Received: 4 December 2023 | Accepted: 28 January 2024

DOI: 10.1002/agm2.12291

Aging Medicine Open Access WILEY

REVIEW ARTICLE

Relationship between Alzheimer dementia and QT interval: A meta-analysis

Simon W. Rabkin

Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence
Simon W. Rabkin, University of British Columbia, 9th Floor 2775 Laurel St. Vancouver, BC V5Z 1M9, Canada.
Email: simon.rabkin@ubc.ca

Abstract

While the link between aging and mortality from dementia is widely appreciated, the mechanism is not clear. The objective of this study was to determine whether there is a direct relationship between Alzheimer dementia (AD) and the QT interval, because the latter has been related to cardiac mortality. A systematic review and meta-analysis were conducted after a Medline and EMBASE search using terms "Alzheimer disease or Dementia AND QT interval, QT dispersion or cardiac repolarization." Four studies with control groups were identified. There were significant differences in QT interval between individuals with AD vs individuals without dementia (controls) (odds ratio (OR)1.665 [random effects model] and 1.879 [fixed effect model]) ($p < 0.001$). There were significant differences in QT interval between individuals with AD vs individuals with mild cognitive impairment (MCI) (OR 1.760 [random effects] and 1.810 [fixed effect]) ($p < 0.001$). A significant ($p < 0.001$) correlation exists between the QTc and the Mini-Mental State Exam (MMSE), a test of cognitive function. Two studies examined QT variability (the difference between the longest and shortest QT interval on a 12 lead ECG); the OR for QT variability AD vs MCI was 3.858 [random effects model] and 3.712 [fixed effects model] ($p < 0.001$). When compared to the control group, the OR for QT dispersion in AD was 6.358 [random effects model] or 5.143 ($P < 0.001$) [fixed effects model]. A qualitative analysis of the data raised questions about paucity of data defining the nature of the control groups, the pathophysiologic mechanism, and the uniform use of a poor QT heart rate correction factor. The longer QT in AD, greater QT variability in AD, and the direct relationship between QT interval and AD severity supports a brain–heart connection in AD that might be fundamental to aging-induced AD and mortality. Issues with defining the control group, limited number of studies, conflicting data in population studies, and the lack of a strong electrophysiological basis underscore the need for additional research in this field.

KEYWORDS
Alzheimer dementia, dementia, meta-analysis, mild cognitive impairment, QT dispersion, QT interval, QT variability

1 | INTRODUCTION

The study of brain–heart interactions has attracted more attention recently not just in the area of vascular diseases but also because of the potential impact of brain diseases on the heart.[1–3] One neurological disease of increasing prevalence is dementia that is associated with a high risk of death from cardiac causes.[4] Several investigators[5,6] have hypothesized that Alzheimer dementia (AD) with a selective loss of cholinergic neurons in specific areas of the brain involved in the autonomic nervous system[7–9], alters neuronal traffic to the heart through sympathetic and parasympathetic fibers that synapse on extrinsic and intrinsic cardiac ganglia and ultimately directly innervate cardiac myocytes.[10] However, the effect of the parasympathetic nervous system on the QT interval is not clear,[11–15] raising questions about the magnitude of the impact of loss of central parasympathetic nervous system on the QT interval.

Cardiac repolarization is traditionally assessed on the surface electrocardiogram (ECG) by measuring the QT interval, recognizing that this interval encompasses the duration of the QRS complex.[16,17] The QT duration or the QT interval on a 12 lead ECG is a risk factor for cardiac mortality, especially sudden cardiac death.[18,19] A meta-analysis of population studies found a consistent association between prolonged QT interval and increased risk of total, cardiovascular, coronary, and sudden cardiac death.[20] Because cardiac mortality is a leading cause of death in persons with dementia,[4] the question has been raised whether dementia prolongs the QT duration. There has been relatively little investigation of the QT interval in AD, and the results are discordant.[6,21,22]

Variation in the QT interval have been recognized, and the difference between the longest and shortest QT interval on the 12 lead ECG has been labeled QT dispersion, which has been proposed to be analogous to the significant correlation between variations in QT interval and the dispersion of repolarization as determined by the dispersion of recovery time and action potential duration in the isolated heart.[23] The term QT dispersion as calculated by the difference in QTc on a 12 lead ECG was found in some patient population studies to be associated with subsequent death from cardiac disease.[24,25] This methodology has fallen into disrepute because of the weak association between variations in QT interval and more accurate evaluations of QT heterogeneity.[26,27] The variability of a biological factor, however, has been identified as a meaningful feature as exemplified by the importance of variability of blood pressure and other cardiovascular risk factors in cardiovascular risk prediction.[28,29] The term QT variability will be used herein, and QT dispersion will be mentioned because the later term has been used historically.[6,21,23–25]

A major problem with studies of QT interval and QT interval variability in AD has been that there are few studies and they usually have small sample sizes. Meta-analysis is a methodology that consolidates small studies, including those that are apparently conflicting, into one large study, thereby increasing the accuracy of the results.[30]

The aim of this study was to assess the data on the QT interval and QT variability in AD and utilize meta-analysis to determine whether these two QT factors are abnormal in AD and whether they relate to cognitive impairment.

