

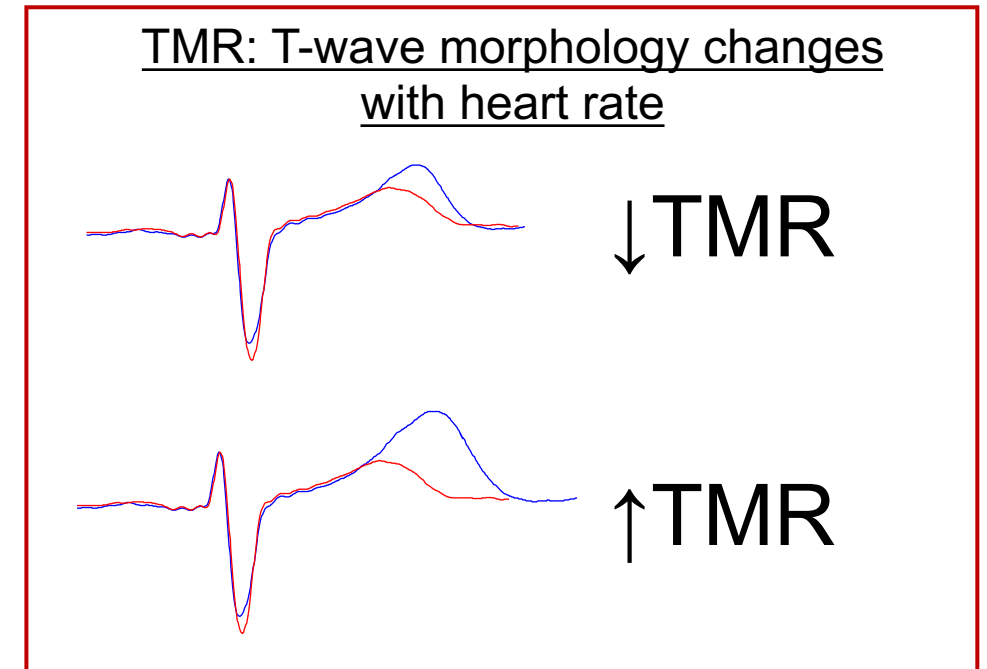
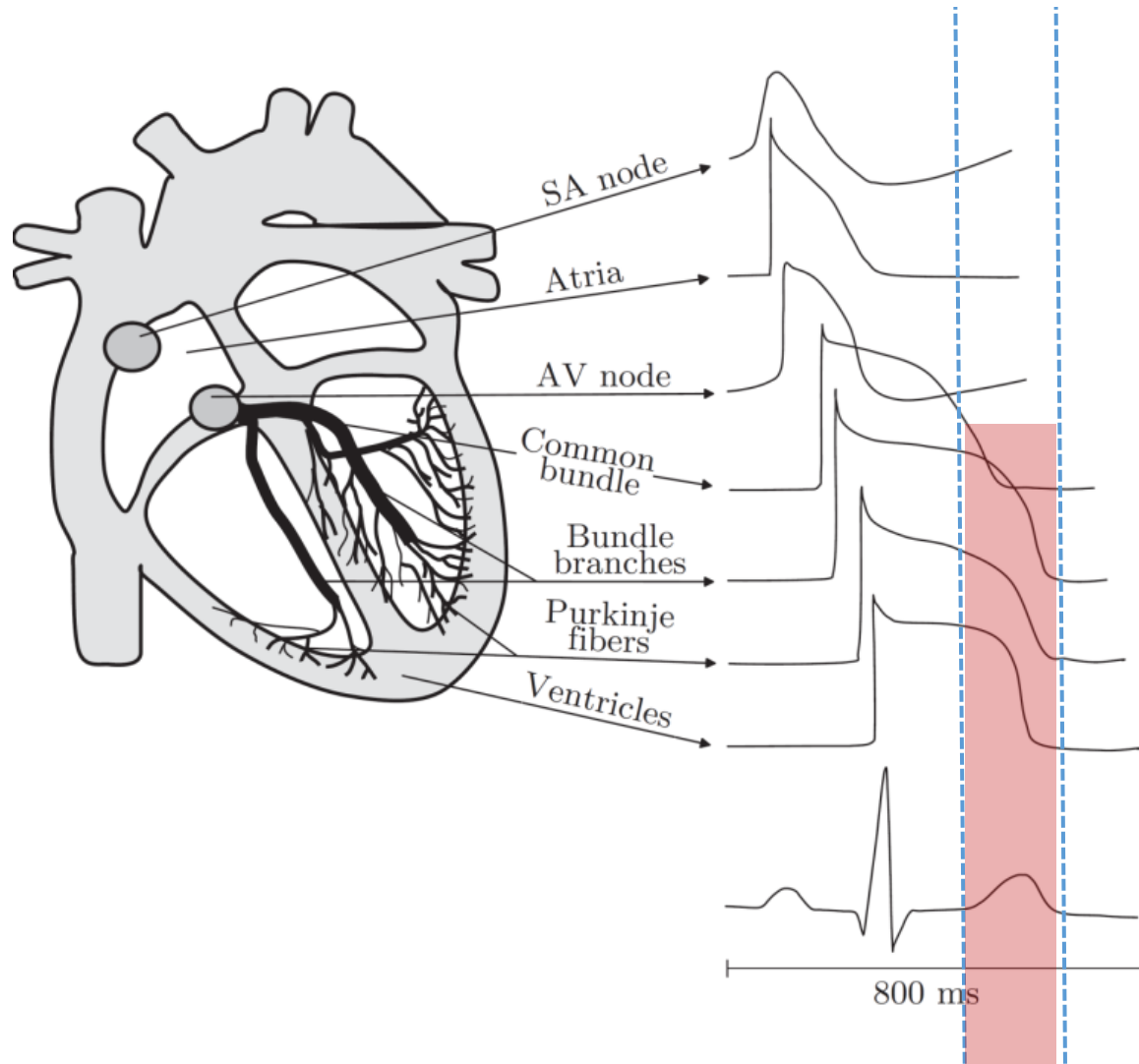


The cardiovascular predictive value and genetic architecture of T-wave morphology restitution

Julia Ramírez, PhD

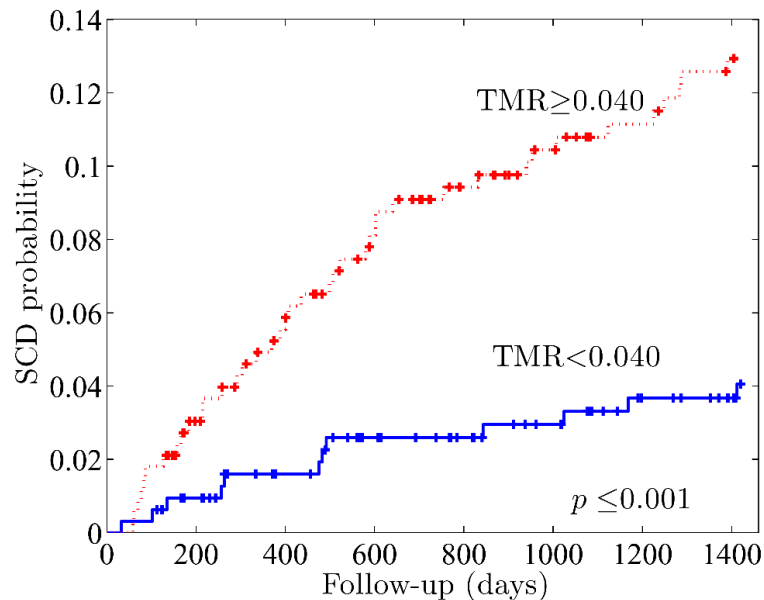


T-wave Morphology Restitution (TMR)



T-wave Morphology Restitution

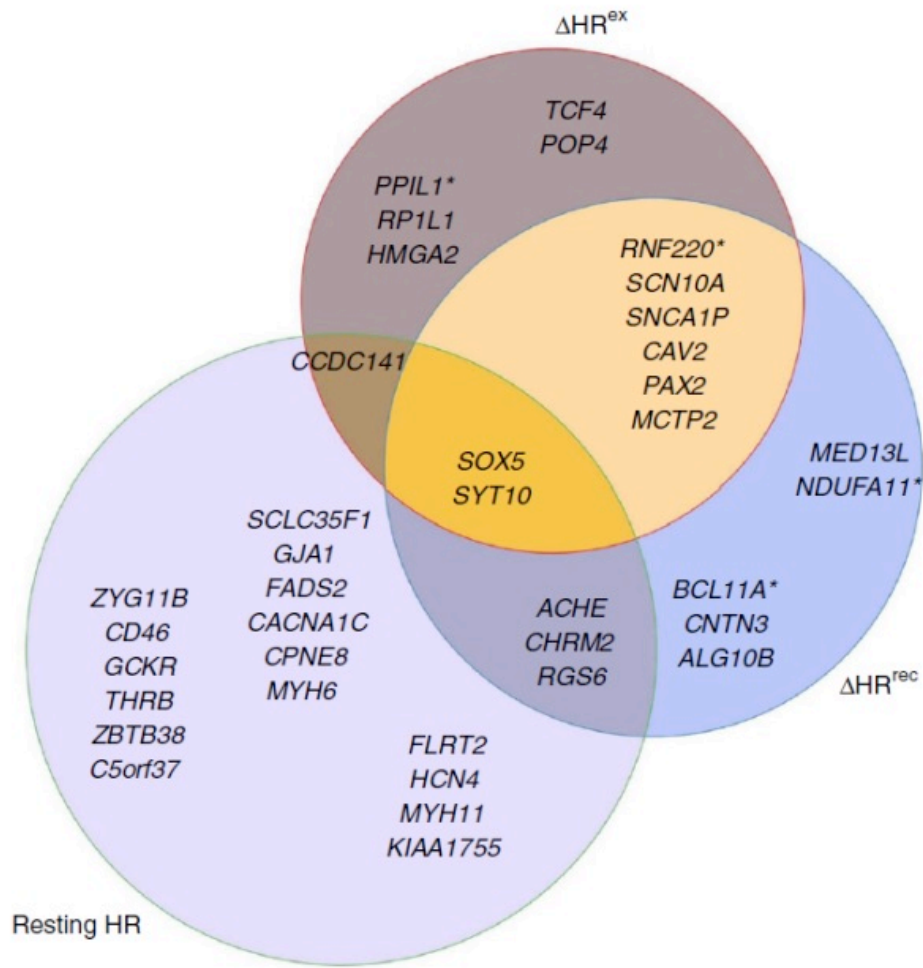
- Original study:
 - 650 CHF consecutive patients
 - 52 SCD victims
 - ECG Holter recordings
- Predictive value in the **general population** never studied



Strongest ECG-derived SCD predictor
(hazard ratio of 3.3)

