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ORIGINAL ARTICLE

The prognostic significance of T-wave inversion according to ECG lead group during long-term follow-up in the general population

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Abstract

Background: Inverted T waves in the electrocardiogram (ECG) have been associated with coronary heart disease (CHD) and mortality. The pathophysiology and prognostic significance of T-wave inversion may differ between different anatomical lead groups, but scientific data related to this issue is scarce.

Methods: A representative sample of Finnish subjects (n = 6,354) aged over 30 years underwent a health examination including a 12-lead ECG in the Health 2000 survey. ECGs with T-wave inversions were divided into three anatomical lead groups (anterior, lateral, and inferior) and were compared to ECGs with no pathological T-wave inversions in multivariable-adjusted Fine–Gray and Cox regression hazard models using CHD and mortality as endpoints.

Results: The follow-up for both CHD and mortality lasted approximately fifteen years (median value with interquartile ranges between 14.9 and 15.3). In multivariate-adjusted models, anterior and lateral (but not inferior) T-wave inversions associated with increased risk of CHD (HR: 2.37 [95% confidence interval 1.20–4.68] and 1.65 [1.27–2.15], respectively). In multivariable analyses, only lateral T-wave inversions associated with increased risk of mortality in the entire study population

(HR 1.51 [1.26–1.81]) as well as among individuals with no CHD at baseline (HR 1.59 [1.29–1.96]).

Conclusions: The prognostic information of inverted T waves differs between anatomical lead groups. T-wave inversion in the anterior and lateral lead groups is independently associated with the risk of CHD, and lateral T-wave inversion is also associated with increased risk of mortality. Inverted T wave in the inferior lead group proved to be a benign phenomenon.

KEYWORDS

coronary heart disease, electrocardiogram, mortality, population study, T wave

1 | INTRODUCTION

Inverted T waves in the electrocardiogram (ECG) defined by the Minnesota codes 5.1-3 (Prineas et al., 1982) have been associated with ischemic heart disease events as well as cardiovascular and total mortality in former population-based studies (Bakhoya et al., 2014; Larsen et al., 2002; Laukkanen et al., 2014; Rautaharju et al., 2012). The pathophysiology and prognostic significance of T-wave inversion may differ between different anatomical lead groups. According to expert recommendations, an inverted T wave is a normal finding in leads III, aVR, aVL, and V1 in adults (Rautaharju et al., 2009). Inverted T waves in the right precordial leads V1-V3 are typical for arrhythmogenic right ventricular cardiomyopathy (Nasir et al., 2004), but in a population study, they were not associated with cardiovascular or total mortality (Aro et al., 2012). A downsloping ST segment with asymmetric T-wave inversion in the lateral leads, the "strain pattern," is a marker of anatomical left ventricular hypertrophy (LVH) and is associated with increased left ventricular mass and mortality (Inoue et al., 2017). Lower T-wave level as a continuous variable was associated with cardiovascular mortality in women in an earlier study of the Health 2000 population, but this was seen only in the lateral lead group (I, aVL, and V5-V6) (Anttila et al., 2010).

We hypothesized that the pathophysiology and prognostic significance of T-wave inversion differ between different anatomical lead groups of the 12-lead resting ECG. Therefore, in this study, we sought to explore the long-term prognostic significance of T-wave inversion in three different anatomical lead groups (anterior, lateral, and inferior) in the general population using new diagnosis of coronary heart disease (CHD) and total mortality as outcomes.

2 | METHODS

2.1 | Study population

The Health 2000 survey was carried out in 2000–2001 and was designed to cover a nationally representative population sample of the Finnish population. This population-based nationwide study consisted of 8,028 individuals aged over 30 years, of whom 79% (6,354 individuals) participated in the health examination, which included a structured examination by a physician, health interviews, series of laboratory tests, and ECG recordings. Participants aged 80 + were oversampled with a double sampling fraction. More detailed descriptions of the methods of the Health 2000 survey have been published previously (Heistaro, 2008). Ethical approval for the Health 2000 study was obtained from Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (HUS).

2.2 | Study covariates

Trained study personnel performed the health interview, and they followed a structural detailed written instruction to gather information about pre-existent diseases. Examining physicians performed another structured interview and physical examination. We included data on prevalent diseases from the Care Register for Health Care (CRHC) maintained by the Finnish Institute for Health and Welfare. CRHC contains data of all inpatient episodes in Finland at the individual level since year 1969 and on outpatients since 1998. The accuracy of the register has been validated previously (Sund, 2012). Information about medication at baseline was gathered by checking the study participants' personal health insurance cards for rights of drug reimbursements and by interviewing the study participants about prescription and nonprescription medicines. In addition, data on drug purchases since year 1995 and special drug reimbursements since year 1964 were gathered from a separate registry (Statistics on reimbursements for prescription medicines: The Social Insurance Institution of Finland).

Height and weight were measured, and body mass index (BMI) was calculated. Blood pressure was measured from the right arm with a standard mercury manometer (Mercuro 300; Speidel & Keller). An average of two measurements was used, of which the first one was measured after rest for at least 5 min in sitting position. Arterial hypertension (HTA) was defined as blood pressure ≥140/90, a previous diagnosis of HTA in the CRHC (ICD-10 I10, ICD-9/8 401),

or right for special drug reimbursements for HTA. Heart rate was obtained from the ECGs. Smoking was determined as a daily use of cigarettes at the time of the interview.

