS	1
MYBPC3	Splice donor variant	rs397516073	P	1
PKP2	Splice donor variant	chr12:32996115 C>A	VUS	1
MYH7	Nonsense	chr14:23900862 G>A	VUS	1
TPM1	Frameshift	chr15:63335123 C>CG	VUS	1
TPM1	Stop lost	rs139159081	VUS	1
DSC2	Nonsense	chr18:28649072 G>A	VUS	1
DSC2	Splice acceptor variant	rs1371049672	VUS	1

AF: Atrial Fibrillation

P: Pathogenic

LP: Likely pathogenic

VUS: Variant of uncertain significance

Table S4. Truncating variant carrier counts in UK Biobank for different AF onset groups and entire study population.

Gene	AF onset <45 years (n%), n = 684	AF population (n%), n = 29,108	Total population (n%), n = 374,289
TTN*	15 (2.19%)	210 (0.72%)	1060 (0.28%)
PKP2	2 (0.29%)	70 (0.24%)	502 (0.13%)
ALPK3	1 (0.14%)	58 (0.20%)	705 (0.19%)
NEXN	0 (0%)	29 (0.10%)	261 (0.07%)
MYH7	0 (0%)	23 (0.08%)	318 (0.08%)
RBM20	1 (0.14%)	22 (0.08%)	152 (0.04%)
MYH6	0 (0%)	22 (0.08%)	247 (0.07%)
TNNT2	0 (0%)	21 (0.08%)	285 (0.08%)
DSP	3 (0.44%)	17 (0.06%)	217 (0.06%)
MYBPC3	0 (0%)	17 (0.06%)	145 (0.04%)
DSG2	0 (0%)	16 (0.05%)	230 (0.06%)
SCN5A	0 (0%)	16 (0.05%)	171 (0.05%)
FLNC	1 (0.14%)	13 (0.04%)	78 (0.02%)
TMEM43	1 (0.14%)	12 (0.04%)	125 (0.03%)
TNNI3	0 (0%)	12 (0.04%)	95 (0.03%)
VCL	1 (0.14%)	12 (0.04%)	124 (0.03%)
TPM1	0 (0%)	11 (0.04%)	114 (0.03%)
ACTN2	1 (0.14%)	10 (0.03%)	68 (0.02%)
DES	0 (0%)	10 (0.03%)	84 (0.02%)
DSC2	0 (0%)	8 (0.03%)	145 (0.04%)
JUP	0 (0%)	6 (0.02%)	70 (0.02%)
LMNA	0 (0%)	6 (0.02%)	82 (0.02%)
PTPN11	0 (0%)	4 (0.01%)	25 (0.01%)
ACTC1	0 (0%)	3 (0.01%)	33 (0.01%)
JPH2	0 (0%)	3 (0.01%)	77 (0.02%)
PLN	0 (0%)	3 (0.01%)	23 (0.01%)
TNNC1	0 (0%)	3 (0.01%)	26 (0.01%)
BAG3	1 (0.14%)	1 (0.003%)	20 (0.005%)
TTR	0 (0%)	1 (0.003%)	15 (0.004%)

AF: Atrial Fibrillation

TTN: TTN PSI>90*

n: number of carriers

Table S5. Missense variant carrier counts in UK Biobank for different AF onset groups and entire study population.

Gene	AF onset <45 years (n%), n = 684	AF population (n%), n = 29,108	Total population (n%), n = 374,289
TTR	6 (0.87%)	214 (0.73%)	2814 (0.75%)
MYH7	1 (0.14%)	35 (0.12%)	486 (0.13%)
FLNC	1 (0.14%)	29 (0.10%)	310 (0.08%)
PTPN11	1 (0.14%)	19 (0.06%)	198 (0.05%)
SCN5A	0 (0%)	15 (0.05%)	194 (0.05%)
MYH6	1 (0.14%)	13 (0.04%)	135 (0.03%)
VCL	1 (0.14%)	14 (0.05%)	134 (0.03%)
ACTC1	2 (0.29%)	15 (0.05%)	111 (0.03%)
TPM1	1 (0.14%)	14 (0.05%)	104 (0.03%)
TTN	0 (0%)	8 (0.02%)	87 (0.02%)
TNNI3	0 (0%)	5 (0.02%)	59 (0.02%)
DSG2	0 (0%)	2 (0.01%)	44 (0.01%)
TNNC1	0 (0%)	1 (0.003%)	42 (0.01%)
ACTN2	0 (0%)	1 (0.003%)	34 (0.009%)
LMNA	1 (0.14%)	5 (0.02%)	33 (0.008%)
DSP	0 (0%)	1 (0.003%)	26 (0.007%)
JUP	0 (0%)	1 (0.003%)	13 (0.003%)
DES	0 (0%)	0 (0%)	8 (0.002%)
TNNT2	0 (0%)	0 (0%)	2 (<0.001%)

AF: Atrial Fibrillation

TTN: TTN PSI>90*

n: number of carriers

Table S6. Count and percentage of carriers of each genetic variant, truncating or missense, from the different age groups of the UK Biobank.

Group	Carriers of Genetic Variant		
	Truncating (n%)	Missense (n%)	Combined (n%)
AF onset <45 years, n = 684	26 (3.80%)	15 (2.19%)	41 (5.99%)
AF onset 45-54 years, n = 2,464	64 (2.59%)	33 (1.34%)	95 (3.85%)
AF onset 55-64 years, n = 7,775	175 (2.25%)	102 (1.31%)	274 (3.52%)
AF onset at or >65 years, n = 18,185	369 (2.02%)	239 (1.31%)	600 (3.29%)
No AF (reference), n = 345,181	4,821 (1.39%)	4,427 (1.28%)	9,195 (2.66%)

AF: Atrial Fibrillation

n: number of carriers