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Association between primary care electrocardiogram markers and Alzheimer's disease

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Highlights

ECG intervals and amplitudes were significantly associated with Alzheimer's disease.

ECG markers significantly improved risk prediction for Alzheimer's disease.

Associations were different with Alzheimer's disease compared to other dementias.

A favorable ECG was associated with only 5–6% 10-year risk of Alzheimer's disease.

A poor ECG was associated with 9–12% 10-year risk of Alzheimer's disease.

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Abstract

Objective

The association between common electrocardiogram (ECG) markers and Alzheimer's disease has been scarcely investigated, and it is unknown if ECG markers can improve risk prediction. Thus, we aimed to examine the association between common ECG markers and Alzheimer's disease in a large population.

Methods

We studied the association between ECG markers and Alzheimer's disease using Cox models with adjustment for age, sex, and comorbidities using a large primary care population of patients aged 60 years or more.

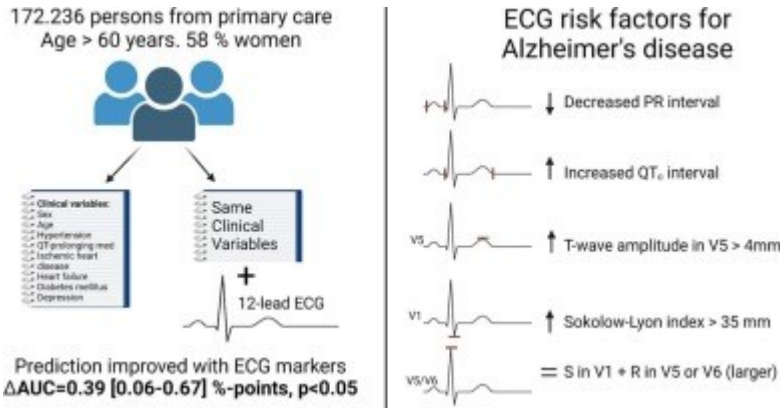
Results

We followed 172,236 subjects for a median of 7.5 years. Increased PR interval (hazard ratio for PR > 188 ms: 0.76 [95% confidence interval: 0.69–0.83, $p < 0.001$) and increased QTc interval (hazard ratio for QTc = [426;439]: 0.90 [0.83–0.98], $p = 0.02$) were associated with a decreased rate of Alzheimer's disease. A positive Sokolow-Lyon index >35 mm (1.22 [1.13–1.33], $p < 0.001$) and increased T-wave amplitude >4.1 mm (1.15 [1.04–1.27]) were associated with an increased rate of Alzheimer's disease. Upon addition of ECG markers to a reference model, 10-year prediction area under the receiver-operator characteristics curve (AUC) improved by 0.39 [0.06–0.67] %-points. The 10-year absolute risk of Alzheimer's disease was 6.5% and 5.2% for an 82-year old female and a male, respectively, with a favorable ECG, and 12% and 9.2%, respectively, with an unfavorable ECG, almost twice as high.

Conclusions

We identified several common ECG markers which were associated with Alzheimer's disease, and which improved risk prediction for Alzheimer's disease.

Graphical Abstract



Keywords

Electrocardiography; Dementia prediction; Alzheimer's disease; Biomarkers

Abbreviations

AD Alzheimer's disease; AUC Area under the receiver-operator characteristics curve; CGPL; Copenhagen General Practitioners' Laboratory; ECG Electrocardiogram; ICD-10 International Classification of Diseases tenth revision; HR Hazard ratio

1. Introduction

With the latest 2020 report of the Lancet Commission [1], it is now estimated that about 40% of dementia cases are attributed to modifiable risk factors and thus potentially preventable. Without a cure, prevention remains the strongest remedy against dementia, but targeted prevention relies on the identification of individuals at risk. Risk stratification based on readily available measures provides a valuable tool as a first-in-line test of the general population, and the electrocardiogram (ECG) is a widely used, inexpensive, and non-invasive test with a high signal-to-noise ratio, which is well suited for automated screening.