Serum high-density lipoprotein (HDL) cholesterol and plasma glucose concentrations were determined enzymatically (Roche Diagnostics, GmbH, Mannheim, Germany, for HDL-cholesterol and Olympus System Reagent, Hamburg, Germany, for glucose) from venous blood samples with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The diagnosis of diabetes mellitus (DM) at baseline included fasting serum glucose (fS-Gluc) ≥7 or a history of use of oral glucose-lowering agents or insulin injections (World Health Organization & International Diabetes Federation, 2006).

A standard 12-lead resting ECG in the supine position was recorded from each subject during the health examination with Marquette Hellige MAC 5000 electrocardiographs (Freiburg, Germany and Milwaukee, WI, USA). ECGs were stored electronically. The ECG data were sent for further analysis to the Social Insurance Institution's research center in Turku, Finland, where the ECGs were analyzed with Magellan software (Marquette Electronics Inc). The Marquette 12SL algorithm uses median complexes of the 10-s ECG tracing using the onset of QRS as the isoelectric line. A wave crossing the baseline level constituting an area of ≥160 μVms represents a separate wave. In addition, the ECGs were Minnesota-coded (Prineas et al., 1982) by two investigators at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, blinded to the clinical data.

2.3 | The definition of T-wave inversion and lead groups

Amplitudes of different parts of the T wave were automatically measured. The T wave was considered negative when the T-wave amplitude was <0 μV. If the T wave was biphasic, the lowest part of the wave indicated the level. T waves were grouped into lead groups: anterior (V2, V3, V4), lateral (I, aVL, V5, V6), and inferior (II, aVF). If a lead group contained at least one negative T wave, the lead group was classified as having T-wave inversion. Participants with negative T waves in more than one lead group were classified into a separate group ("multiple locations"). The T waves in leads III, aVL, and V1 were separately tested before inclusion into their respective lead groups, because an inverted T wave in these leads is considered normal, but the T waves in these leads can also be affected by different disease processes. Lead aVR was not included in the analyses, as the T wave is normally negative in that lead.

2.4 | Follow-up and study endpoints

The data for mortality and causes of death were gathered from the Causes of Death register maintained by Statistics Finland. It contains 100% of deaths of Finnish citizens in Finland and almost 100% abroad. Information on the incident diseases was obtained from the CRHC. Databases were linked using a personal identity code. The follow-up lasted until the end of the year 2015.

The study endpoints were total mortality and a new diagnosis of CHD. The endpoints were tested separately. Classification of prevalent CHD required at least one of the following: diagnosed angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI) or bypass surgery by examining physician or diagnosed PCI or bypass surgery in the health interview, ICD codes I20-25 (ICD-10) or 410–14 (ICD8/9) in the CRHC, the right for drug reimbursements for CHD, or interventional code for coronary artery revascularization in the CRHC. For the diagnosis of incident CHD, we included above-mentioned ICD codes and interventional codes for CHD, ICD codes I21-25, I46, R96, and R98 (ICD-10) in the Causes of Death register, and a new right for drug reimbursements for CHD.

2.5 | Exclusion criteria

We excluded subjects with missing ECG data (number of participants [n] = 55). Of those, the recording was not successful in 36 participants with entries such as "difficult to move," "wheelchair," "denial," "leg/hand amputated," "in geriatric chair," "massive hernia," and "plaster in leg/ hand." In the further process, 19 ECGs were lost (diskette lost [9], coupling error [4], data reading failure [5], and unspecific reason [1]). We also excluded subjects with Q/QS waves in the ECG according to the Minnesota codes (Prineas et al., 1982) 1–1, 1–2, and 1–3 ($n = 127$), left or right bundle branch block or left anterior hemiblock (Minnesota code 7, $n = 565$), Wolff–Parkinson–White pattern (Minnesota code 6–4, $n = 1$), paced rhythm (Minnesota code 6–8, $n = 4$), or left ventricular hypertrophy in the ECG (Minnesota codes 3–1, 3–3, and 3–4, $n = 820$) from the analysis. The final study sample consisted of 4,793 participants. In the analysis where we used CHD as an endpoint, we also excluded prevalent CHD as defined earlier.

2.6 | Statistical analyses

Because the T wave may normally be positive or negative in leads III, aVL, and V1 (Rautaharju et al., 2009), we tested the prognosis for each of these leads separately with unadjusted Cox proportional hazard models using both total mortality and CHD as endpoints. After this analysis, we included leads with detrimental prognosis in the lead groups. In these analyses, T-wave inversions in other leads were not excluded as there was no isolated T-wave inversion in III, aVL, or V1. Comparisons in variables were calculated with one-way ANOVA for continuous variables and chi-square test for categorical variables. Cox proportional hazard models were constructed for total mortality. The Fine–Gray proportional subdistribution hazards model treating death as a competing risk was used to study the association of T-wave inversions with CHD in different lead groups. The proportional hazard assumption was checked visually