Ramírez et al. J Am Heart Assoc 2017

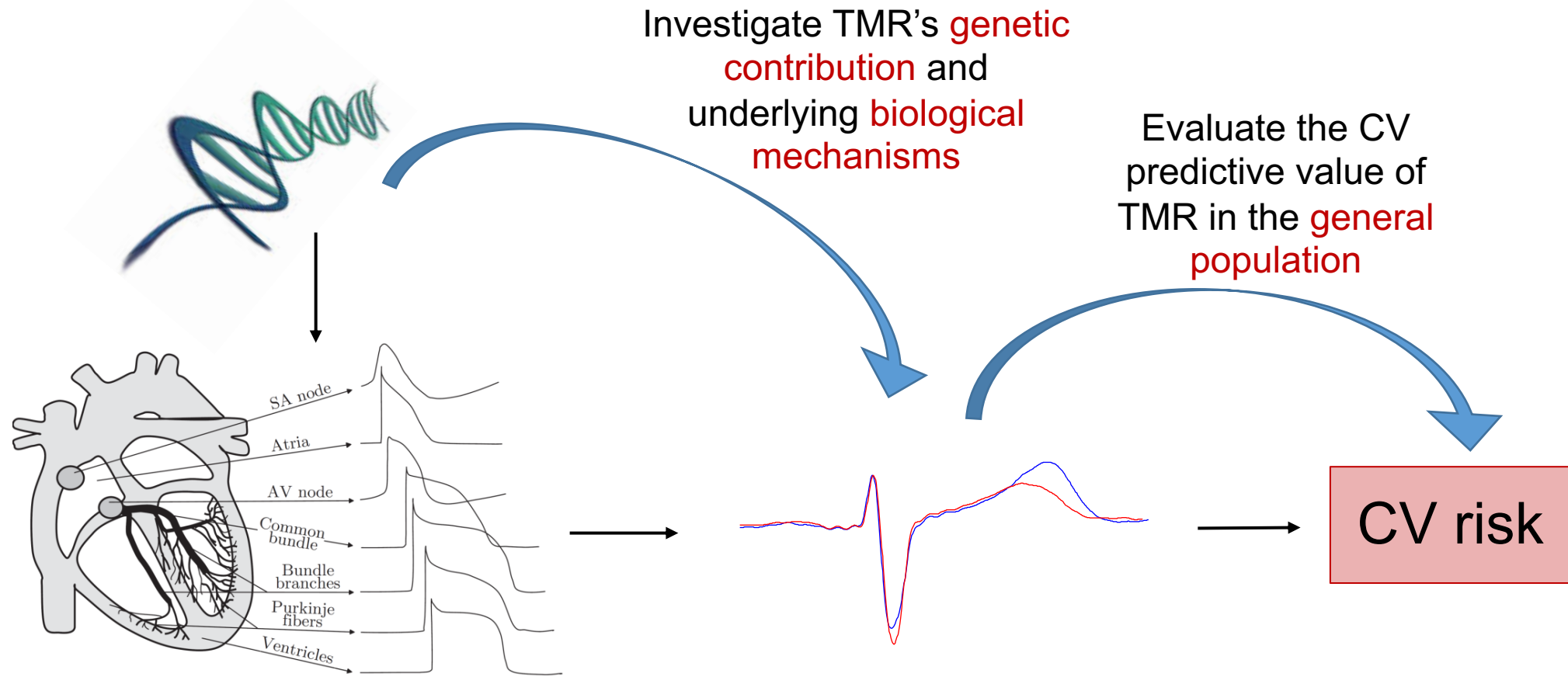
Genetics of ECG markers



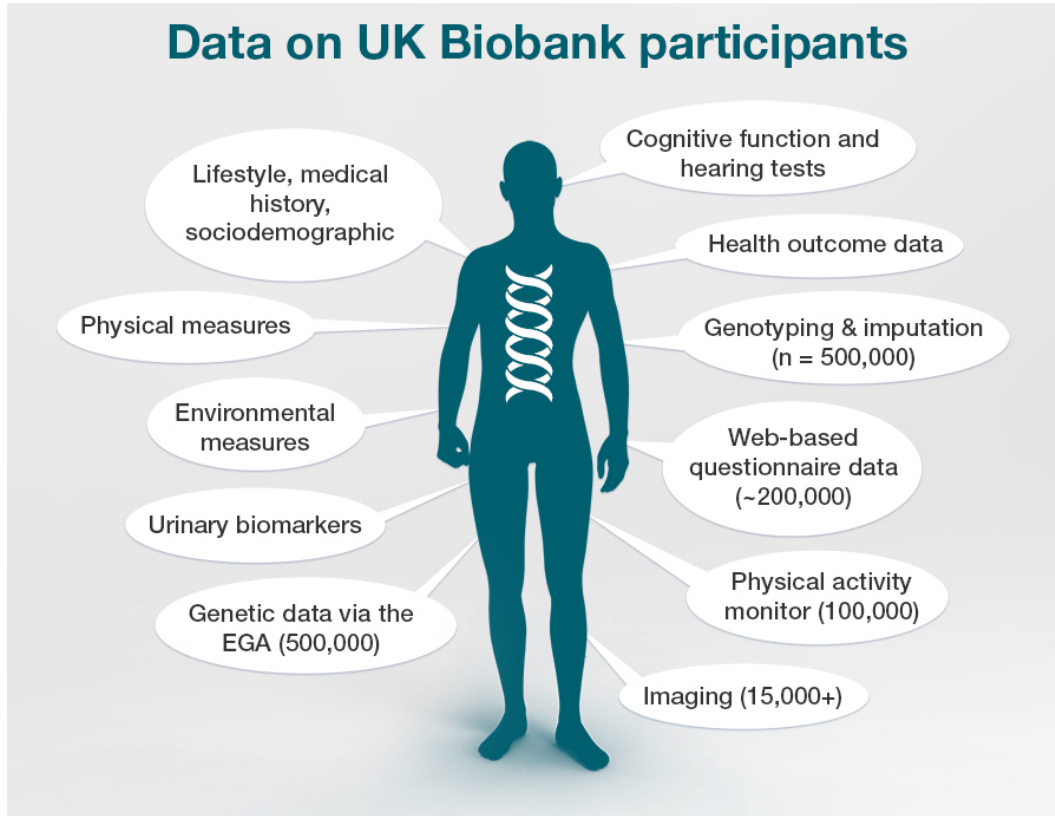
Ramírez et al. Nat Comms 2018

- Resting heart rate is heritable (30%)
- Heart rate response to exercise and heart rate response to recovery are also **heritable** (17% and 12%, respectively)
- Identified genes module **autonomic nervous system**
- Resting QT also heritable (28%) and 57 identified genes
- Mechanisms underlying TMR **not yet investigated**

Objectives



Materials

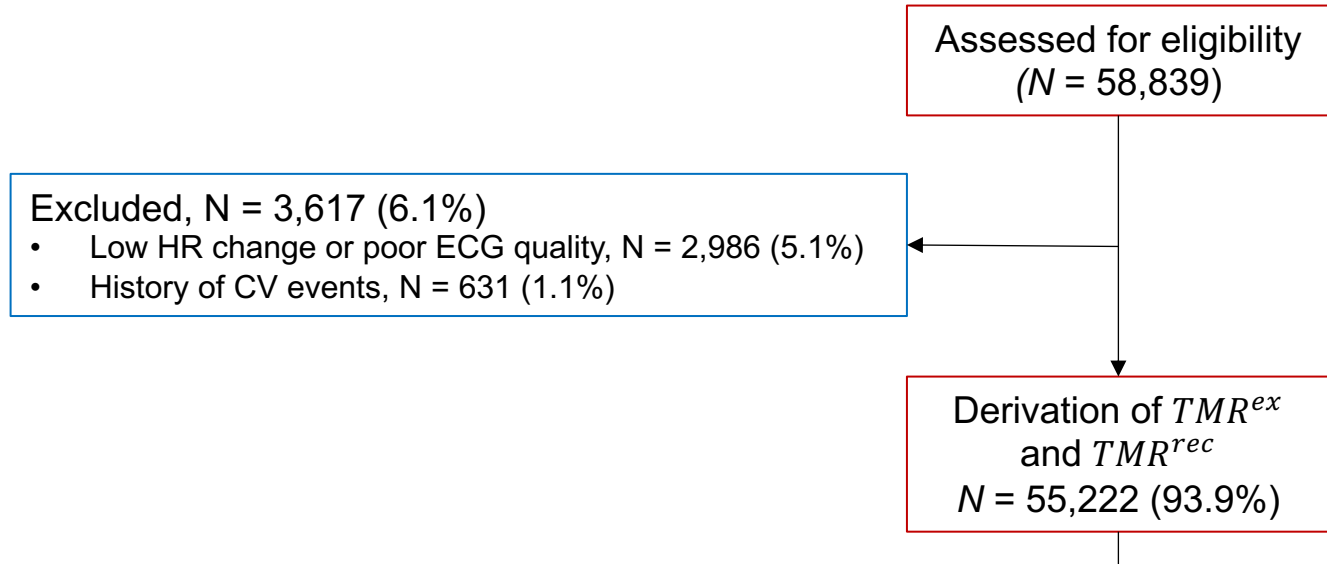


- ~95,000 participants invited for moderate exercise test between 2006-2010
- Raw ECG recordings available in **58,839**
- Follow-up still on-going (our data stops in March 2017)

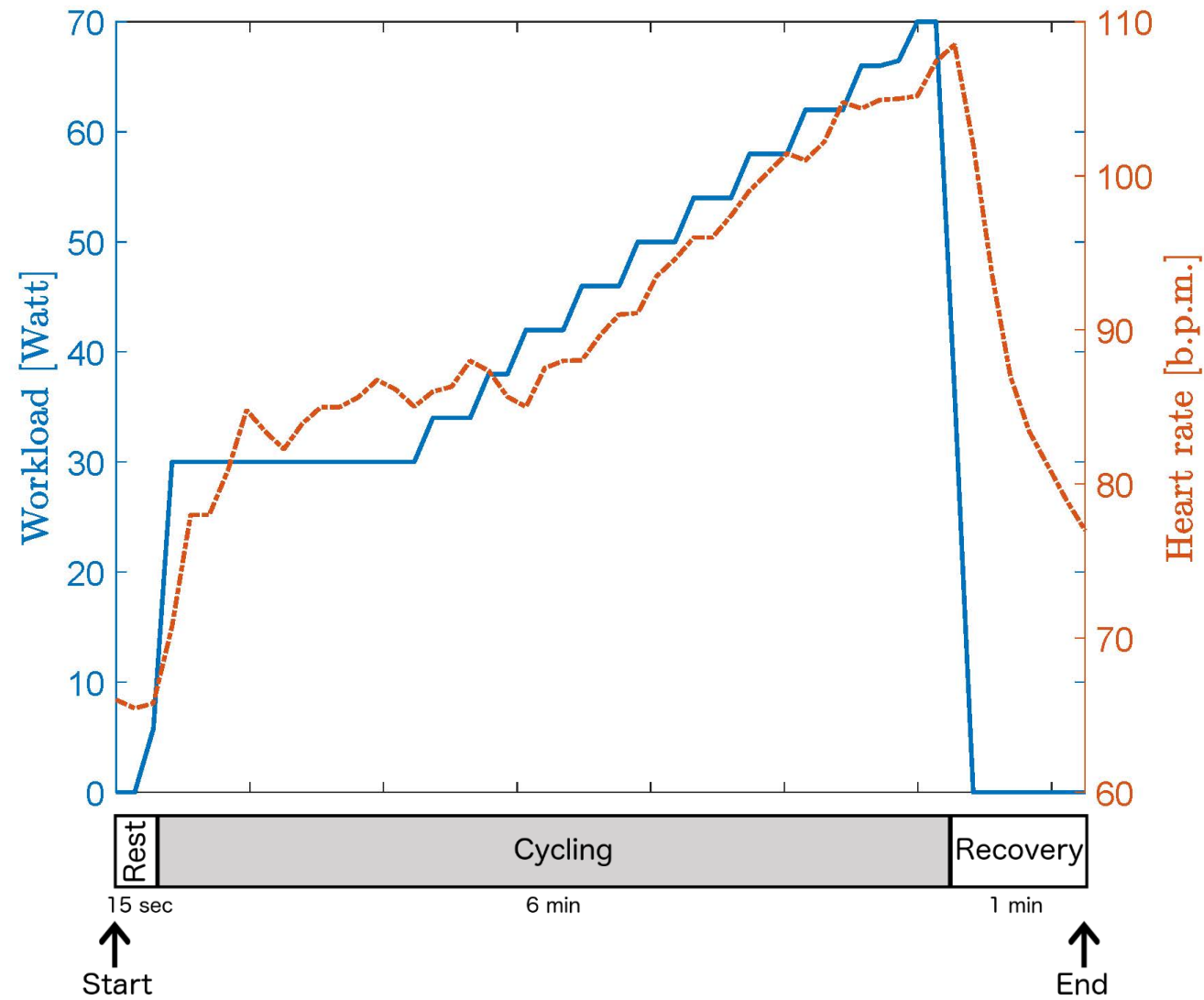
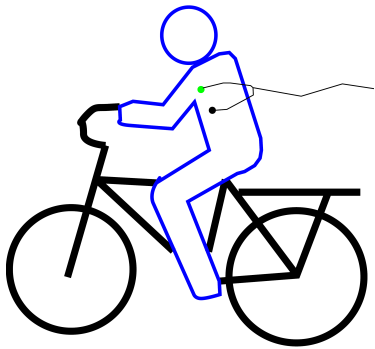
- UK Biobank application number 8256