The literature is scarce and inconclusive regarding ECG markers and cognitive impairment, dementia, and particularly dementia from Alzheimer's disease (AD). Furthermore, many papers have not made the distinction between different kind of dementia. We previously identified associations between common ECG markers and vascular dementia, but that study explicitly excluded outcomes of AD arguing that the difference in pathophysiology between vascular dementia and AD warrants separate studies [2]. Supporting that argument, atrial fibrillation, is the arguably most well-established marker of cognitive decline and dementia [[2], [3], [4]] and particularly vascular dementia [5]. However, a Mendelian randomization study found no evidence of a causal link between atrial fibrillation and AD [6].

Left ventricular hypertrophy was associated with cognitive decline and all-cause dementia [7,8], and left atrial enlargement and P-wave markers were associated with cognitive decline [[9], [10], [11], [12]]. ECG abnormalities were associated with need of support in one study [13], the mixed depolarization/repolarization marker, QRS-T angle, was associated with cognitive decline [8], but (perhaps surprisingly) the QT interval was not associated with cognitive decline in two studies [14,15] although increased QTc was associated with vascular dementia [2]. To our knowledge, no study has undertaken an investigation of many common ECG markers and AD. It is also currently unknown whether any associations between ECG markers and AD may lead to improved risk prediction for AD.

Therefore, we aimed to investigate 1) whether common ECG markers were associated with AD in a large primary care population, and 2) whether ECG markers improved risk prediction for AD.

2. Methods

2.1. Population

At the Copenhagen General Practitioners' Laboratory (CGPL), 978,358 ECGs were recorded on 449,191 people during 2001–2015. In the present study, we included participants from the age of 60 years and up. The full flow chart is presented as Fig. 1. We used automated ECG analysis to exclude ECGs with missing or extreme measurements (outside of 4 standard deviations from the population mean), and we excluded ECGs from people with a pacemaker, an implantable cardioverter defibrillator, or who were taking digoxin on the day of the ECG. We used the first available ECG from each person, and we excluded people with prevalent AD at the start of follow-up. Per Danish law, no consent was needed for this register study, however the use of de-identified data was approved by the Danish Data Protection Agency (2007-58-0015).