TABLE 1 Baseline characteristics of the Health 2000 Survey participants

	No TWI		Anterior TWI		Lateral TWI		Inferior TWI		Multiple TWI		
	n/mean	%/(*SD*)	*n*/ mean	%/(*SD*)	*n*/ mean	%/(*SD*)	*n*/mean	%/(*SD*)	*n*/ mean	%/(*SD*)	*p* Value
N	3,852	80.4%	60	1.3%	440	9.2%	303	6.3%	138	2.9%	
Age	49.5	(13.3)	53.7	(16.9)	58.1	(14.9)	56.2	(14.0)	68.9	(13.6)	<.001
Men	1,577	40.9%	7	11.7%	197	44.8%	129	42.6%	38	27.5%	<.001
BMI (kg/m^2)	26.9	(4.6)	27.4	(5.2)	26.4	(5.4)	28.9	(4.9)	28.7	(6.0)	<.001
Heart rate/min	63.5	(10.5)	61.5	(11.6)	64.9	(12.6)	63.8	(11.7)	65.2	(13.7)	.014
Regular smoking	868	22.6%	10	16.9%	121	27.6%	42	13.9%	16	11.7%	<.001
Hypertension	1,482	38.6%	24	40.0%	237	54.0%	175	57.9%	97	70.3%	<.001
Diabetes	170	4.4%	2	3.3%	50	11.4%	21	6.9%	25	18.1%	<.001
CHD	151	3.9%	3	5.0%	67	15.2%	31	10.2%	47	34.1%	<.001
HDL (mmol/L)	1.3	(0.4)	1.4	(0.4)	1.3	(0.4)	1.2	(0.3)	1.2	(0.4)	<.001
LDL (mmol/L)	3.8	(1.2)	3.7	(1.1)	3.8	(1.2)	3.8	(1.2)	3.7	(1.4)	.924

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; *N*, number; *SD*, standard deviation; TWI, T-wave inversion.

from the Kaplan–Meier curves for mortality and from cumulative incidence function curves for CHD. Only the first diagnosis of CHD was considered. The four mutually exclusive groups (anterior, lateral, inferior, and multiple locations) were compared to ECGs with no T-wave inversions (excluding aVR, V1, and III). Both hazard models were constructed with and without adjustment for age and for multivariate analysis for age, sex, BMI, HDL-cholesterol, LDL-cholesterol, regular smoking, heart rate, HTA, DM, and CHD (not for CHD as an endpoint). In addition, to test for a possible confounding effect of the ST level, we performed a sensitivity analysis, where we included the amplitude of the ST level at the J point (as dichotomous variable ≥ 0 μV or < 0 μV) in the multivariate adjustment. From a clinical point of view, the results of this sensitivity analysis did not differ significantly from the results without ST-level adjustment. Therefore, the results with the ST-level adjustment are not included. The interaction was tested between different lead groups and sex for both endpoints and between lead groups and CHD for mortality in unadjusted Cox models. No significant sex-related interactions were observed, and all the analyses were performed without sex stratification. The interaction term between lead groups and CHD was significant. Therefore, we performed the mortality analysis also after dividing the data by CHD. Analyses

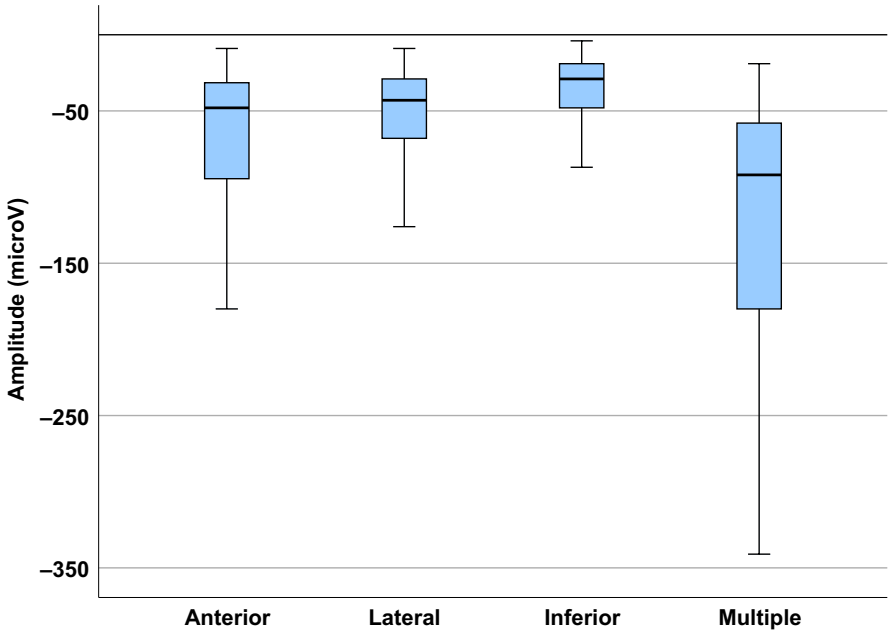

FIGURE 1 Minimum amplitudes of negative T waves in box plot analysis divided by lead groups. Outliers have been removed