Diagram Flow

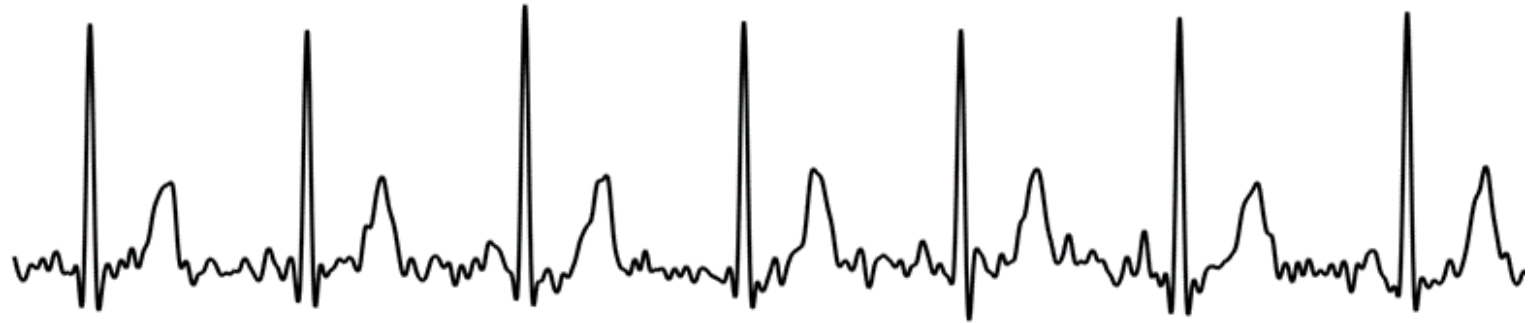
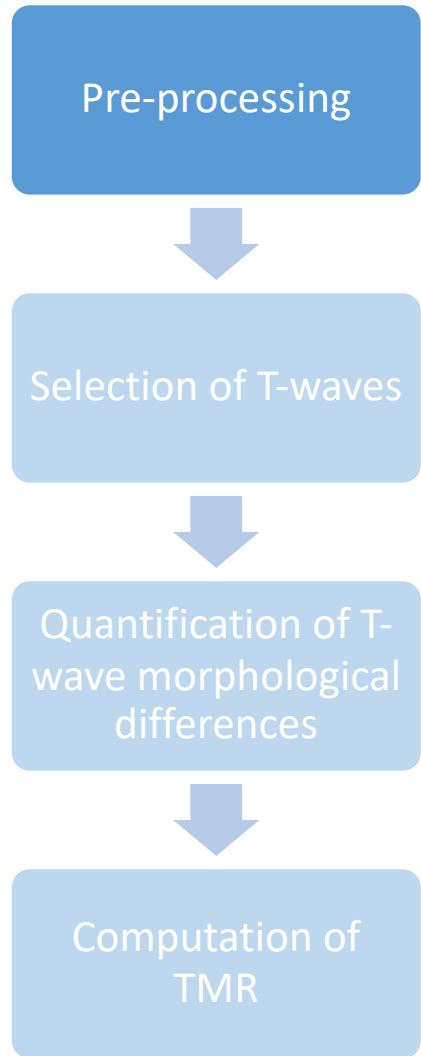
EST-UKB cohort



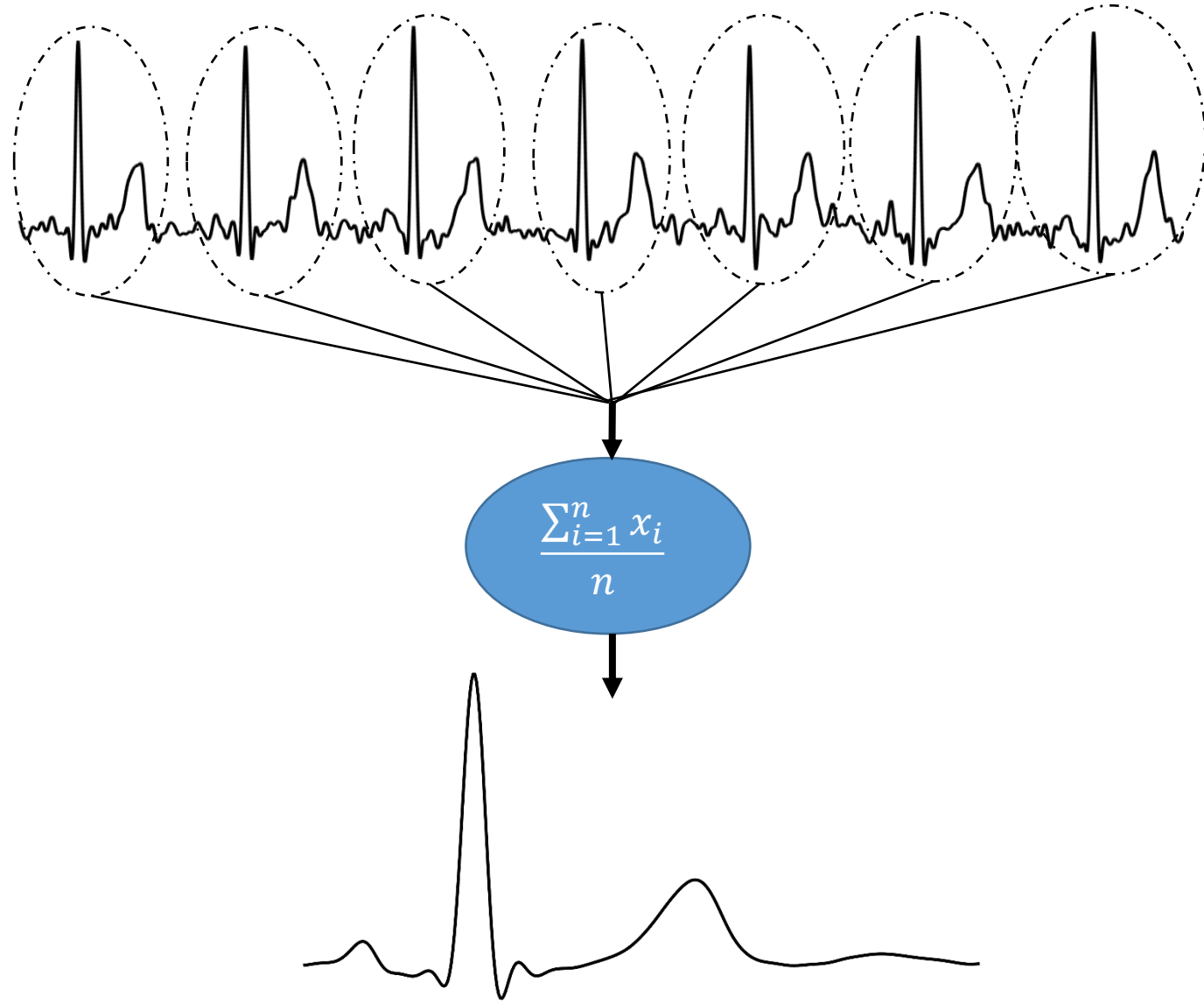
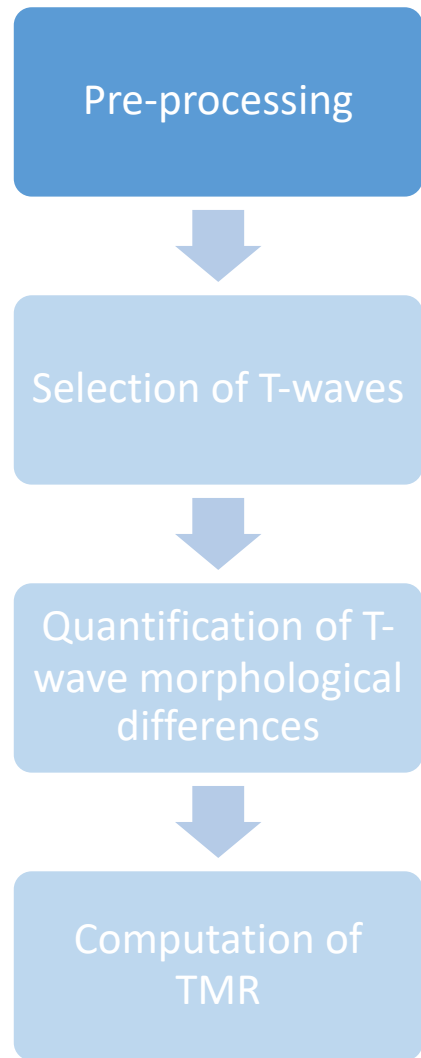
Exercise stress test