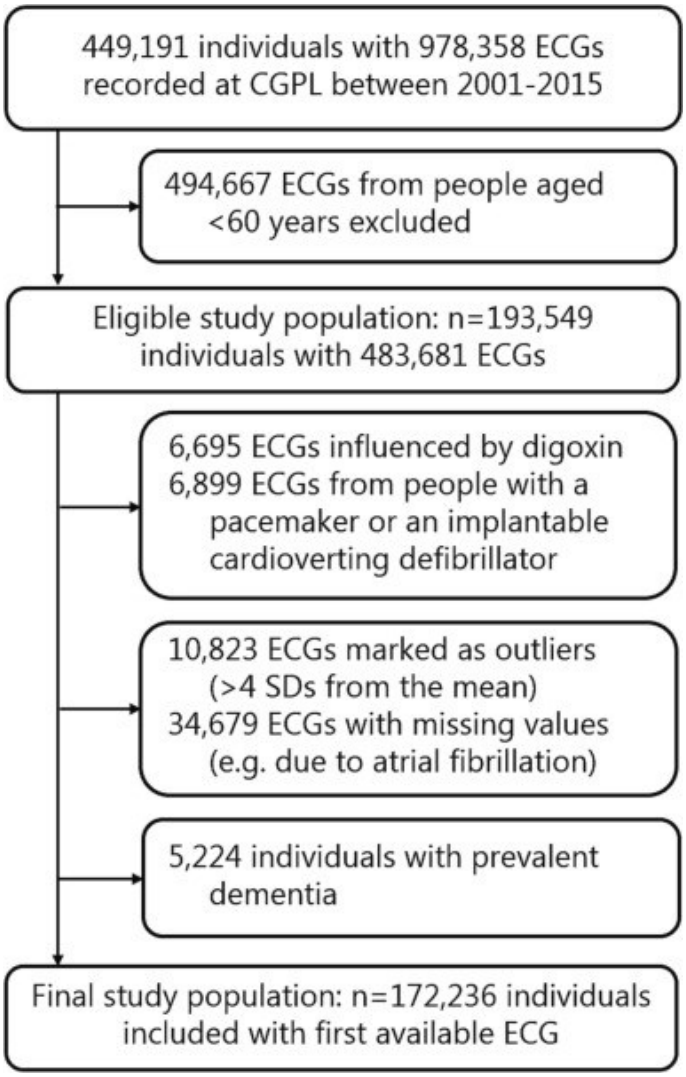


Fig. 1. Flow chart of participant selection. CGPL, Copenhagen General Practitioners' Laboratory; ECG, electrocardiogram; SD, standard deviation.

2.2. Electrocardiogram analysis

All ECGs were analyzed using version 23 of the 12SL algorithm (GE Healthcare, Wauwatosa, WI). [16] The 12SL algorithm uses all 12 simultaneous leads to construct a representative median beat in each lead from non-ectopic PQRST complexes and measures global intervals from the earliest onset in any lead to the latest offset in any lead. Global parameters that were automatically assessed were heart rate, PR interval, QRS duration, and the QT interval. J-point elevation and T-wave amplitude were measured automatically in lead V5 using 12SL. The QT interval was corrected for heart rate using the Fridericia method (QTcF) by dividing the measured value (in ms) with the cubic root of the RR-interval (in seconds).

The Sokolow-Lyon index was defined as the absolute S-peak amplitude in V1 plus the largest R-peak amplitude among leads V5 and V6 and dichotomized into normal (0–35 mm) or abnormal (>35 mm) [8]. The QRS-T angle was defined as the angle between the average spatial QRS and T loop vectors (0–180 degrees). We used the Kors transformation to derive the vectorcardiogram, which previously yielded better associations between QRS-T angle and mortality [17]. The QRS-T angle was categorized into normal (<80th percentile, 103 degrees), borderline, and abnormal (>95th percentile, 147 degrees).

2.3. Outcome, covariates and follow-up

Using Danish nationwide health registers, we followed individuals from the day of the ECG to outcome, death without outcome, emigration, or 31 December 2016, whichever occurred first. The outcome of interest was AD, defined by the International Classification of Diseases tenth revision (ICD-10) codes DF00 or DG30. Competing risks were death from any cause and dementia from other causes. We identified the following baseline comorbidities using a combination of register diagnoses and/or claimed prescriptions: atrial fibrillation, diabetes mellitus, ischemic heart disease, congestive heart failure, hypertension, and depression. The specific codes are detailed in the Supplementary methods.

2.4. Statistical analyses

We constructed cause-specific Cox regression models for each outcome to model the hazard rate. These models were combined for the assessment of risk prediction [18]. We stratified the Cox regression models on age groups and sex to allow for different baseline hazard rates. The models included additive effects of ECG markers heart rate, PR interval, QRS duration, QT interval, J-point elevation in V5, and T-wave amplitude in V5, all categorized into five quintile groups to allow for non-linear effects, Sokolow-Lyon index coded as increased/normal, and QRS-T angle coded as normal/borderline/abnormal. The models were adjusted for use of QT-prolonging drugs at the time of the ECG, history of atrial fibrillation, diabetes mellitus, ischemic heart disease, congestive heart failure, hypertension, and depression, all coded as yes/no. We reported hazard ratios (HRs) from these models using the lowest group for each marker as the reference and with 95% confidence intervals in brackets. We assessed the discriminative ability of the model's 10-year AD risk predictions and compared it to a reference model without ECG markers using cross-validated area under the time-dependent receiver-operator characteristics curve (AUC). The cross-validation bootstrap design used 100 random splits of the data into 100 training sets (63%) and corresponding validation sets (37%). Repeating the training and validation process 100 times allowed us to avoid the random effect of using one particular split of the population ("lucky split" with favorable results or an "unlucky split" with unfavorable results). The models were fitted using least-squares regression techniques. In validation, the AUCs for models with ECG markers added were compared to the AUCs for models with only clinical variables (i.e. full model except ECG markers). We reported the difference in AUC between the models and also the AUC for the full model.