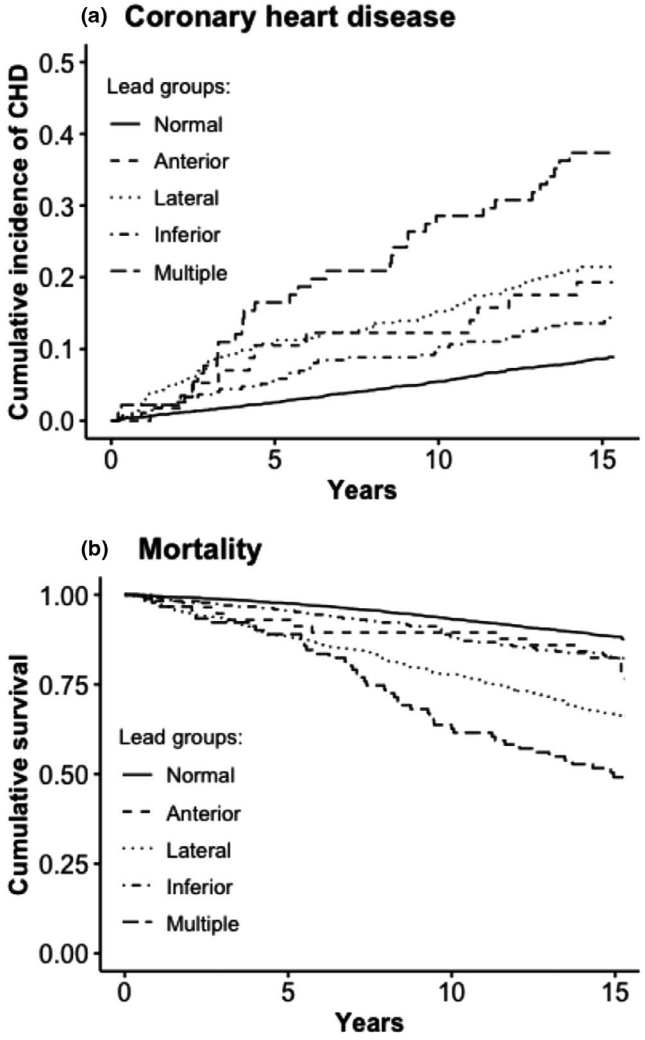

FIGURE 2 (a) Cumulative incidence function curves for coronary heart disease and (b) Kaplan–Meier survival curves for mortality of T-wave inversions in different lead groups in participants without known coronary heart disease at the baseline

were performed using SPSS 25 and R 3.6.3. Statistical significance was based on $p < .05$.

3 | RESULTS

3.1 | Forming ECG lead groups

To form final lead groups, we tested the prognostic significance of T-wave inversion separately for leads III, aVL, and V1 using both mortality and CHD as endpoints, because both a positive and a negative T wave is considered normal in these leads (Rautaharju et al., 2009). Negative T waves in leads III and V1 were associated with lower risk of CHD and mortality, and therefore, these leads were not included in any lead group. For lead III, unadjusted hazard ratio (HR) was 0.84 (95% confidence interval [CI]: 0.74–0.97, $p = .015$) for mortality and 0.87 (0.72–1.04, $p = .113$) for CHD and for V1 HR was 0.61 (0.53–0.70, $p < .001$) for mortality and 0.59 (0.49–0.71, $p < .001$) for CHD. T-wave inversion in lead aVL was associated with higher mortality risk (HR: 3.33 [2.84–3.90, $p < .001$]) as well as a higher risk for a new CHD diagnosis (HR: 3.05 [2.45–3.81, $p < .001$]). Therefore, lead aVL was included in the lateral lead group. Hence, the final lead groups were anterior (V2, V3, V4), lateral (I, aVL, V5, V6), and inferior (II, aVF).

3.2 | Study sample

Table 1 shows the baseline characteristics and the prevalence of T-wave inversions in different lead groups. There were 59.4% women in the study sample versus 40.6% men. T-wave inversion was a rare finding in the anterior lead group with the prevalence of 1.3%. T-wave inversion in the lateral, inferior, and multiple lead groups was found in 9.2%, 6.3%, and 2.9%, respectively. Individuals with inverted T waves were significantly older than those without. Anterior T-wave inversions were far more prevalent among women (88.3%), while lateral and inferior T-wave inversions were slightly less frequent in women than in men. The rate of HTA, DM, and CHD was clearly higher in individuals with inverted T waves in more than one lead group than in those with T-wave inversion in only one lead group or no T-wave inversion.

Figure 1 shows the amplitudes of the inverted T waves. Inverted T waves in the anterior lead group were deeper than those in the lateral or inferior lead groups. Among individuals with T-wave inversions in two or three lead groups, the T waves were much deeper than in those with T-wave inversions only in one lead group.

3.3 | T-wave inversion and incident CHD

There were 489 (10.9%) new CHD diagnoses during the median follow-up time of 15.2 years (interquartile range: 14.9–15.3). T-wave inversions in all lead groups were associated with a new diagnosis of CHD in unadjusted models. Figure 2a shows the cumulative incidence function curves. Table 2 shows the unadjusted and adjusted HRs for the association between T-wave inversion and CHD in the different lead groups. Lateral T-wave inversions, as well as negative T waves in two or more lead groups, were associated with higher risk for a new CHD diagnosis. Regarding anterior T-wave inversion, there was an association between the studied ECG phenomenon and higher CHD rates in crude and multivariate-adjusted analysis. The association between inferior T-wave inversion and CHD was not statistically significant after adjusting for age and after multivariate adjustment.