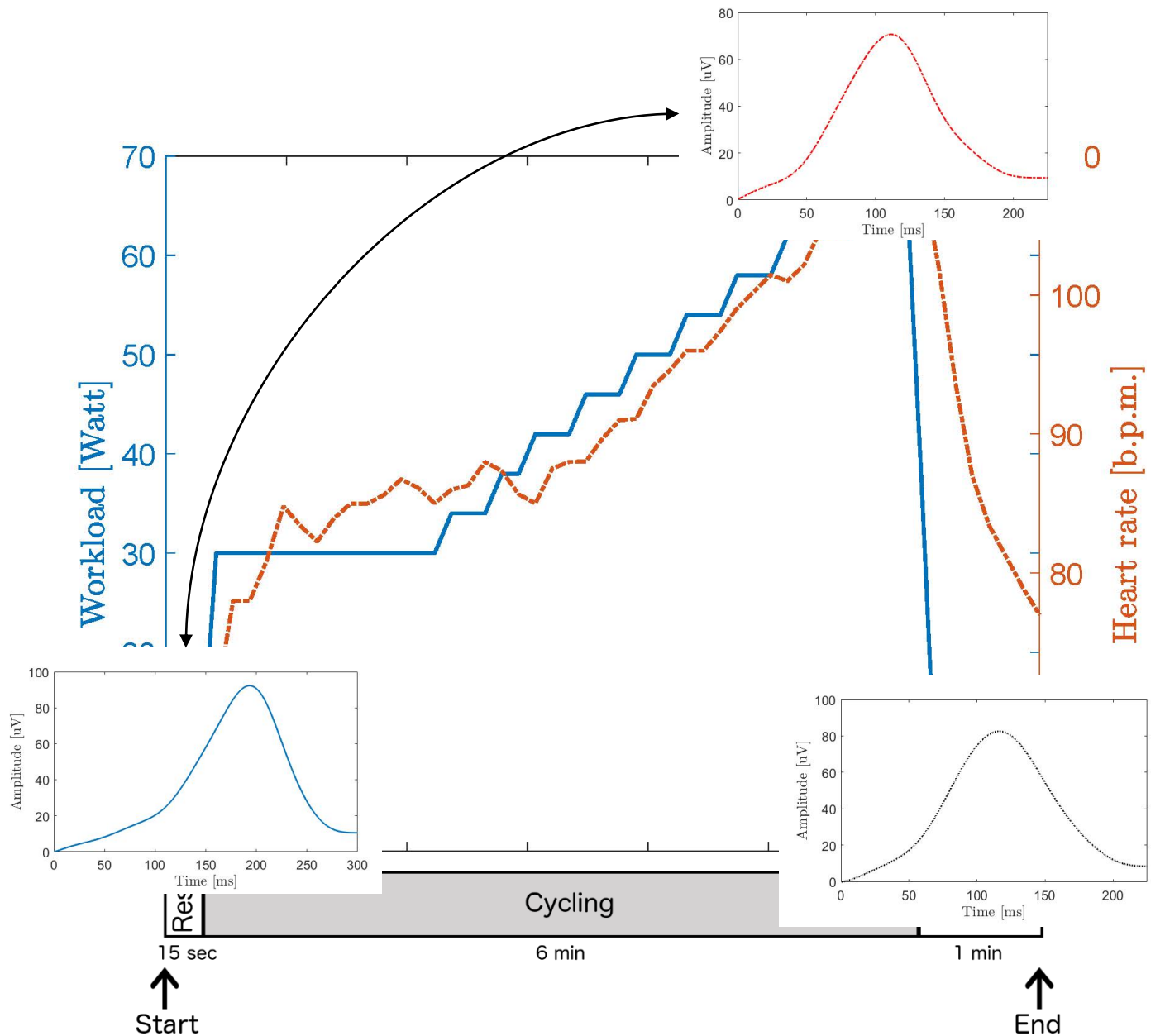
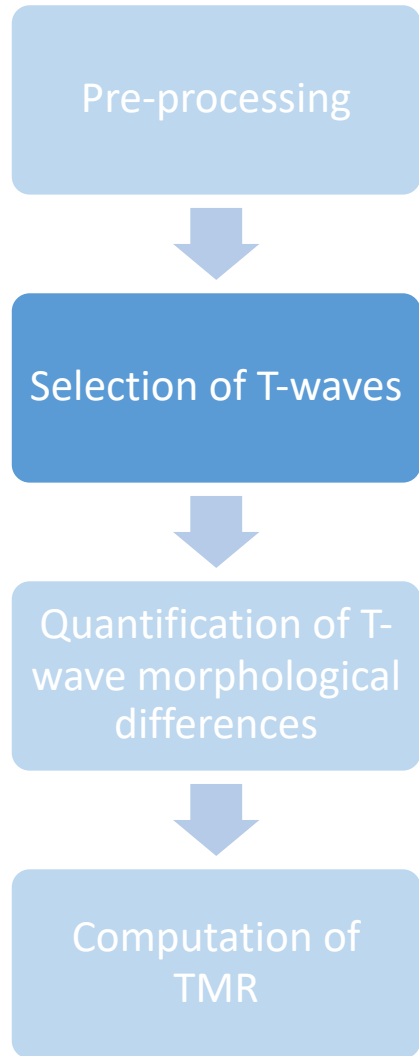
ECG analysis



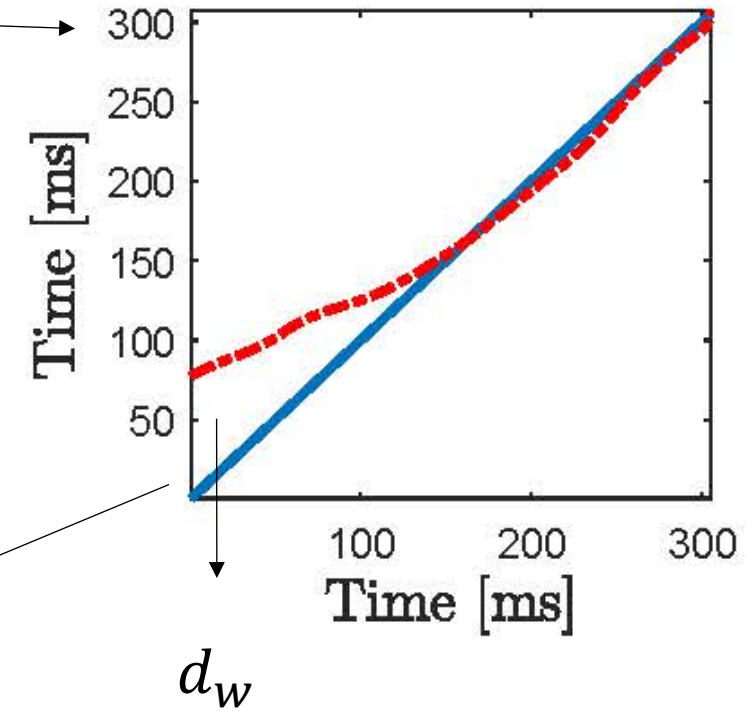
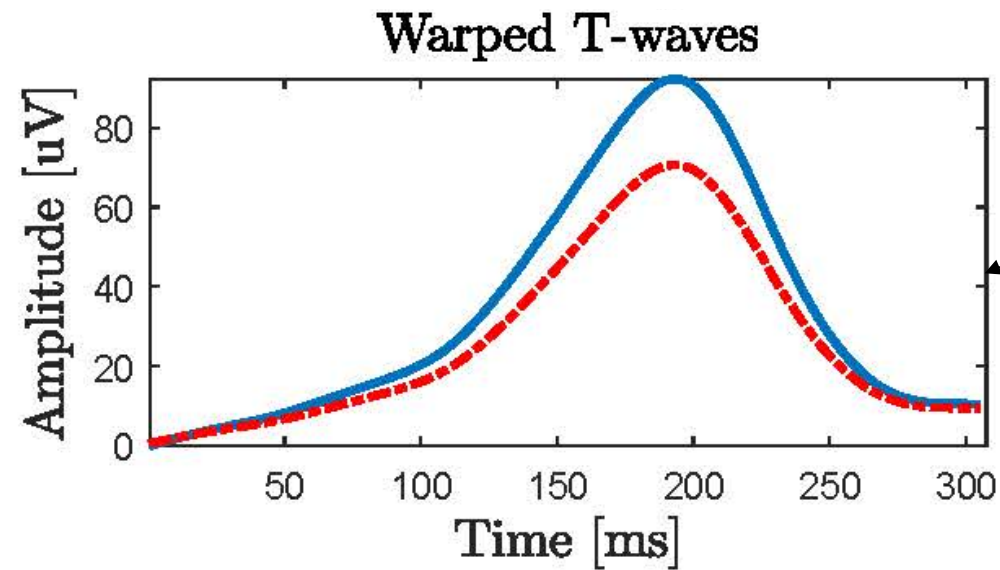
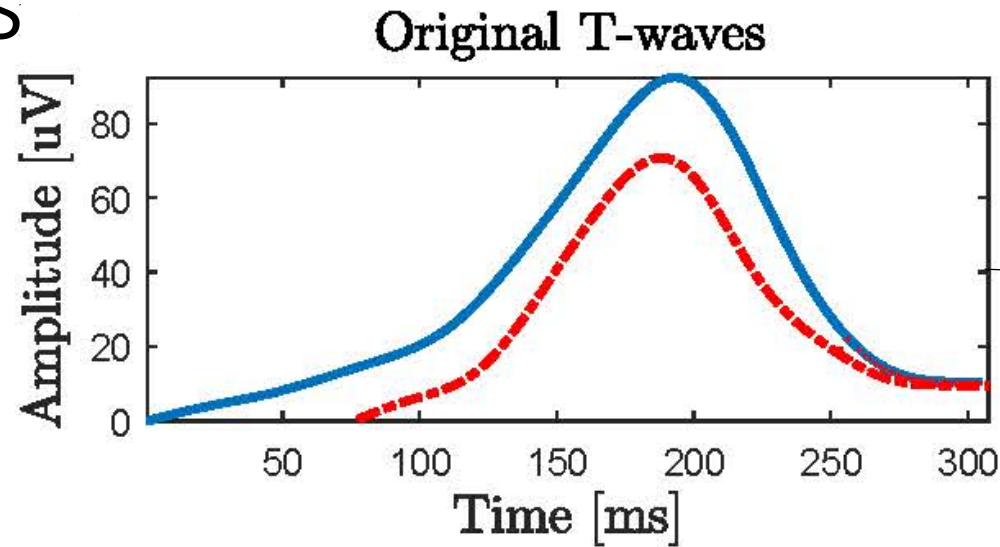
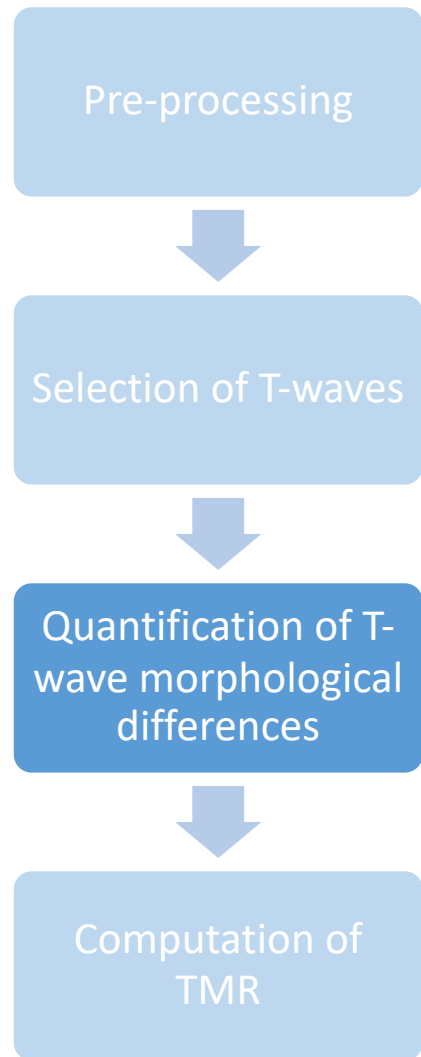
ECG analysis