We constructed examples for two patients aged 82 years with a history of diabetes, one female and one male, and predicted the 10-year risk of AD given an average ECG as well as a favorable ECG and a poor ECG, based on the hazard ratios, to illustrate the absolute difference in risk of AD.

A two-sided p-value ≤ 0.05 was considered statistically significant. Analyses were conducted using Stata (version 16, StataCorp LLC, College Station, Texas) and R (version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Follow-up and baseline characteristics

In total, 172,236 participants (89% of those aged 60 years or older) met the inclusion criteria (Fig. 1) and were followed for a median of 7.5 years (interquartile range, IQR: 3.9–11.3 years), totaling 1,003,451 person-years (Table 1). 5322 persons met the primary end-point of AD during follow-up, and the 10-year cumulative incidence of AD was 3.9%. The

population consisted of individuals aged 60 years and up (inter-quartile range, IQR, of age at inclusion: 64–78 years) and slightly more women (58%) than men (42%).

Table 1. – Baseline clinical characteristics at day of ECG and ECG findings. Continuous variables are presented as median [inter-quartile range].

Variable	Entire cohort
n	172,236
Women, % (n)	57.8% (99,480)
Age, years	69.7 [64.1;77.7]
Follow up, years	7.5 [3.9;11.3]
On QT-prolonging drugs, % (n)	3.7% (6443)
Diabetes mellitus, % (n)	12.2% (21,078)
Hypertension, % (n)	44.2% (76,097)
Ischemic heart disease, % (n)	14.7% (25,403)
Heart failure, % (n)	18.5% (31,875)
Depression, % (n)	27.5% (47,406)
Heart rate, bpm	71 [63;80]
PR interval, ms	164 [150;182]
QRS duration, ms	92 [84;100]
QT interval, ms	398 [378;420]
QTc Fridericia, ms	420 [407;435]
J-point elevation V5, µV	-15 [−40;4]
T-wave amplitude V5, µV	268 [166;380]
Sokolow-Lyon index >35 mm	3.6% (6155)
QRS-T angle, degrees	66 [44;95]

ECG, electrocardiogram.

3.2. ECG predictors of Alzheimer's disease

Hazard ratios for the association between ECG markers and AD are depicted on Fig. 2. A longer PR interval was associated with a decreased rate of AD (HR for longest vs. shortest

groups: 0.76 [95% confidence interval: 0.69–0.83], $p < 0.001$). However, we found no association between a history of atrial fibrillation and AD (HR: 0.96 [0.83–1.10], $p = 0.52$). An increased Sokolow-Lyon index >35 mm (HR: 1.18 [1.04–1.35], $p = 0.01$) and an increased T-wave amplitude in lead V5 (HR for largest vs. smallest: 1.15 [1.04–1.35], $p = 0.006$), respectively, were associated with an increased rate of AD. Increased QTcF interval was associated with a decreased rate of AD (HR for second longest vs. shortest: 0.90 [0.83–0.98], $p = 0.02$), although with a tendency towards a U-shape (HR for longest vs. shortest: 0.92 [0.84–1.00], $p = 0.06$).

