Relationship between Titin and lifestyle risk factors on incident AF risk among the UK Biobank

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Background

Titin truncating variants (TTNtv) have been associated with heightened arrhythmogenic risk among the dilated cardiomyopathy population. However, it is unclear whether TTNtv could enhance risk stratification in evaluating incident AF risk.

Aim

We evaluated the interaction between TTNtv and lifestyle AF risk factors on incident AF risk among the UK Biobank..

Method

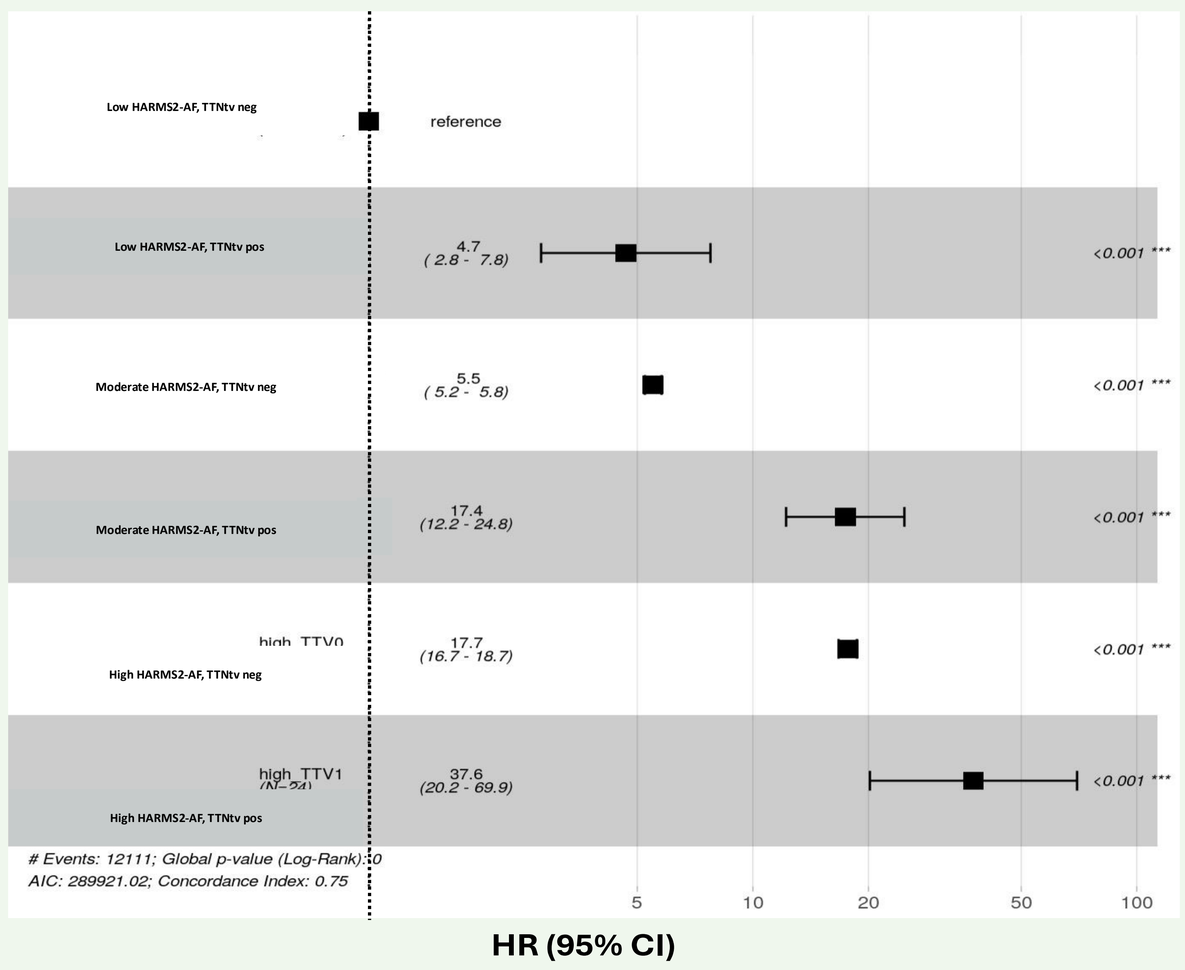
TTNtv was examined in those with and without incident AF based on ICD-10 coding (baseline AF was an exclusion). Univariate and multivariable regression examined the association between TTNtv, components of the previously validated $HARMS_2$-AF lifestyle AF risk score, and incident AF risk. We then compared TTNtv prevalence stratified by low (score <5) and high (score ≥5) $HARMS_2$-AF clinical risk categories.