ECG analysis

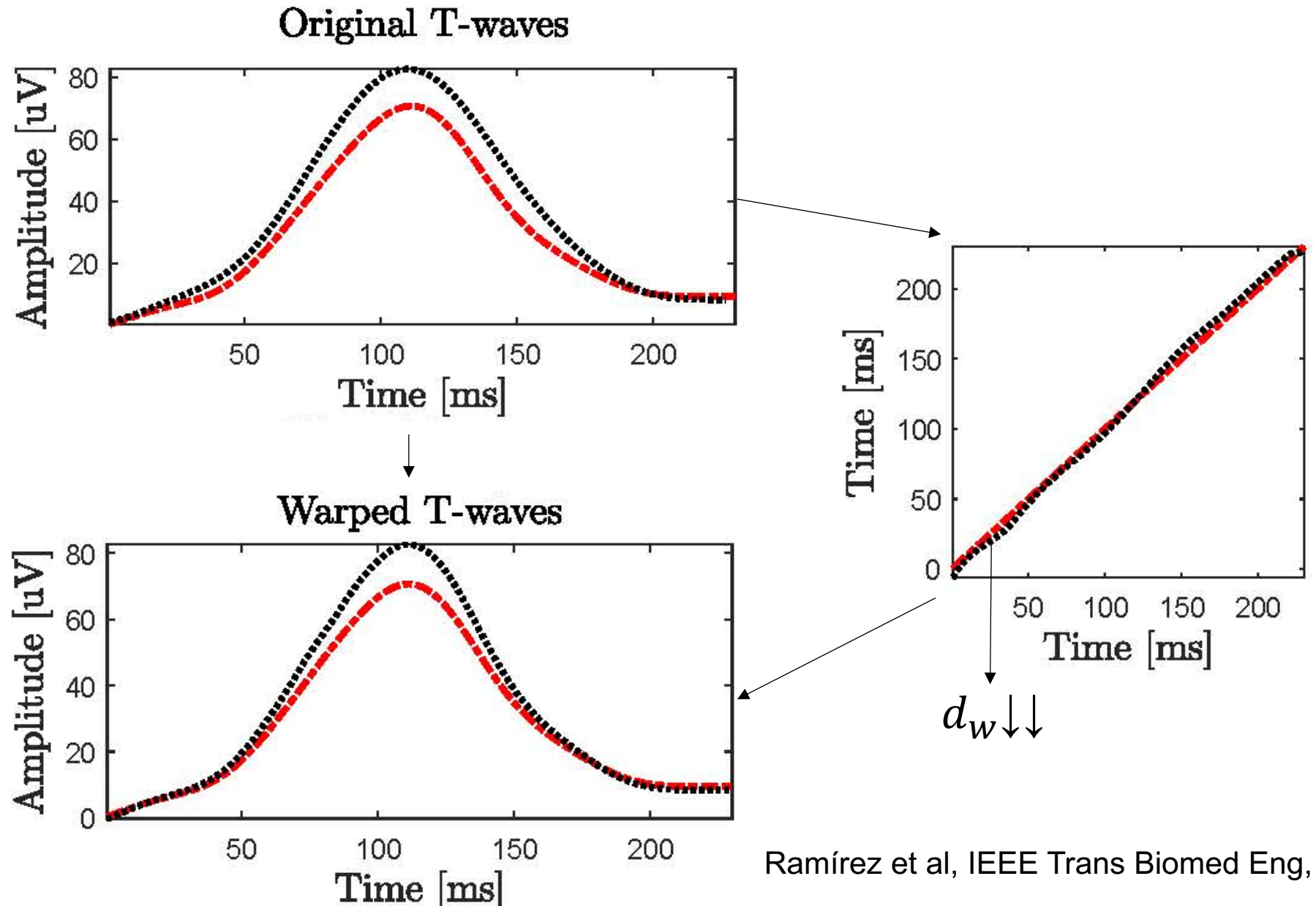
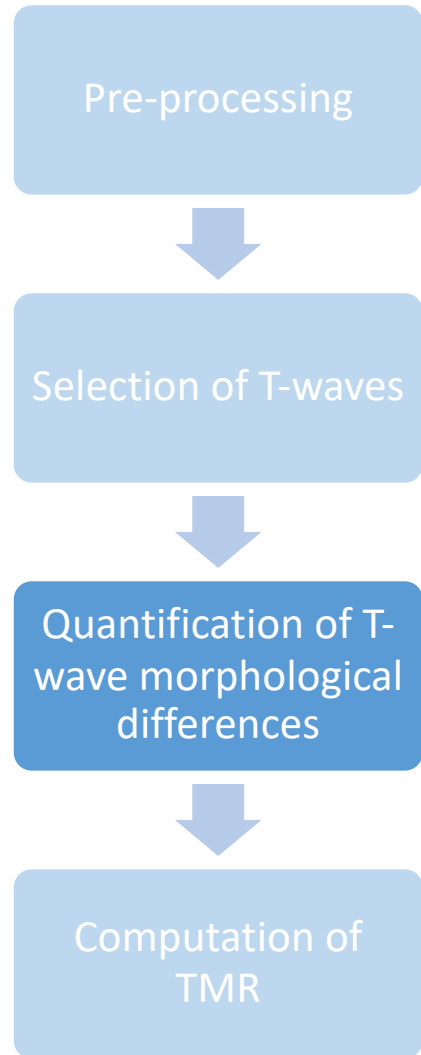


ECG analysis



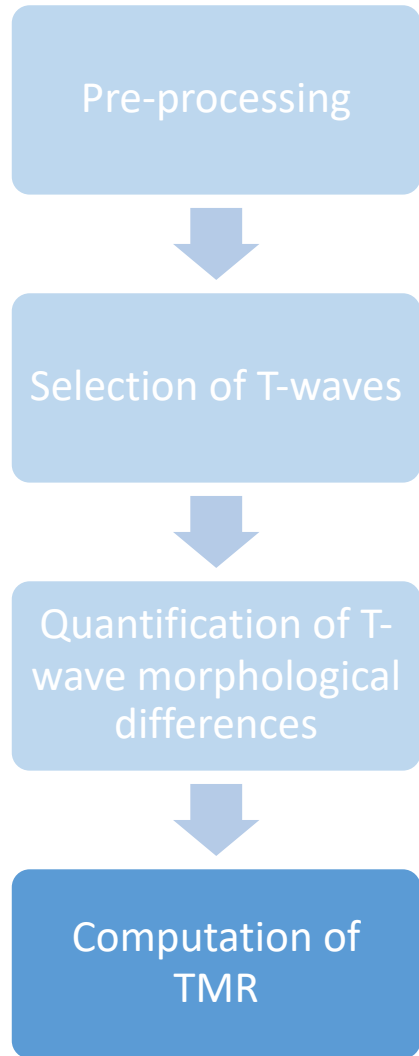
Ramírez et al, IEEE Trans Biomed Eng, 2017