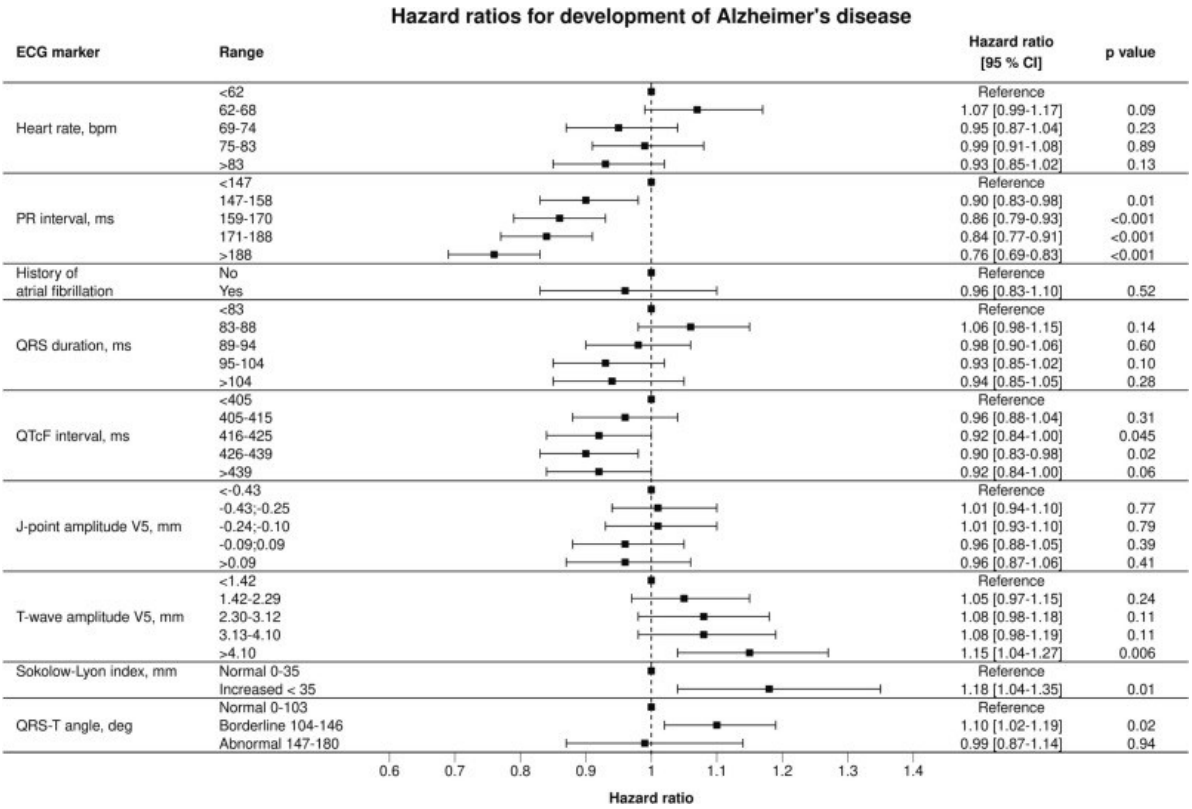


Fig. 2. Hazard ratios for rate of Alzheimer's disease by ECG variables. The model included all depicted ECG markers with adjustment for age, sex, use of QT-prolonging medication, ischemic heart disease, congestive heart failure, hypertension, diabetes mellitus, and depression. CI, confidence interval; ECG, electrocardiogram.

Risk prediction of AD improved significantly upon addition of ECG markers to the reference model. The 10-year AD prediction AUC improved by 0.39 [0.06–0.67] %-points to a final 70.6%.

In terms of absolute 10-year risk, the ECG was associated with an almost two-fold increased risk comparing a favorable ECG to a poor ECG for an 82-year-old female (6.5% to 12%) and male (5.2% to 9.2%), respectively (Fig. 3). An average ECG was associated with an 8.7% and 7.2% 10-year risk of AD for females and males, respectively, in this cohort.