3.4 | T-wave inversion and total mortality

The median follow-up time for mortality was 15.1 years (14.9–15.2) and 842 (17.6%) individuals died during the follow-up period. T-wave inversions in the lateral (HR 3.29 [2.76–3.92, $p < .001$]) and inferior (HR 1.75 [1.35–2.25, $p < .001$]) lead groups were associated with

TABLE 2 Fine–Gray proportional subdistribution hazards analysis of T-wave inversion by location for CHD

Lead groups	Amount of CHD diagnoses/ participants (%)	Hazard ratio (95% CI)					
		Unadjusted	*p* Value	Age-adjusted	*p* Value	Multivariate-adjusted[a]	*p* Value
Anterior	11/57 (19.3%)	2.36 (1.29–4.33)	.006	1.72 (0.90–3.30)	.100	2.37 (1.20–4.68)	.013
Lateral	80/373 (21.4%)	2.68 (2.09–3.43)	<.001	1.78 (1.38–2.30)	<.001	1.65 (1.27–2.15)	<.001
Inferior	39/272 (14.3%)	1.70 (1.22–2.37)	.002	1.22 (0.87–1.73)	.250	1.11 (0.78–1.58)	.560
Many sites	34/91 (37.4%)	5.12 (3.59–7.30)	<.001	2.06 (1.40–3.03)	<.001	2.18 (1.49–3.21)	<.001

Abbreviations: CHD, coronary heart disease; CI, confidence interval.

[a]Age, sex, diabetes, hypertension, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, heart rate, body mass index, and regular smoking.

TABLE 3 Cox proportional hazard analysis of T-wave inversion by location for mortality in participants with and without known CHD at baseline

Lead groups	Deaths/ participants (%)	Hazard ratio (95% CI)					
		Unadjusted	*p* Value	Age-adjusted	*p* Value	Multivariate-adjusted[a]	*p* Value
Interaction		CHD × lead groups	<.001				
Participants without CHD							
Anterior	11/57 (19.3%)	1.72 (0.94–3.13)	.076	1.08 (0.59–1.97)	.796	1.40 (0.75–2.64)	.293
Lateral	125/373 (33.5%)	3.32 (2.73–4.06)	<.001	1.84 (1.50–2.25)	<.001	1.59 (1.29–1.96)	<.001
Inferior	48/272 (17.6%)	1.56 (1.16–2.10)	.004	1.04 (0.77–1.40)	.813	1.06 (0.78–1.43)	.719
Many sites	46/91 (50.5%)	5.66 (4.18–7.67)	<.001	1.65 (1.21–2.26)	.002	1.72 (1.26–2.36)	.001
Participants with CHD							
Anterior	2/3 (66.7%)	1.57 (0.39–6.40)	.526	0.93 (0.23–3.80)	.924	1.34 (0.33–5.56)	.684
Lateral	39/67 (58.2%)	1.14 (0.78–1.66)	.507	1.41 (0.96–2.08)	.078	1.32 (0.89–1.97)	.174
Inferior	19/31 (61.3%)	1.29 (0.78–2.12)	.324	1.11 (0.68–1.84)	.671	1.33 (0.79–2.23)	.284
Many sites	32/47 (68.1%)	1.55 (1.03–2.34)	.035	1.15 (0.76–1.73)	.503	1.18 (0.76–1.81)	.463

Abbreviations: CHD, coronary heart disease; CI, confidence interval; *N*, number.

[a]Age, sex, diabetes, hypertension, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, heart rate, body mass index, and regular smoking.

higher mortality rates in the crude Cox models. After adjusting for age, the increase in mortality rates was significant only in the lateral leads (HR 1.77 [1.48–2.11, $p < .001$]). This was also the case for multivariate adjustment (HR 1.51 [1.26–1.81, $p < .001$]). The associated risk for mortality was also significant among participants with negative T waves in more than one lead group and of similar magnitude as for participants with only lateral T-wave inversions (HR 1.49 [1.16–1.92, $p = .002$]).

We noticed a significant interaction ($p < .001$) in unadjusted analysis between the lead groups and CHD with regard to the mortality risk during follow-up. We performed these analyses again after dividing the data by existing prevalent CHD and noticed that the adverse prognosis of T-wave inversion in different lead groups was not significant in participants with known CHD. Table 3 shows the HRs in the mortality analyses in individuals with and without known CHD at baseline. Figure 2b shows the cumulative survival rates for negative T waves in different lead groups in participants without known CHD at baseline.

4 | DISCUSSION

The main finding of this population-based study is that the prognostic significance of T-wave inversion differs between the different anatomical lead groups of the 12-lead ECG. Inverted T waves in the anterior and lateral lead groups at baseline were independently associated with a new CHD diagnosis during long-term follow-up. T-wave inversions in the lateral lead group were independently associated with increased mortality. The risk did not differ between the sexes. The results of interaction analyses showed a significantly pronounced mortality risk among subjects with no CHD at baseline. T-wave inversion in the inferior lead group proved to be a benign phenomenon.

4.1 | The prevalence of T-wave inversion

The prevalence of T-wave inversions varies between different studies depending on the population, exclusion criteria, and

definition of T-wave inversion. In a population study of Larsen et al. (Larsen et al., 2002), the prevalence of T-wave inversions increased with age. Also in our study, participants with negative T waves were older than those without (53.7–68.9 versus 49.5 years, $p < .001$). In our study population, T-wave inversions were prevalent in 1.3% (anterior), 9.2% (lateral), and 6.3% (inferior) of the participants. In the BIRNH study (De Bacquer et al., 1998), the age-standardized prevalence of inverted T waves was 9.3% among women and 6.1% among men. Anterior T-wave inversions were found in 2.3% of asymptomatic participants with a mean age of 21.7 years (±5.7) and were more frequent among women and in athletes (Malhotra et al., 2017). In a study by Aro et al. (Aro et al., 2012), the prevalence of anterior T-wave inversions (in all of the leads V1-V3) was 0.5%. In their study, the prevalence of anterior T-wave inversions was much higher among women than among men, and this was the case also in the present study. The prevalence in other leads was opposite between the sexes, as was the case also in our study.