ECG analysis



Ramírez et al, IEEE Trans Biomed Eng, 2017

ECG analysis



$$TMR^{ex} = \frac{d_w^{ex}}{\Delta RR^{ex}} [a.u.]$$

$$TMR^{rec} = \frac{d_w^{rec}}{\Delta RR^{rec}} [a.u.]$$

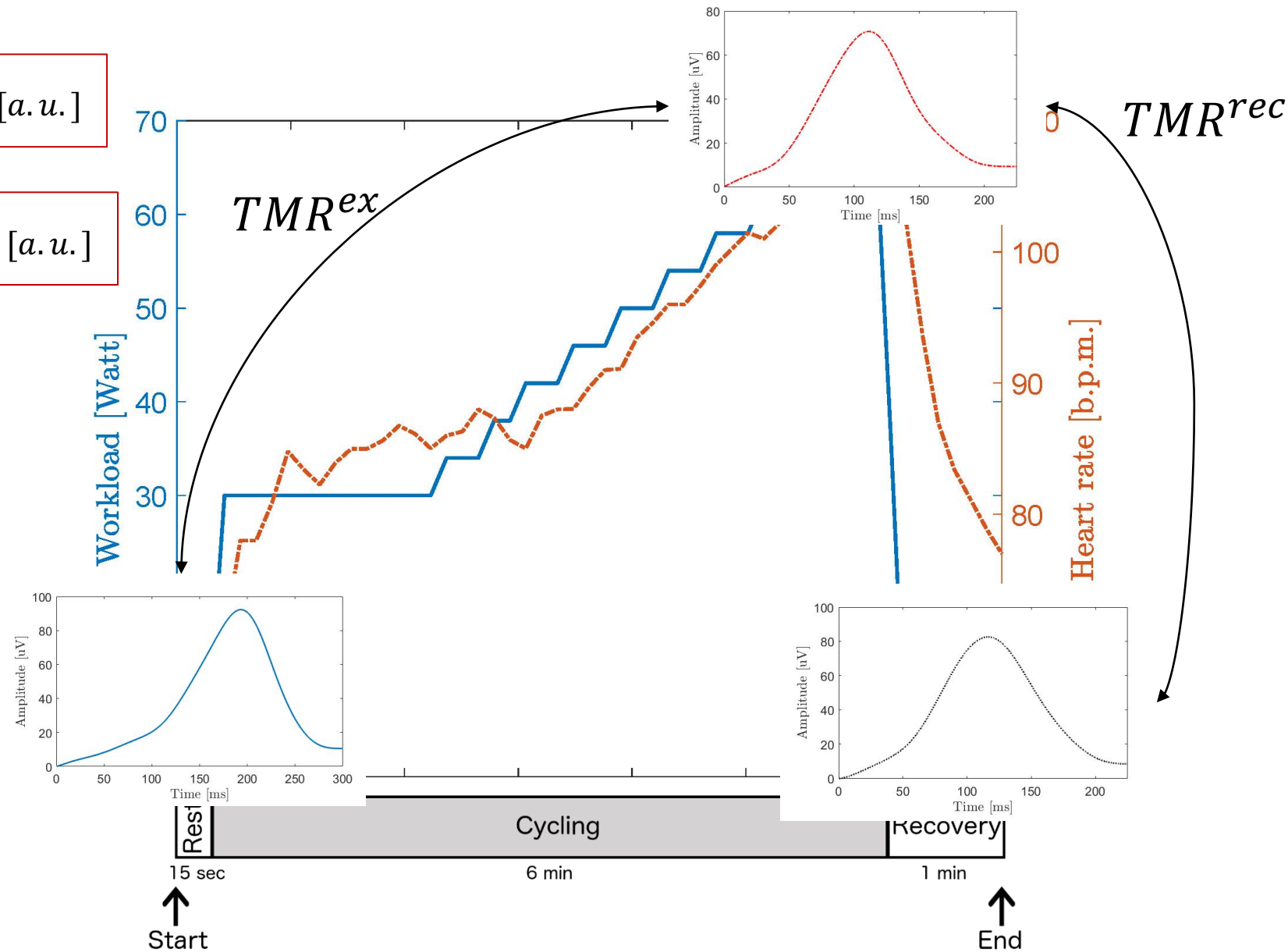


Diagram Flow

EST-UKB cohort

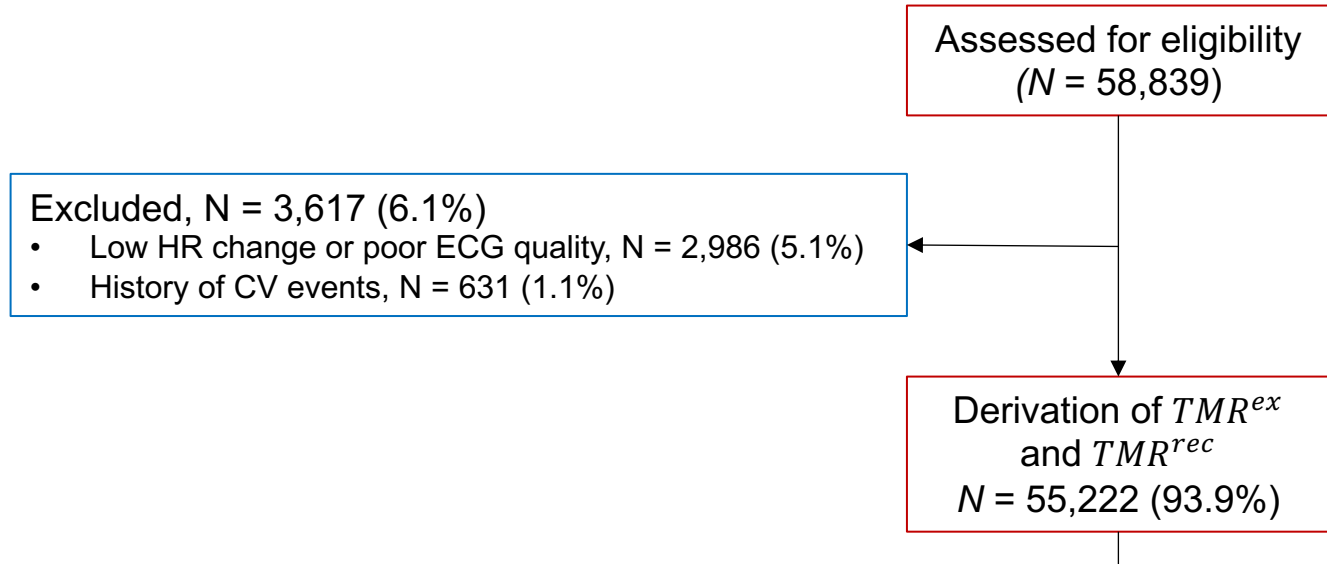
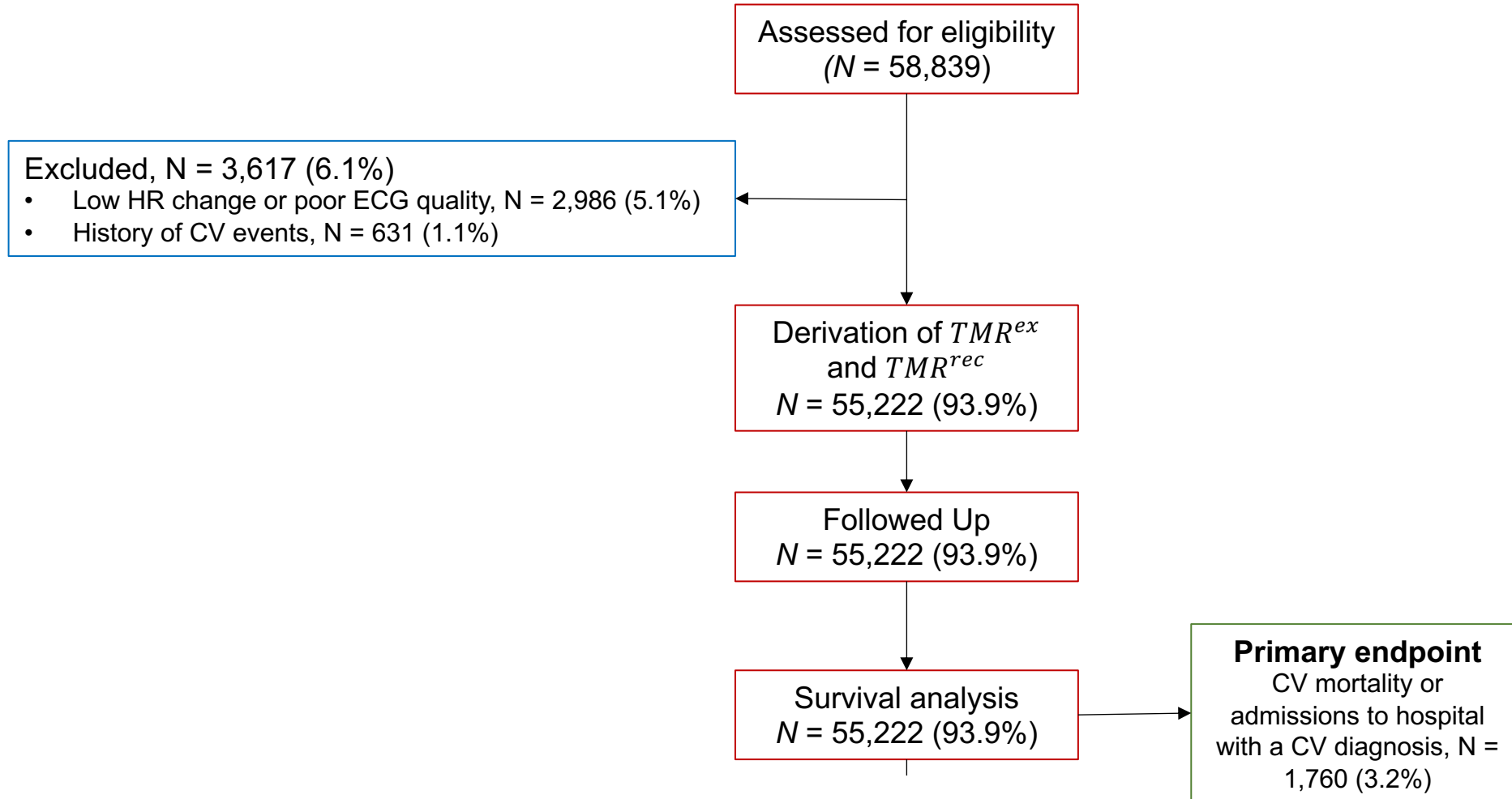


Diagram flow

EST-UKB cohort



Characteristics of the study population

	Cardiovascular events group	Cardiovascular event-free group	
Characteristics	N = 1,760	N = 53,462	P-value
Median age (IQR), years	62 (9)	58 (13)	2.20E-16
Males, n(%)	1,253 (71.2)	24,416 (45.7)	2.20E-16
Diabetes mellitus, n(%)	179 (10.2)	2,126 (4.0)	2.20E-16
Median BMI (IQR), kg/m ²	27.8 (5.6)	26.4 (5.3)	2.20E-16
Median SBP (IQR), mmHg	142.5 (23)	135 (24)	2.20E-16
High cholesterol, n(%)	341 (19.4)	5,956 (11.1)	2.20E-16
Median resting heart rate (IQR), bpm	71.3 (16.7)	70.3 (15.0)	3.50E-04
Median heart rate response to exercise (IQR)	37.0 (15.3)	40.8 (16.5)	2.20E-16
Median heart rate response to recovery (IQR)	23.7 (12.0)	27.5 (13.0)	2.20E-16
Median QTc (IQR), ms ⁻¹	399.5 (33.4)	395.6 (30.4)	7.50E-09
Median QRS duration (IQR), ms	68 (18)	68 (18)	5.50E-01
T-wave inversions, n(%)	8 (0.5%)	82 (0.2%)	9.00E-03
Median TMR during exercise (IQR), d.u.	0.046 (0.034)	0.043 (0.029)	4.50E-08
Median TMR during recovery (IQR), d.u.	0.053 (0.060)	0.044 (0.044)	2.20E-16

Clinical

ECG

Cardiovascular events prediction

	Univariate	
	HR (95% CI)	p
Clinical Variables		
Age [per 1 SD]	1.87 (1.77-1.99)	$<2 \times 10^{-16}$
Sex (male)	3.00 (2.70-3.34)	$<2 \times 10^{-16}$
Diabetes (yes)	2.72 (2.32-3.20)	$<2 \times 10^{-16}$
High cholesterol (yes)	1.94 (1.72-2.20)	$<2 \times 10^{-16}$
BMI [per 1 SD]	1.28 (1.22-1.33)	$<2 \times 10^{-16}$
SBP [per 1 SD]	1.44 (1.37-1.51)	$<2 \times 10^{-16}$
ECG variables		
Resting heart rate [per 1 SD]	1.10 (1.05-1.15)	6.7×10^{-5}
Heart rate response to exercise [per 1 SD]	0.70 (0.66-0.74)	$<2 \times 10^{-16}$
Heart rate response to recovery [per 1 SD]	0.74 (0.71-0.76)	$<2 \times 10^{-16}$
Corrected QT [per 1 SD]	1.15 (1.10-1.20)	8.5×10^{-10}
T-wave inversion (yes)	2.78 (1.39-5.56)	4.0×10^{-3}
TMR during exercise [per 1 SD]	1.17 (1.12-1.21)	9.7×10^{-15}
TMR during recovery [per 1 SD]	1.23 (1.19-1.28)	$<2 \times 10^{-16}$

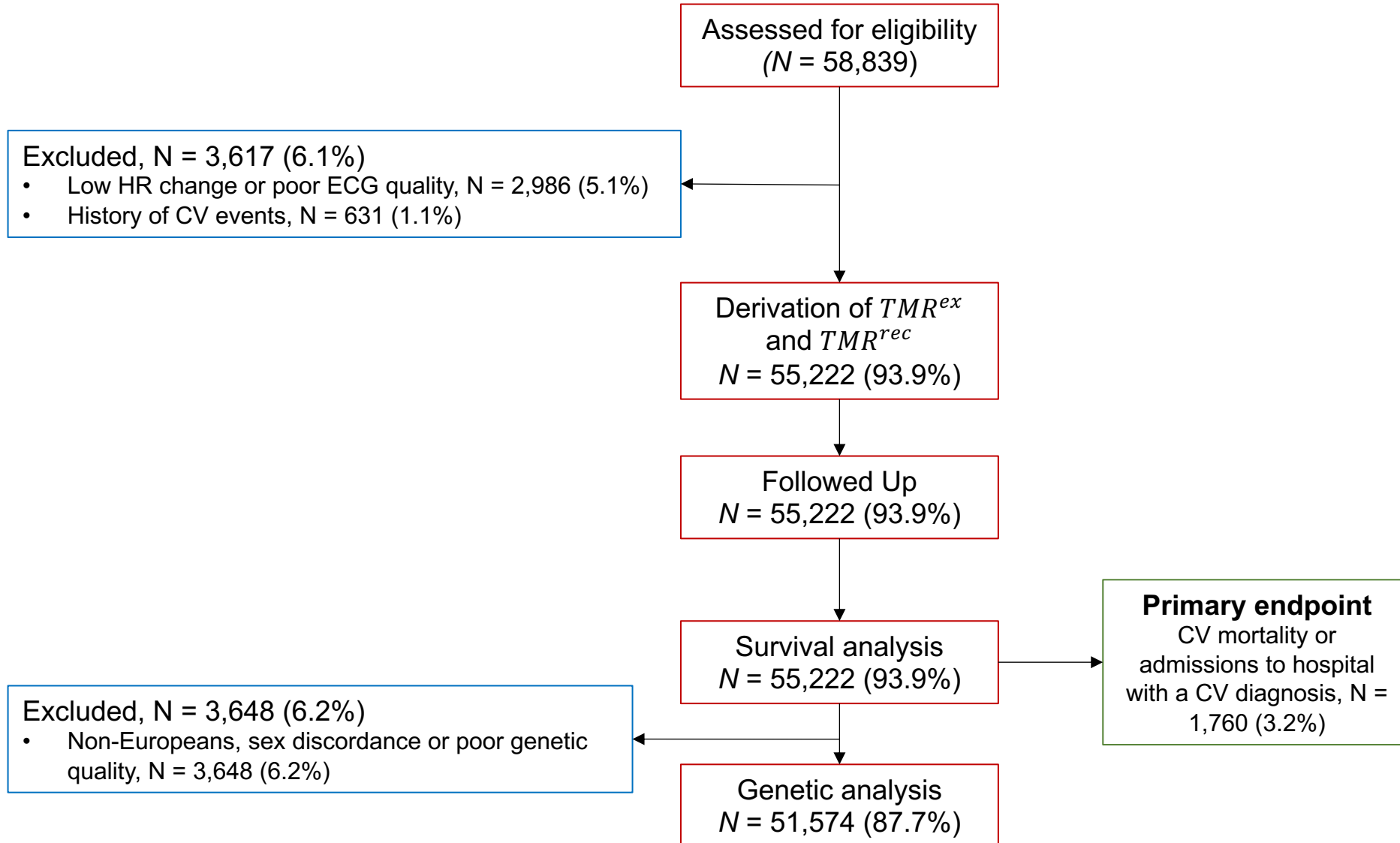
Ventricular arrhythmic events prediction