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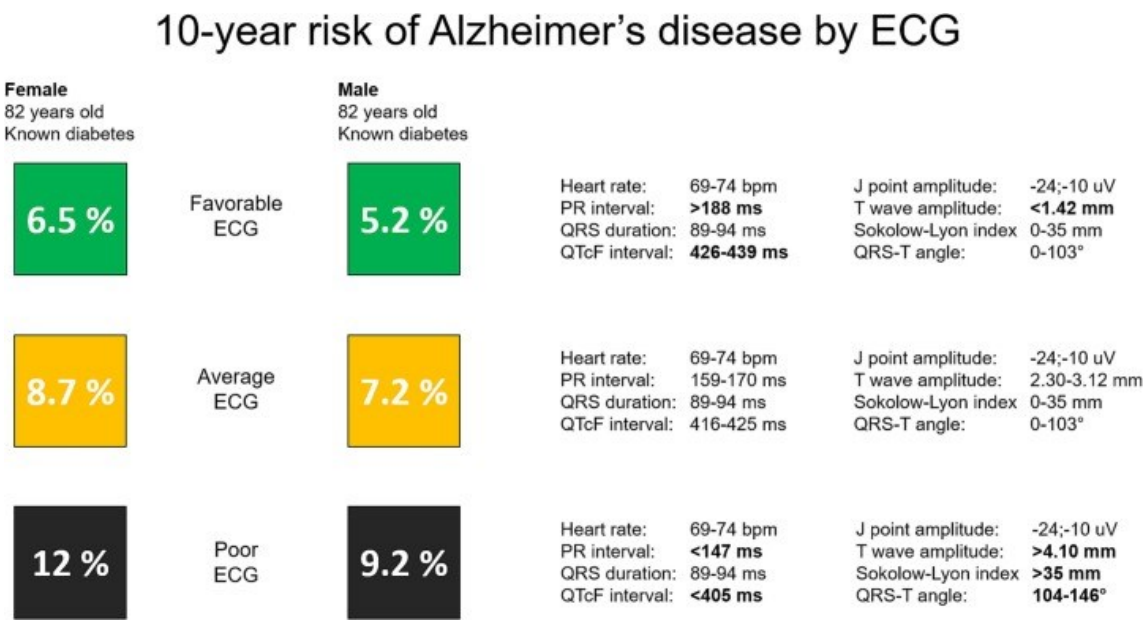

Fig. 3. 10-year absolute risk of developing Alzheimer's disease with different ECGs. The "Average ECG" used the center or most common category for each ECG marker. The "Favorable ECG" and "Poor ECG" were based on the hazard ratios from Fig. 1 and are thus specific to risk of Alzheimer's disease. ECG markers different from the average ECG are marked with bold font. ECG, electrocardiogram.

4. Discussion

We found that ECG markers of cardiac depolarization and repolarization were associated with the development of AD in a large primary care population, and that the ECG markers improved the prediction of AD.

4.1. Risk prediction

Our study showed that the 10-year absolute risk of AD was higher for those with the poorest ECG profile compared to those with the most favorable profile, as exemplified with two 82 year old patients. The AUC increased only modestly, but significantly, by 0.4%-points. Our findings were made in a primary care population not specifically referred for dementia, which is a relevant population for an early risk stratification tool with low accuracy since patients may then subsequently be referred for more specific risk stratification [19], screening [20], or prevention [21]. Predictors from the ECG are particularly well-suited for such an initial screening because ECGs are commonly obtained on a variety of indications, including annual health check-ups, and early recognition may help initiate targeted preventive action in time.

4.2. Left ventricular hypertrophy

Previous reports have investigated ECG markers of left ventricular hypertrophy with all-cause dementia, vascular dementia, and cognitive decline [2,7,8]. We were able to reproduce and extend these findings and show that left ventricular hypertrophy assessed by Sokolow-Lyon index was associated with risk of AD in a primary care population. The Sokolow-Lyon Voltage Product (i.e. multiplying the Sokolow-Lyon index by the QRS duration) was previously suggested as a marker for dementia [8], but that would assume a positive association between QRS duration and AD. Since we found no association between QRS

duration and AD in the present study, multiplication with the QRS duration would not produce a better marker in the present study.
Left ventricular hypertrophy is closely related to hypertension, which has been established as an independent risk factor for dementia [1]. However, it is noteworthy that even with adjustment for hypertension, indices of left ventricular hypertrophy were consistently associated with dementia and/or cognitive decline in the present study as well as in previous studies [7,8]. Previous studies also adjusted for systolic blood pressure (not available in the present study) in addition to hypertension [7,8], reducing the risk that the association stems from insufficient adjustment for hypertension although residual confounding can never be excluded in an observational study. Hypertension shares a genetic overlap with atrial fibrillation [22], but we and others either excluded [8] or adjusted [7] for known atrial fibrillation. Other potential drivers include physical activity and aortic stenosis. Thus, although we and others have not been able to explain why, the results appear to be independent of hypertension. The findings warrant a role for ECG-assessed left ventricular hypertrophy in dementia risk stratification since they add information on top of hypertension status.