Results

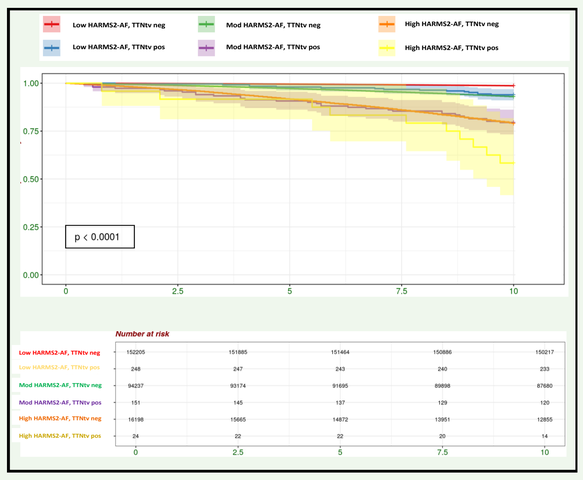
Among 301,865 participants with available whole genome sequencing data (48.0% male, age 57 years (IQR 50-63), 84.8% caucasian), AF incidence was 6.5% with a median time to AF 8.5 (IQR 5.0-11.2) years.

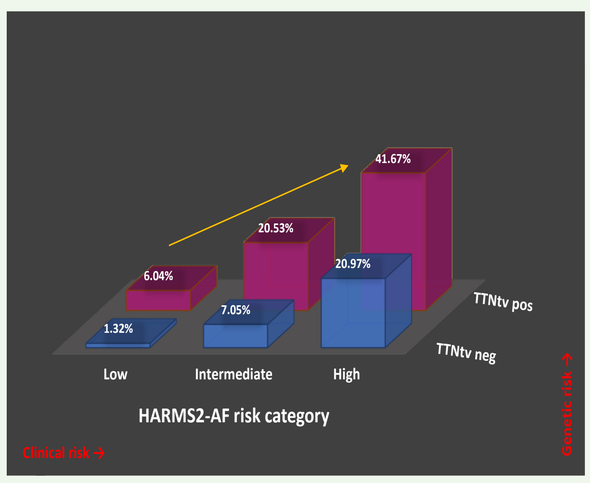
Prevalence of TTNtv was 0.2% overall and higher among the incident AF group (0.4% vs 0.1%). The AF population were older (63.0 (IQR 59.0-66.0) vs 57.0 (IQR 49.0-62.0), with a greater prevalence of hypertension (68.1% vs 26.1%), diabetes (9.3% vs 4.0%), sleep apnea (5.6% vs 1.6%) and obesity (32.7% vs 20.6%).

TTNtv was the strongest independent predictor of incident AF risk, conferring a 4-fold higher risk independent of modifiable AF risk factors (OR 4.15, 95% CI 2.97-5.50, P<0.001; figure 1a) and was consistent across both sexes (figure 1b). TTNtv was more strongly associated with incident AF risk than AF polygenic risk score (AF PRS: OR 1.67, 95% CI 1.62-1.74). The TTNtv gene positive individuals who developed AF had a lower median HARMS2-AF risk score (median 6.0 (IQR 4.2-8.8) compared to gene negative AF individuals (HARMS2-AF score 8.0 (IQR 5.0-10.0).



	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Hypertension	6.083 (5.855, 6.319)	<0.001	3.594 (3.449, 3.745)	<0.001
Age	1.124 (1.121, 1.128)	<0.001	1.098 (1.095, 1.102)	<0.001
Raised BMI (Obesity)	2.132 (2.046, 2.223)	<0.001	1.375 (1.313, 1.440)	<0.001
Male sex	2.302 (2.218, 2.389)	<0.001	1.880 (1.804, 1.960)	<0.001
Sleep apnoea	3.632 (3.344, 3.945)	<0.001	2.103 (1.919, 2.304)	<0.001
Smoking	1.586 (1.531, 1.644)	0.345	1.135 (1.092, 1.179)	<0.001
Alcohol (sdd)	1.013 (1.012, 1.015)	0.994	1.004 (1.003, 1.006)	<0.001
Diabetes	2.332 (2.187, 2.486)	<0.001	0.977 (0.911, 1.048)	0.522
Physical inactivity	1.076 (1.028, 1.125)	0.001	1.010 (0.963, 1.060)	0.673
TTNtv	3.194 (2.401, 4.250)	<0.001	3.792 (2.750, 5.229)	<0.001
AF PRS (high)	2.057 (1.985, 2.131)	<0.001	2.121 (2.043, 2.202)	<0.001





Conclusion

TTNtv status was strongly associated with incident AF risk irrespective of lifestyle risk factors and identified an AF subset with minimal AF risk factors. Further studies incorporating clinical and genetic risk factors are needed to enhance AF risk prediction.