N = 198 (0.4%)

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Clinical Variables				
Age [per 1 SD]	1.91 (1.61-2.27)	1.00E-13	1.75 (1.48-2.08)	1.60E-10
Sex (male)	2.37 (1.76-3.20)	1.60E-08	2.20 (1.62-2.97)	3.10E-07
Diabetes (yes)	1.81 (1.05-3.12)	3.30E-02	1.08 (0.62-1.90)	7.80E-01
BMI [per 1 SD]	1.17 (1.03-1.33)	1.70E-02	1.07 (0.92-1.24)	3.70E-01
Hypertensive Stage 1	1.32 (0.84-2.06)	2.20E-01	0.95 (0.61-1.50)	8.40E-01
Hypertensive Stage 2	2.20 (1.55-3.13)	9.70E-06	1.27 (0.88-1.84)	2.00E-01
ECG variables				
HR response to exercise [per 1 SD]	0.73 (0.62-0.85)	6.80E-05	1.08 (0.92-1.26)	3.50E-01
Heart rate response to recovery [per 1 SD]	0.71 (0.65-0.78)	6.60E-14	0.82 (0.69-0.97)	2.10E-02
Corrected QT [per 1 SD]	1.13 (1.03-1.25)	1.10E-02	1.08 (0.96-1.22)	2.00E-01
TMR during exercise [per 1 SD]	1.13 (1.00-1.27)	4.70E-02	0.97 (0.84-1.13)	7.30E-01
TMR during recovery [per 1 SD]	1.28 (1.16-1.41)	1.30E-06	1.16 (1.03-1.30)	1.40E-02

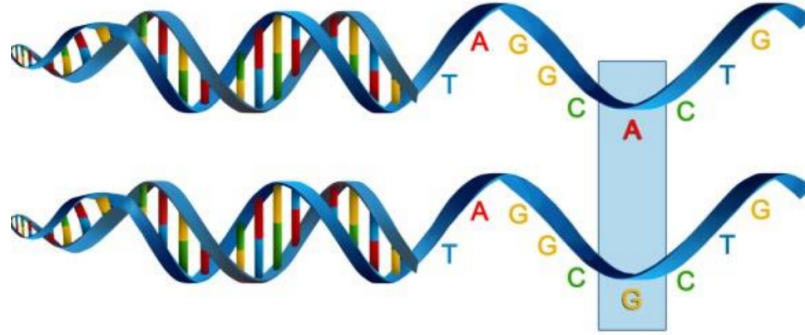
Diagram flow

EST-UKB cohort



Genetic analyses

- **Genome-wide association study**: tests if a genetic variant is found more/less often than expected in individuals with the phenotype of interest



Presence/absence
of genetic variant



Might affect the
functionality of the
gene



Abnormal
biomarker (TMR)

Linear mixed model



~ 10 million genetic variants



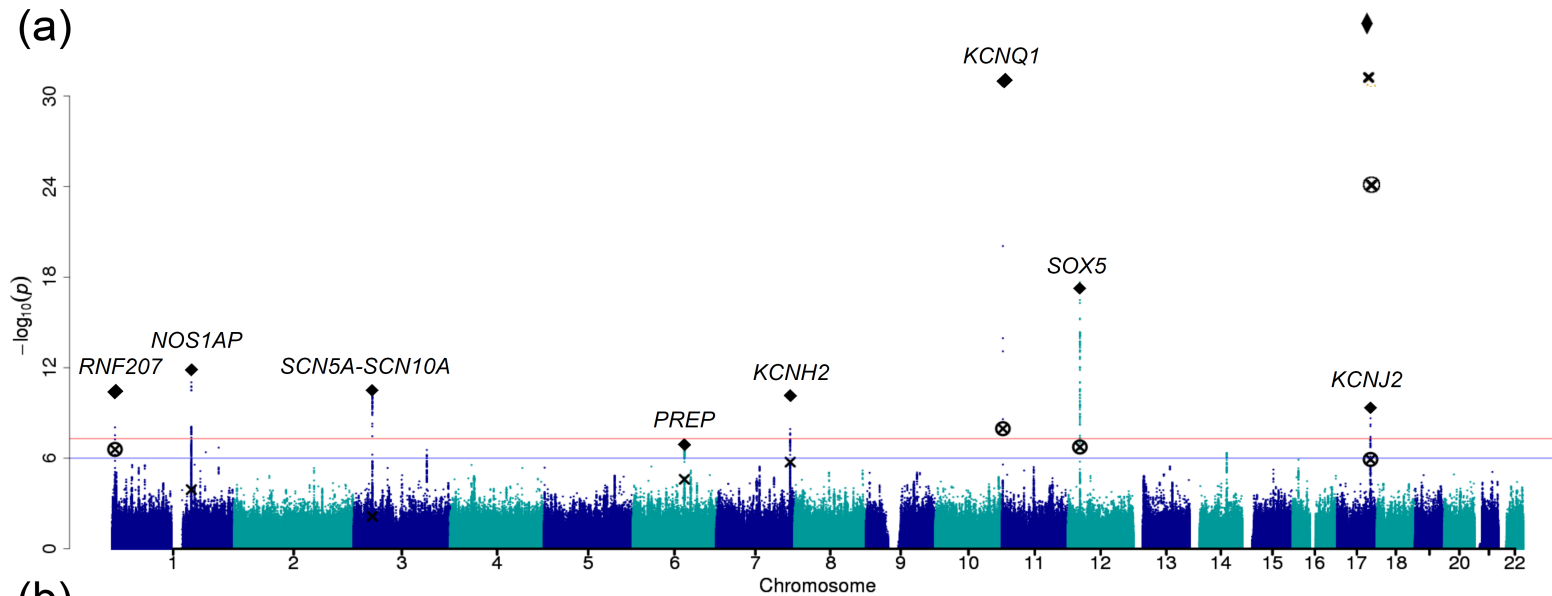
$\text{TMR} \sim \text{sex} + \text{age} + \text{BMI} + \text{resting HR} + \text{peak HR}$



~ 10 million linear mixed models $\rightarrow P < 5 \times 10^{-8}$

12 loci associated with TMR^{ex} or TMR^{rec}

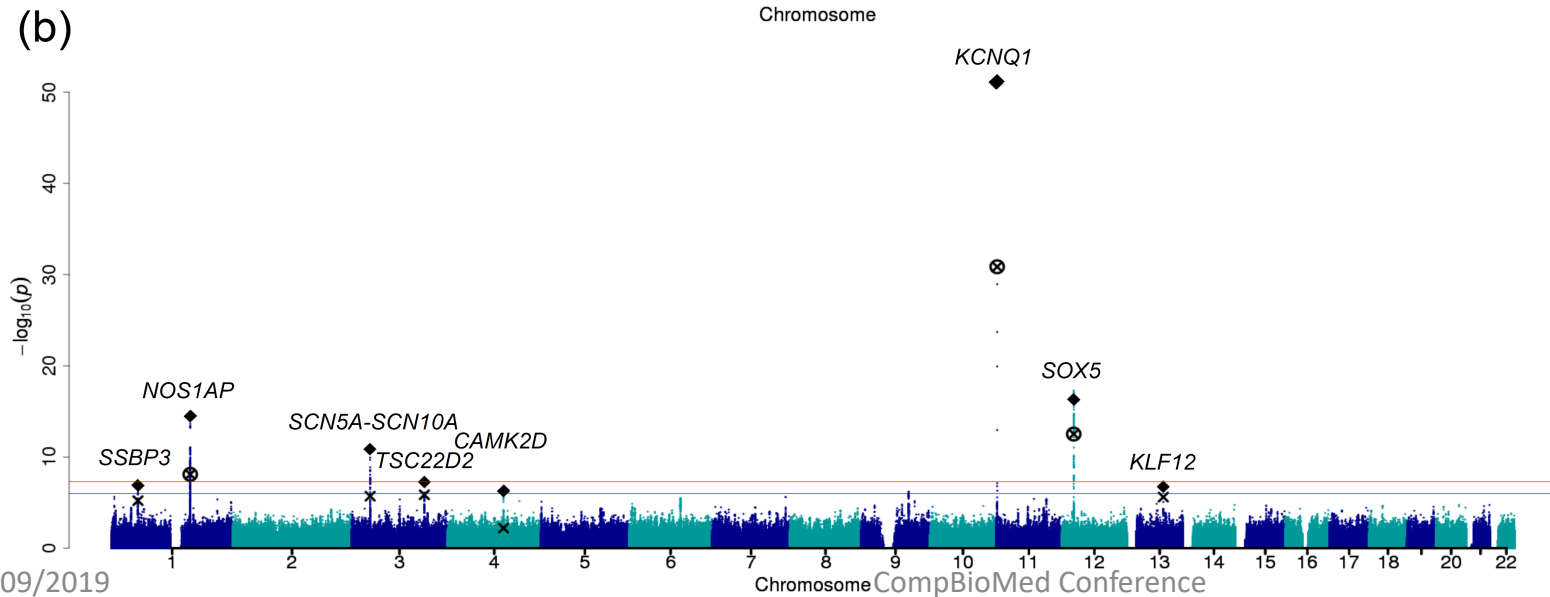
(a)