4.3. Depolarization markers

Atrial fibrillation has been associated with cognitive decline and dementia [[2], [3], [4]], but the association may not be causal [6] and was weaker for AD than for vascular dementia [5]. Thus, even though the PR interval was previously associated with atrial fibrillation in this population [23] and others [24], increasing PR interval need not be associated with AD. The fact that shortened PR interval was associated with AD in this study is still in contrast to the ARIC study, but the numerous differences in population and outcome may explain that. First, the present study excluded people with unmeasurable PR interval, e.g., due to atrial fibrillation. Second, the present population consists primarily of Caucasians unlike the ARIC study [10], which included also a significant portion of blacks. Differences in P-waves have previously been identified between races [10,25]. Third, we assessed a primary care population unlike the previous studies [[10], [11], [12]]. Fourth, the present study assessed AD specifically, whereas previous studies [[10], [11], [12]] assessed cognitive decline or dementia from any cause, which may be a cause of heterogeneity. Unlike for other causes of dementia [2], we did not find any association between AD and ventricular depolarization time (i.e. QRS duration) or heart rate.

4.4. Repolarization markers

We found that a decreased QTc interval was associated with an increased rate of AD. Two studies have not found an association between QTc interval and cognitive function. However, we previously reported that an increased QTc interval was associated with dementia without AD. Thus, up to two mechanisms may explain these findings. If the directionality of association is truly opposite for AD and other causes of dementia, those associations would cancel out with the assessment of non-specific cognitive performance. However, reverse causation might exaggerate the association: Patients with heart disease are more likely to have an increased QTc [26] and may also be more likely to receive a diagnosis of vascular dementia than AD in case of mixed dementia or when the cause is difficult to ascertain.
The finding that a borderline QRS-T angle was associated with a hazard ratio of 1.10 ($p = 0.02$), whereas an abnormal QRS-T angle was not associated with AD, is curious. The lack of dose-response and the size of the *p*-value may be suggestive of a chance association (type I error). The previously reported associations between QRS-T angle and cognitive decline [2,27] may thus be specific to other dementias than AD, or there may be unknown mechanisms involved.

The association between T-wave amplitude and AD is novel and opposite of the relation between T-wave amplitude and dementia from other causes [2]. Although reverse causation cannot be ruled out, these findings on repolarization and depolarization markers demonstrate substantial heterogeneity among cardiac repolarization and causes of dementia. We believe the findings should encourage the use of cause-specific outcomes over unspecific cognitive decline whenever it is feasible.

4.5. Strengths and limitations

The main advantages of the study include the high number of subjects from a relevant population with respect to early detection of subjects at risk of AD, thorough and complete follow-up using Danish registers, and use of easy-to-obtain automated ECG measurements. The registers do not contain information on degree of disease. The spatial QRS-T angle is not directly readable from the ECG, however, with access to raw waveforms it can be readily calculated by computer software, or it may be estimated using R-wave and T-wave amplitudes [28].

The study used 10-s ECGs, which precludes analyses of non-linear dynamics [29] and heart rate variability [30], which could potentially carry additional prognostic information not identified in this study.

In the present study, we were able to adjust for atrial fibrillation, but we did not have information on other important risk factors such as diet, alcohol consumption, blood pressure, and exercise; thus, the study may suffer from residual confounding. However, we were able to adjust for clinically relevant conditions such as hypertension, diabetes, heart failure, ischemic heart disease, and use of QT-prolonging medication at time of the ECG.

5. Conclusions

We found that longer electrocardiographic PR interval, Sokolow-Lyon index>35 mm, and increased T-wave amplitude were associated with Alzheimer's disease. Increased QTc interval was associated with a decreased rate of Alzheimer's disease. The ECG markers improved risk prediction for Alzheimer's disease and an unfavorable ECG profile was associated with a two-fold increased 10-year risk of Alzheimer's disease.

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Declaration of Competing Interest

A.G.H. is an employee of Acesion Pharma. J.B·N is employed by Regeneron Pharmaceuticals, Inc. The remaining authors have no conflict of interests to declare.

Appendix A. Supplementary data

Refer to online version: https://doi.org/10.1016/j.jns.2023.120581

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