4.2 | The prognostic significance of inverted T waves

Inverted T waves and minor T-wave abnormalities have been associated with incident CHD and cardiovascular mortality in many previous population-based studies (Bakhoya et al., 2014; Greenland et al., 2003; Larsen et al., 2002; Laukkanen et al., 2014; Rautaharju et al., 2012). In the majority of these studies, the location of the T-wave changes was not specified, and the studies included T-wave changes in general. We found that the association between T-wave inversion and CHD was highly dependent on the location of the ECG abnormality and concerned only the anterior and lateral lead groups. In the anterior lead group, we noticed a more than twofold increase in the associated risk to receive a new diagnosis of CHD including acute coronary events, also after adjusting for traditional CHD risk factors. It is possible that inverted T waves in the anterior and lateral lead groups reflect underlying asymptomatic CHD (Luna et al., 2014). The association between T-wave inversion and CHD is highlighted by the fact that in the anterior lead group, the association with worse prognosis was seen only for CHD and not for mortality. After adjusting for age, inferior T-wave inversions were not associated with CHD or total mortality. This may at least partly be explained by the fact that the direction of the T-wave in the extremity leads is dependent on body habitus. In lean individuals with right axis deviation in the frontal plane, the T wave in lead II and aVF is normally positive, but T-wave inversion in lead aVF may be present (Bayés de Luna, 2012).

A negative T wave in the precordial leads (V1-V3) is a normal condition in children, but in adults, of these leads, only in lead V1, T-wave inversion is clearly a normal finding (Rautaharju et al., 2009). Negative T waves in the anterior leads may accompany arrhythmogenic right ventricular cardiomyopathy and Takotsubo syndrome (Luna et al., 2014). In a study of asymptomatic athletes and nonathletes with a mean age of 21.7 years (±5.7), none of the 338 study participants with anterior T-wave inversions had cardiomyopathy and none experienced an adverse event during 2-year follow-up (Malhotra et al., 2017). In a population study of Aro et al., T-wave inversions in leads V1-V3 were not associated with increased risk of cardiovascular or total mortality (Aro et al., 2012). Our study confirms these findings: Inverted T waves in the anterior lead group (V2-V4) were not associated with increased risk of mortality.

The "strain pattern," ST depression with asymmetric, downsloping ST segment, and T-wave inversion in the lateral ECG leads, is a marker of anatomical LVH and is associated with larger left ventricular mass and worse outcome in HTA (Okin et al., 2009); this ECG pattern was associated with all-cause mortality, systolic dysfunction, and myocardial scar in a population study (Inoue et al., 2017). In a study of Inoue et al. (Inoue et al., 2017), the associated risk of myocardial infarction, cardiovascular events, mortality, and heart failure for lateral strain (I, II, aVL, or V3 to V6) was seen independently of ECG-LVH. In their study, left ventricular scar was associated with strain but not with ECG-LVH and they hypothesized that the mechanism underlying the strain pattern would be silent subendocardial and mid-wall ischemia, which could explain the increased risk for adverse cardiovascular events.

In acute coronary syndrome, T-wave inversions can occur in the acute stage together with ST segment deviation as a sign of myocardial ischemia. Isolated "postischemic" T-wave inversions may persist for weeks after the acute phase. After myocardial infarction, T-wave inversions often accompany pathological Q waves, but they may also appear in isolation. The location of the postischemic T-wave inversions within the 12-lead ECG usually reflects the site of the ischemia during the acute phase (Luna et al., 2014), and persistent T-wave inversions after ST-elevation myocardial infarction have been associated with worse prognosis and larger infarct size (Lancellotti et al., 2002; Reindl et al., 2017). In our study, in participants with known CHD at baseline, T-wave inversions did not seem to associate significantly with mortality. The related risk estimate was increased but not as pronounced as among other subjects. We excluded individuals with Q/QS waves in their ECG, which can be one explanation for this finding. In addition, the prevalence of CHD at baseline was low, and it is possible that the groups were too small to enable the detection of statistically significant differences.

In the group with T-wave inversions in more than one lead group, the crude HRs were considerably higher than in individuals with T-wave inversions located to one lead group. The participants with more widespread T-wave inversions were also older and had more comorbidities which explain the decrease in HRs when adjusting for age and other cardiovascular risk factors. Despite the similar multivariate-adjusted HRs compared to some of the groups with T-wave inversions in only one lead group, it is possible that participants with widespread and deep T-wave inversions are at higher risk of adverse events because of the unfavorable risk profile. As we did not analyze the impact of different combinations of

lead groups with inverted T waves, no conclusions can be drawn regarding differences in outcome between combinations of lead groups.

We tested the effect of sex on the prognosis in the interaction analysis and did not find significant interactions. There was also no significant interaction between the sexes in the Copenhagen City Heart Study, where the prognostic impact of inverted T waves on myocardial infarction, ischemic heart disease events, and cardiovascular mortality was studied (Larsen et al., 2002). De Bacquer et al. (De Bacquer et al., 1998) studied the prognosis of inverted T waves separately for men and women and noticed that the adverse effect on all-cause mortality was seen only in men. The relative risk for cardiovascular mortality was slightly higher for women than for men, while the opposite was true for CHD mortality. In a former study of the Health 2000 population, the negative prognostic impact of inverted lateral T waves (as a continuous parameter) on cardiovascular mortality was seen only among women (Anttila et al., 2010).