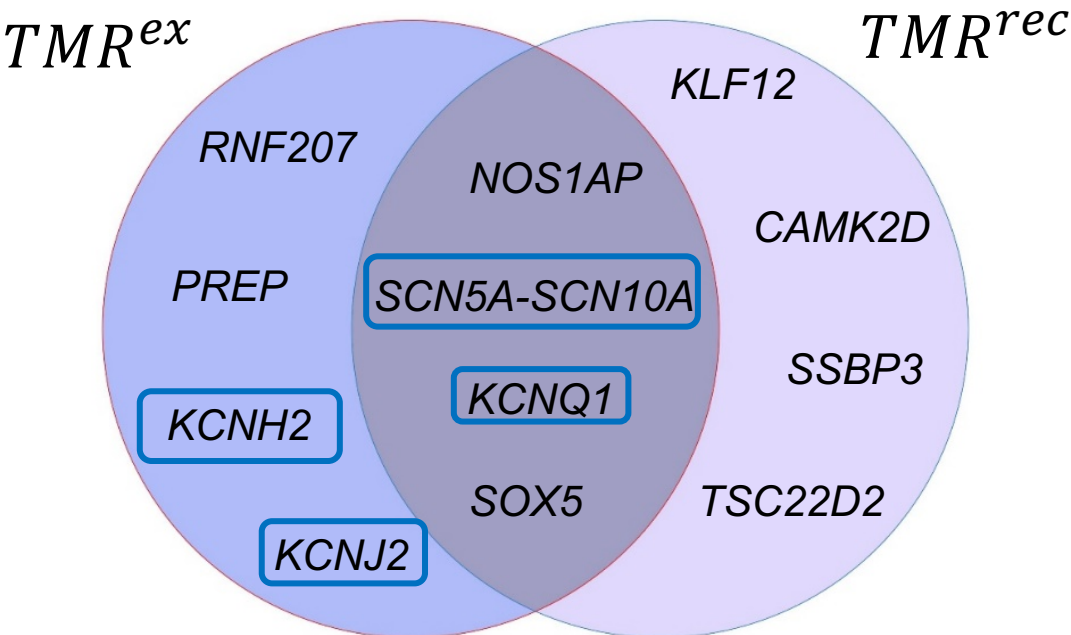
Heritability:

- 3.5% for TMR^{ex}
- 4.9% for TMR^{rec}

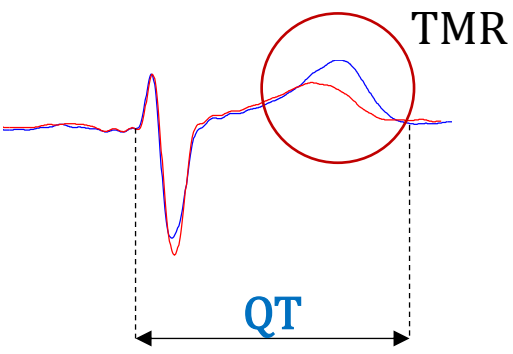
(b)



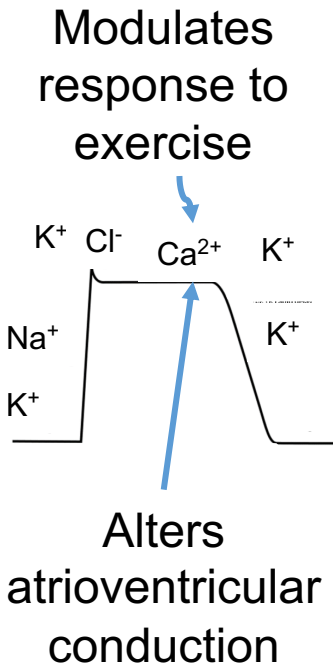
Bioinformatics

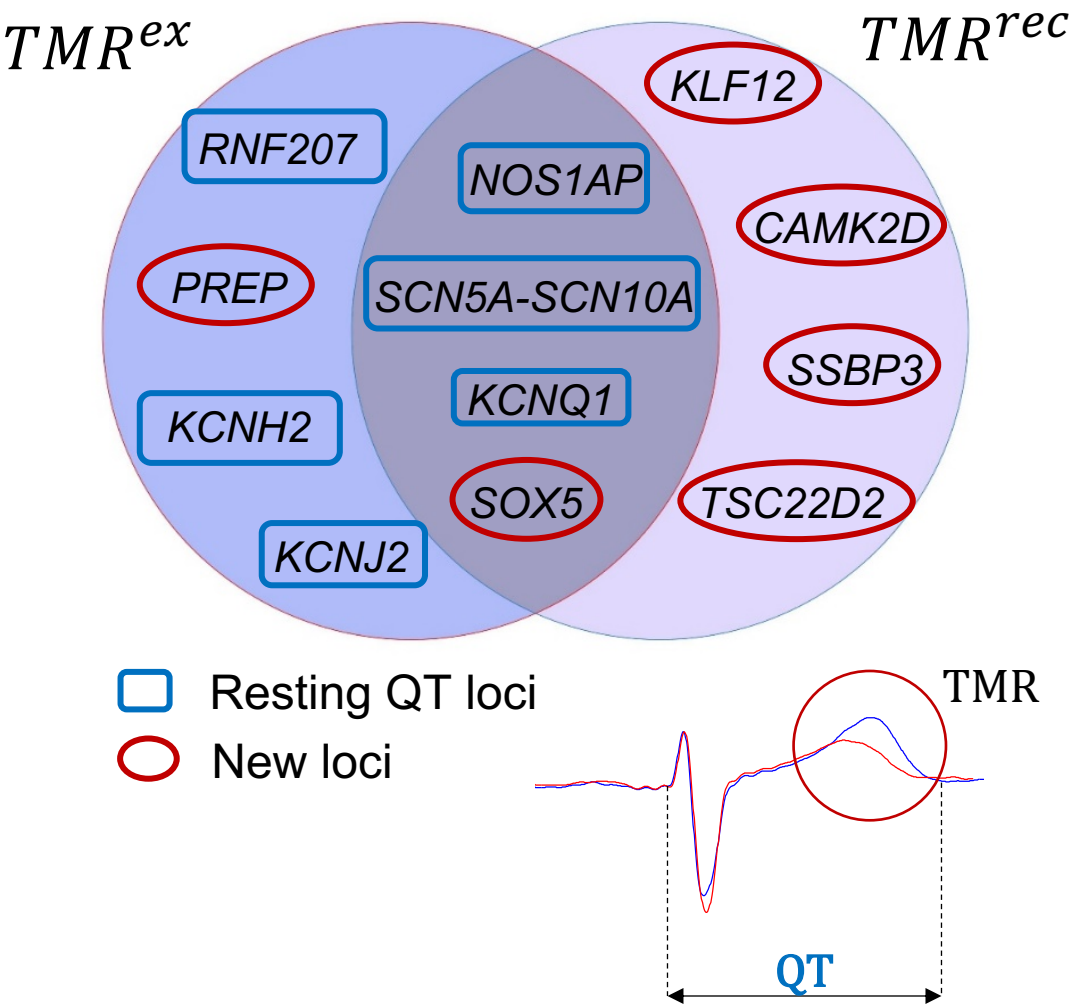


 Inherited long QT



New loci	Protein expression	
	CV system	Nervous system
PREP	✓	✓
<u>CAMK2D</u>	✓	✓
KLF12		✓
<u>SOX5</u>	✓	✓
SSBP3	✓	✓
TSC22D2		✓

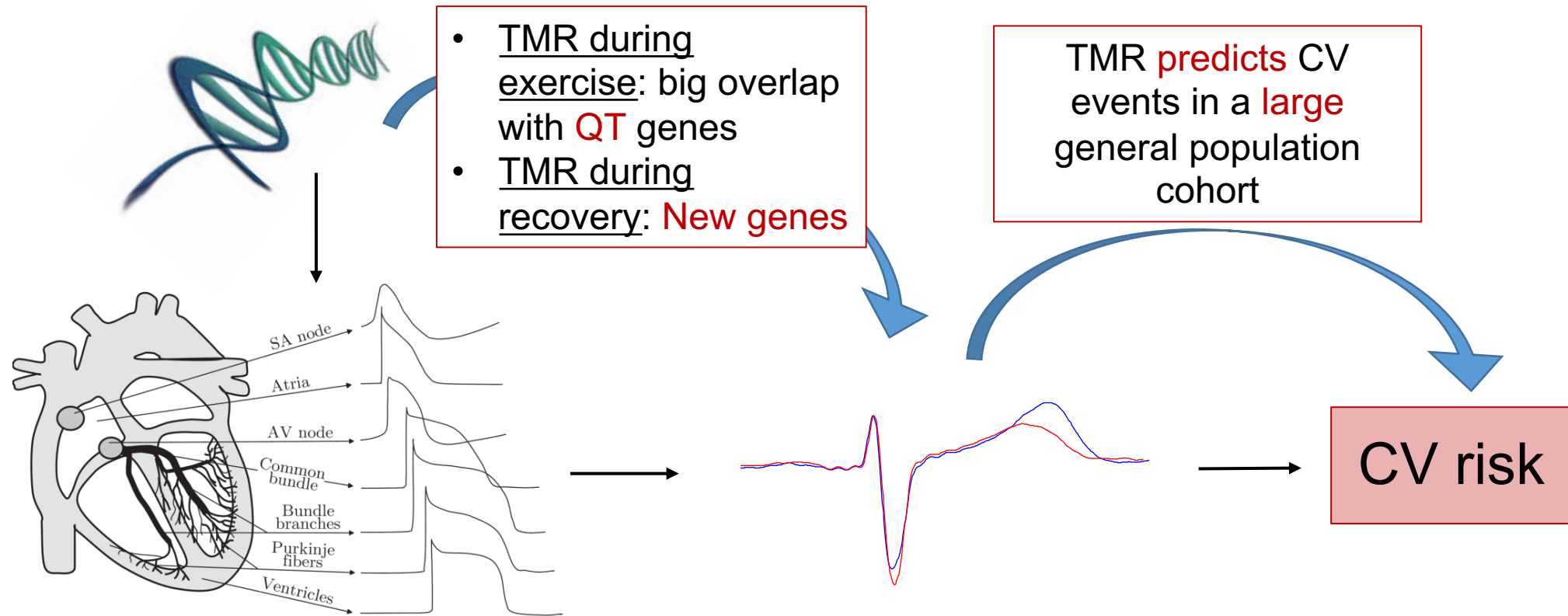




TMR^{ex} biological mechanisms	G:Profiler term	P value
Cardiac muscle cell action potential	GO:0086001	4.0E-10
Regulation of ventricular cardiac muscle cell membrane repolarization	GO:0060307	4.7E-10
Ventricular cardiac muscle cell membrane repolarization	GO:0099625	1.1E-9

TMR^{rec} biological mechanisms	G:Profiler term	P value
Cardiac muscle cell action potential	GO:0086001	6.6E-8
Regulation of cardiac muscle contraction	GO:0055117	1.2E-7
Regulation of heart rate	GO:0002027	3.8E-7

Conclusions



Future work: (1) Perform functional work to confirm the novel genes for TMR and (2) investigate the correlation between TMR and intracardiac parameters of ventricular repolarization

Queen Mary University London

Dr. Nay Aung
Prof. Andrew Tinker
Prof. Patricia Munroe

University College London

Dr. Stefan van Duijvenboden
Prof. Pier Lambiase
Dr. Michele Orini

University of Zaragoza

Prof. Pablo Laguna
Prof. Esther Pueyo

Manuscript just accepted!

J Ramírez et al. *The cardiovascular predictive value and genetic basis of ventricular repolarization dynamics*.
Circulation: Arrhythmia and Electrophysiology 2019



Electrogenomics Group



25/09/2019

CompBioMed Conference

• Acknowledgements:

- WHRI-ACADEMY-COFUND (Marie Curie Actions) FP7/2007/2013/608765
- Marie Skłodowska-Curie Individual Fellowship
- UK Biobank Resource (application 8256)
- MRC grant MR/N025083/1
- National Institute of Health Research
- UCLH Biomedicine NIHR
- European Research Council
- MINECO (Spain)
- European Social Fund and Gobierno de Aragón
- UK Biobank volunteers