2 | METHODS

2.1 | Study design

A systematic search from the inception of Medline and EMBASE through August 30, 2023 was conducted. Search terms "dementia or Alzheimer disease AND QT interval," QT dispersion, or cardiac repolarization were used in conjunction with Boolean operators to identify articles reporting dementia and QT interval. There was no requirement for approval from our research ethics committee because there was no primary patient or animal contact. The meta-analysis was not registered. The search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[31,32]

First, duplicates were removed. Titles and abstracts were screened to identify articles for full-text review. The single author extracted the data. The inclusion criteria were QT interval or QT dispersion and Alzheimer disease or dementia. The exclusion criteria were: (i) articles reporting the effect of drugs for AD or dementia on the QT interval (ii) not published in English; (iii) non-primary research articles (reviews, editorials, or letters commenting on an article); (iv) involved non-human subjects; (v) unrelated to the investigated topic and (vii) did not provide a direct comparison of a control or comparator group; (vii) relevant data could not be extracted from the paper.

Extracted from each paper were primary author's name, details of QT measurement and heart rate adjustment, QT variability or so-called QT dispersion, study inclusion, and exclusion criteria.

The initial search produced 135 references after the elimination of duplicates. After filtering the titles and abstracts, 43 were eliminated because they dealt with the effect of drugs on the QT interval and 70 were eliminated because the QT abbreviation was for another entity, e.g., Qualitative Trait (Figure 1). The text review eliminated 18 reports that dealt with subjects that met the exclusion criteria. Studies that did not deal with dementia or dealt with subsequent cognition testing were not included.

2.2 | Statistical analysis

Results were quantified using forest plots depicting the standard difference of means, 95% confidence interval, and P value. The meta-analysis was performed using Comprehensive Meta-Analysis (Biostat Inc., NJ). Because of the small number of studies in the field, both the fixed effect and random effects analysis were conducted. Study heterogeneity in the meta-analysis was tested using Cochran's Q, I^2, and Tau statistic. Data are presented as the mean ± SD. Publication bias was assessed by examination of funnel plots and calculation of the Failsafe N.