The changes in the T waves reflect changes in ventricular repolarization and may be present with or without ST deviation. We performed an additional analysis to study the possible confounding of the ST level, but at least in this population study, the polarity of the ST level had no influence on the results. Primary T-wave inversion may be present in various conditions including perimyocarditis, acute or chronic pulmonary hypertension, cardiomyopathies, alcoholism, stroke, certain drugs, and hypokalemia and in athletes. Because this was a population study, stroke and acute pulmonary embolism are very unlikely etiologies of the T-wave inversions.

4.3 | Study limitations and strengths

The Health 2000 population is a representative sample of the Finnish population 30 years of age or older. The results may not be applicable to other populations. The long follow-up time up to 15 years resulted in a relatively high mortality rate (17.6%) for a population study. We excluded participants with LVH based on Minnesota ECG criteria (3–1, 3–3, and 3–4). It is possible that some participants with anatomical LVH were included in this study and vice versa. Lack of echocardiographic data, including LVH data, could be considered as a limitation of the study. We had no access to the health records of the study participants, which is a limitation very typical for a large population study. In general, T-wave alterations in the general population are minor, and therefore, we decided not to further separate the patient groups according to T-wave amplitudes. We used computer-based measurements, which helps to correct for artifacts caused by wandering baseline and some other technical disturbances. However, it has to be pointed out that the smaller magnitudes of T-wave inversion detected in the automated measurements are not possible with naked-eye detection.

Inclusion of lead groups for T-wave analyses is important, because the prognostic information clearly differs between the different lead categories and the prognostic aspects of T-wave inversions have not been extensively studied before from this standpoint. We wanted to study lead groups instead of individual leads, because different disease processes in the heart typically affect more than one ECG lead. Therefore, ECG diagnoses, for example related to CHD, rely on changes in parallel leads. We tested the prognosis for leads III, aVL, and V1 separately before the decision to include any of these leads to their corresponding lead group. This was done because the direction and amplitude of the T wave in these leads may be affected by different disease states although T-wave negativity is considered as normal.

5 | CONCLUSIONS

The present general population study showed that the prognostic information of T-wave changes differs between anatomical lead groups. Lateral T-wave inversion is associated with increased risk of mortality and CHD. Additionally, T-wave inversion in the anterior lead group is independently associated with the risk of CHD, but not mortality, highlighting the need to consider CHD when anterior T-wave inversions are observed. Inverted T wave in the inferior lead group proved to be a benign phenomenon.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

ETHICS

Ethical approval for the Health 2000 study was obtained from Ethical Committee for Research in Epidemiology and Public Health at the Hospital District of Helsinki and Uusimaa (HUS).

AUTHOR CONTRIBUTIONS

Conceived the study, contributed to methodology, performed the formal analysis, and wrote the original draft of the manuscript: Tiia Istolahti. Developed the software and wrote, reviewed, and edited the manuscript: Leo-Pekka Lyytikäinen. Contributed to methodology and performed the formal analysis: Heini Huhtala. Wrote, reviewed, and edited the manuscript: Tuomo Nieminen. Wrote, reviewed, and edited the manuscript, and supervised the study: Mika Kähönen. Wrote, reviewed, and edited the manuscript: Terho Lehtimäki. Wrote, reviewed, and edited the manuscript: Markku Eskola. Wrote, reviewed, and edited the manuscript: Ismo Anttila. Curated the data and wrote, reviewed, and edited the manuscript: Antti Jula. Collected the resources and wrote, reviewed, and edited the manuscript: Harri Rissanen. Conceived the study, contributed to methodology, wrote the original draft of the manuscript, supervised the study, and administered the project: Kjell Nikus. Contributed to methodology; performed the formal analysis; wrote, reviewed, and edited the manuscript; and supervised the study: Jussi Hernesniemi.

DATA AVAILABILITY STATEMENT

Data are not available due to containing information that could compromise the privacy of research participants.

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REFERENCES

Anttila, I., Nikus, K., Kähönen, M., Jula, A., Reunanen, A., Salomaa, V., … Nieminen, T. (2010). Prognostic implications of quantitative ST-segment characteristics and T-wave amplitude for cardiovascular mortality in a general population from the Health 2000 Survey. *Annals of Medicine*, *42*(7), 502–511. https://doi.org/10.3109/07853890.2010.505932

Aro, A. L., Anttonen, O., Tikkanen, J. T., Junttila, M. J., Kerola, T., Rissanen, H. A., … Huikuri, H. V. (2012). Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. *Circulation*, *125*(21), 2572–2577. https://doi.org/10.1161/CIRCULATIONAHA.112.098681

Bakhoya, V. N., Kurl, S., & Laukkanen, J. A. (2014). T-wave inversion on electrocardiogram is related to the risk of acute coronary syndrome in the general population. *European Journal of Preventive Cardiology*, *21*(4), 500–506. https://doi.org/10.1177/2047487312460022