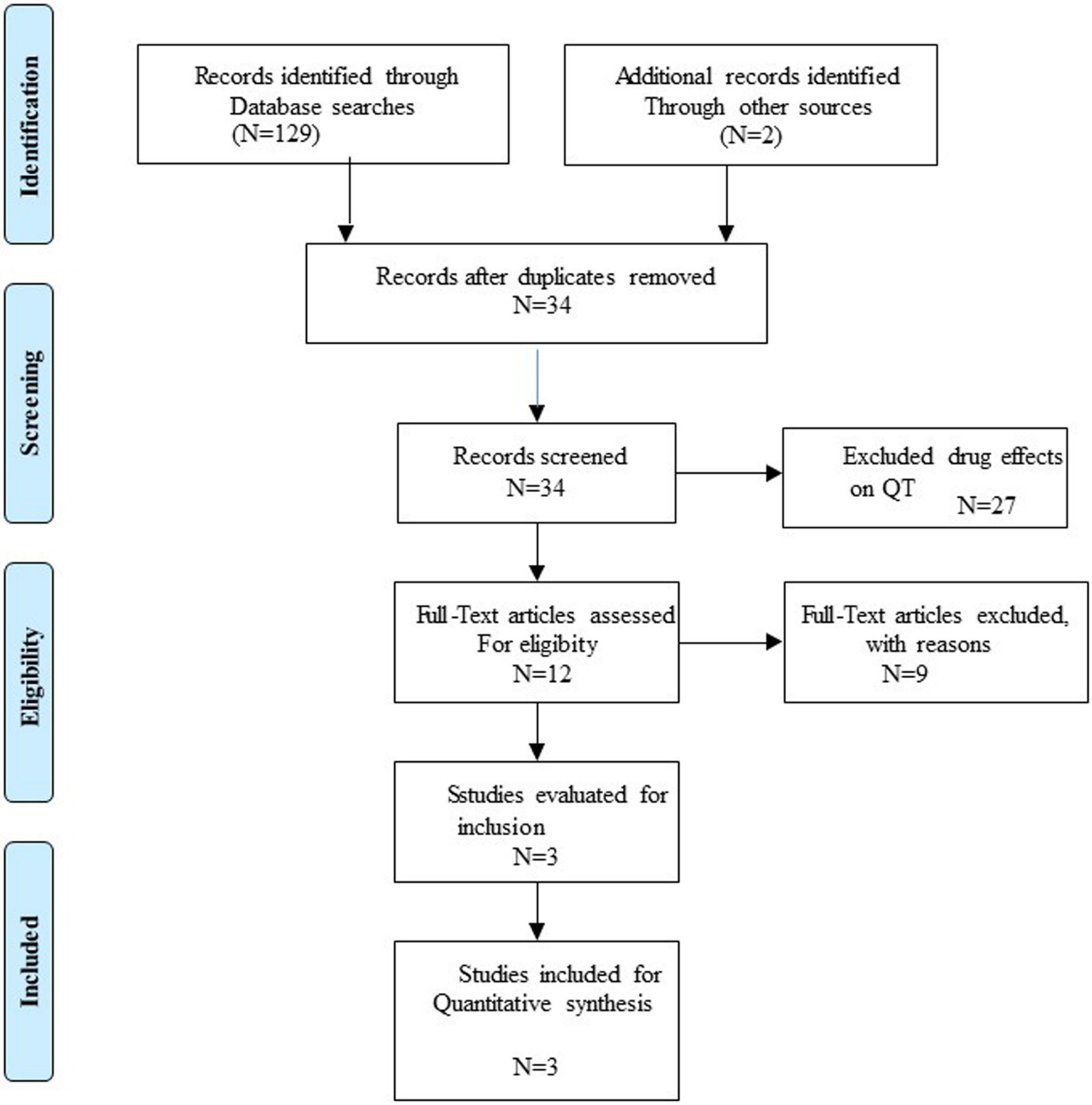

FIGURE 1 The flow diagram to identify papers examining the QT interval in dementia.

3 | RESULTS

There were four studies with control groups that presented data for comparison (Table 1). Zulli et al. evaluated 33 individuals with Alzheimer dementia (AD), 39 individuals with mild cognitive impairment (MCI), and 29 "cognitive healthy subjects" (controls) who were matched for demographic characteristics.[21] Coppola et al. studied 31persons with AD patients, 77 persons with MCI, and 116 "cognitively normal subjects."[6] Danese et al. studied 108 individuals with dementia, 44 individuals with MCI, and 56 controls. The dementia group consisted of "27 AD, 5 frontotemporal dementia, 5 dementia-Parkinson complex, 19 vascular dementia, 1 normotensive hydrocephalus, 1 Lewy body dementia, 21 mixed dementia (vascular dementia and AD) and 29 other neurological conditions."[22] Mao et al. reported on a cross-sectional population study in which 5.2% had dementia of which 194 had AD, 94 had vascular dementia, and 11 had other kinds of dementia.[33] Dementia was defined according to standardized references. MCI was defined somewhat differently in one of the three studies. In three of these studies, the QT interval was reported to be measured from the start of the QRS complex to the end of the T wave defined as "the point of return of the isoelectric

TABLE 1 Details of studies that examined the QT interval in dementia.

Author/Study definitions	Zulli et al. 2005	Coppola et al. 2013	Danese et al. 2019	Mao et al. 2023
QT measurement	Start of QRS complex to the end of the T wave. The end of the wave was defined as the point of return to the isoelectric line	Start of the QRS complex …to the end of the T wave …defined as the point of return of the isoelectric line	Start of the QRS complex to the end of the T wave, The leads showing the longest QT	Computer QT Algorithm
Heart rate correction	Bazett	Bazett	Bazett	Bazett
QT variability	Difference between maximum and minimum QTc calculated from the 12 lead ECG (QTc max–QTc min)	Difference between maximum and minimum QTc calculated from the 12 lead ECG (QTc max–QTc min)	Not done	Not done
Criteria for mild cognitive impairment	Mayo Clinic criteria	Petersen criteria (1999). These are (i) memory complaint; (ii) normal activity of daily living; (iii) normal general cognitive function; (iv) abnormal memory for age; and (v) not demented	Mayo Clinic criteria	Not done
Criteria for controls	Matched for demographic characteristics, hypertensive condition, smoking habits, and laboratory parameters. Enrolled consecutively	Not defined in detail	Not defined in detail	No dementia ($N=4854$)
MMSE	Measured	None	Measured	Measured

line." In the other study, the QT interval was assessed by the ECG computer algorithm and details were not specified.[33] In each study, the QT interval was adjusted for heart rate by the Bazett formula,[34] hereafter referred to by its abbreviation QTcBZT.[35]

There was an overall significant difference in QTc between patients with dementia and those with MCI after pooling the three studies (Figure 2). The finding was significant in two of the three studies. The odds ratio was 1.810 in the fixed and 1.760 in the random effects model. There was significant heterogeneity between studies with Q value of 7.048 ($P=0.029$), I^2 of 71.621, and $\text{Tau}^2=0.367\pm0.516$ (SEM). An analysis of publication bias found the classic fail-safe N was 3, i.e., if three negative studies would be found, it would make the relationship not significant.