De Bacquer, D., De Backer, G., Kornitzer, M., & Blackburn, H. (1998). Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. *Heart*, *80*(6), 570–577. https://doi.org/10.1136/hrt.80.6.570

de Luna, A. B., (Ed.). (2012). *Clinical electrocardiography: A textbook*. Chapter 7, pages 67–94. (Vol. *2012*). West Sussex, UK: Wiley-Blackwell.

de Luna, A. B., Zareba, W., Fiol, M., Nikus, K., Birnbaum, Y., Baranowski, R., … Wellens, H. (2014). Negative T wave in ischemic heart disease: a consensus article. *Annals of Noninvasive Electrocardiology*, *19*(5), 426–441. https://doi.org/10.1111/anec.12193

Greenland, P., Xie, X., Liu, K., Colangelo, L., Liao, Y., Daviglus, M. L., … Stamler, J. (2003). Impact of minor electrocardiographic ST-segment and/or T-wave abnormalities on cardiovascular mortality during long-term follow-up. *American Journal of Cardiology*, *91*(9), 1068–1074. https://doi.org/10.1016/S0002-9149(03)00150-4

Heistaro, S. (Ed.). (2008). *Methodology report: Health 2000 survey*. Helsinki, Finland: Publications of the National Public Health Institute B26; 2008. Retrieved from http://urn.fi/URN:NBN:fi-fe20120419 3320

Inoue, Y. Y., Soliman, E. Z., Yoneyama, K., Ambale-Venkatesh, B., Wu, C. O., Sparapani, R., … Ashikaga, H. (2017). Electrocardiographic strain pattern is associated with left ventricular concentric remodeling, scar, and mortality over 10 years: The Multi-Ethnic Study of atherosclerosis. *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease*, *6*(9), e006624. https://doi.org/10.1161/JAHA.117.006624

Lancellotti, P., Gérard, P. L., Kulbertus, H. E., & Piérard, L. A. (2002). Persistent negative t waves in the infarct-related leads as an independent predictor of poor long-term prognosis after acute myocardial infarction. *American Journal of Cardiology*, *90*(8), 833–837. https://doi.org/10.1016/S0002-9149(02)02703-0

Larsen, C. T., Dahlin, J., Blackburn, H., Scharling, H., Appleyard, M., Sigurd, B., & Schnohr, P. (2002). Prevalence and prognosis of electrocardiographic left ventricular hypertrophy, ST segment depression and negative T-wave. The Copenhagen City Heart Study. *European Heart Journal*, *23*(4), 315–324. https://doi.org/10.1053/euhj.2001.2774

Laukkanen, J. A., Di Angelantonio, E., Khan, H., Kurl, S., Ronkainen, K., & Rautaharju, P. (2014). T-wave inversion, QRS duration, and QRS/T angle as electrocardiographic predictors of the risk for sudden cardiac death. *American Journal of Cardiology*, *113*(7), 1178–1183. https://doi.org/10.1016/j.amjcard.2013.12.026

Malhotra, A., Dhutia, H., Gati, S., Yeo, T.-J., Dores, H., Bastiaenen, R., … Sharma, S. (2017). Anterior T-wave inversion in young white athletes and nonathletes. *Journal of the American College of Cardiology*, *69*(1), 1–9. https://doi.org/10.1016/j.jacc.2016.10.044

Nasir, K., Bomma, C., Tandri, H., Roguin, A., Dalal, D., Prakasa, K., … Calkins, H. (2004). Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: A need to broaden diagnostic criteria. *Circulation*, *110*(12), 1527–1534. https://doi.org/10.1161/01.CIR.0000142293.60725.18

Okin, P. M., Oikarinen, L., Viitasalo, M., Toivonen, L., Kjeldsen, S. E., Nieminen, M. S., … Devereux, R. B. (2009). Prognostic value of changes in the electrocardiographic strain pattern during antihypertensive treatment: The Losartan Intervention for End-Point Reduction in Hypertension Study (LIFE). *Circulation*, *119*(14), 1883–1891. https://doi.org/10.1161/CIRCULATIONAHA.108.812313

Prineas, R. J., Crow, R. S., & Blackburn, H. W. (1982). *The Minnesota code manual of electrocardiographic findings* (June, 1982). Littleton, MA: John Wright-PSG Inc.

Rautaharju, P. M., Menotti, A., Blackburn, H., Parapid, B., & Kircanski, B. (2012). Isolated negative T waves as independent predictors of short-term and long-term coronary heart disease mortality in men free of manifest heart disease in the Seven Countries Study. *Journal of Electrocardiology*, *45*(6), 717–722. https://doi.org/10.1016/j.jelectrocard.2012.07.006

Rautaharju, P. M., Surawicz, B., & Gettes, L. S. (2009). AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. *Journal of the American College of Cardiology*, *53*(11), 982–991. https://doi.org/10.1016/j.jacc.2008.12.014

Reindl, M., Reinstadler, S. J., Feistritzer, H.-J., Niess, L., Koch, C., Mayr, A., … Metzler, B. (2017). Persistent T-wave inversion predicts myocardial damage after ST-elevation myocardial infarction. *International Journal of Cardiology*, *241*, 76–82. https://doi.org/10.1016/j.ijcard.2017.03.164

Sund, R. (2012). Quality of the Finnish Hospital Discharge Register: A systematic review. *Scandinavian Journal of Public Health*, *40*(6), 505–515. https://doi.org/10.1177/1403494812456637

World Health Organization & International Diabetes Federation (2006). *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: Report of a WHO/IDF consultation*. Retrieved from http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

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