There was an overall significant difference in QTc between individuals with dementia compared with controls (cognitively normal or no dementia) (Figure 3). The finding was significant in two of the four studies—the studies with the largest sample size. The overall odds ratio was 1.879 (fixed effect) and 1.665 (random effects model). There was significant heterogeneity between studies with Q value of 9.920 ($P=0.019$) and I^2 of 69.759 and $\text{Tau}^2=0.057\pm0.073$. An analysis of publication bias found the classic fail-safe N was 16, i.e., if 16 negative studies were found it would make the relationship not significant. One of these studies evaluated the relationship in a multivariate analysis adjusting for age, gender, education, smoking, alcohol intake, BMI, *APOE* genotype, resting heart rate, the number of chronic diseases, and use of anti-thrombotic agents, cardiac agents, and QT prolonging drugs.[33] In that multivariable analysis, QT was associated with dementia.[33]

Three studies examine QTc and the degree of cognitive impairment as assessed by MMSE. Danese et al. reported a significant correlation between QTc and both raw MMSE data as well as MMSE adjusted for age and gender.[22] Mao et al. reported a significant correlation between QTc and JTc intervals with MMSE.[35] Coppola et al. reported a significant correlation between QT and MMSE but only in the MCI group.[6] The data for their entire study population were not available. Recognizing this limitation, their MCI group[6] and the entire study population from Danese et al.[22] and Mao et al.[33] were assessed (Figure 4). There was a significant ($P<0.001$) correlation between MMSE and QTc. There was no significant heterogeneity between studies ($Q=2.859$, $I^2=30.040$, $P=0.239$; $\text{Tau}^2=0.002\pm0.005$). Publication bias analysis indicated that it would require 119 negative studies to negate the significance of this analysis. Another study was identified but could not be combined because it did not utilize MMSE.[36] Zonneveld et al. examined the relationship between QTc, calculated by the infrequently used Hodges formula, and correlated it with several measurements of cognitive function specifically the Stroop test, letter-digit coding test, and picture word learning tests.[37] Adjusting for cardiovascular risk factors in multivariable linear regression models, QTc was not associated with cognitive function while JTc was associated with cognitive function as assessed by the Stroop test.[37]

It is noteworthy that the prevalence of prolonged QTc was significantly higher in patients with greater impairment of attention,

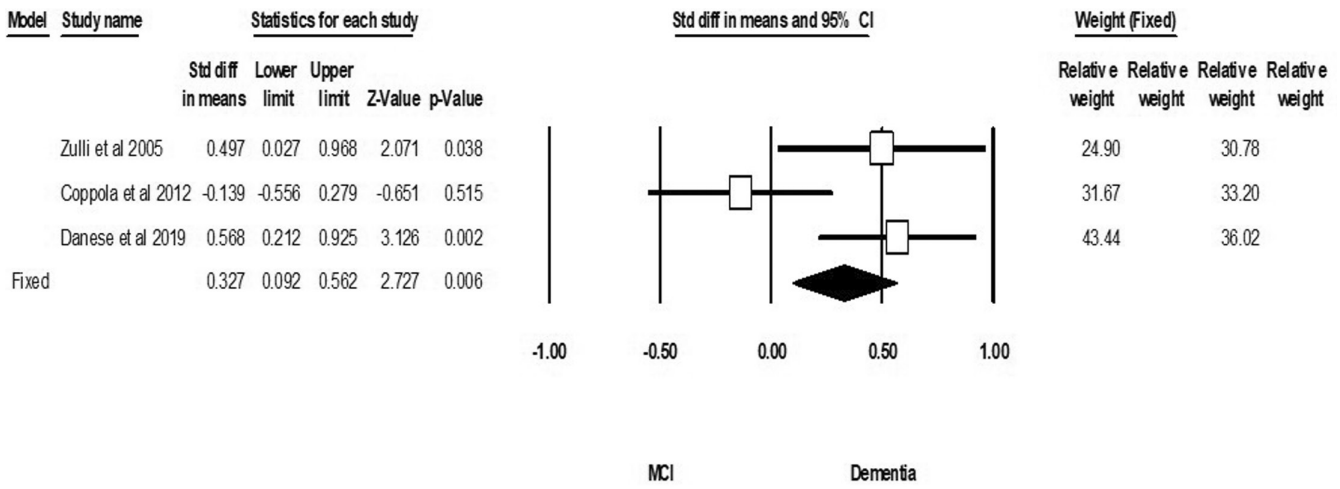

FIGURE 2 The Forest plot for QT interval in studies that examined it in patients with AD compared to a comparator control group with MCI. The relative weight that each study contributed to the overall effect is shown.

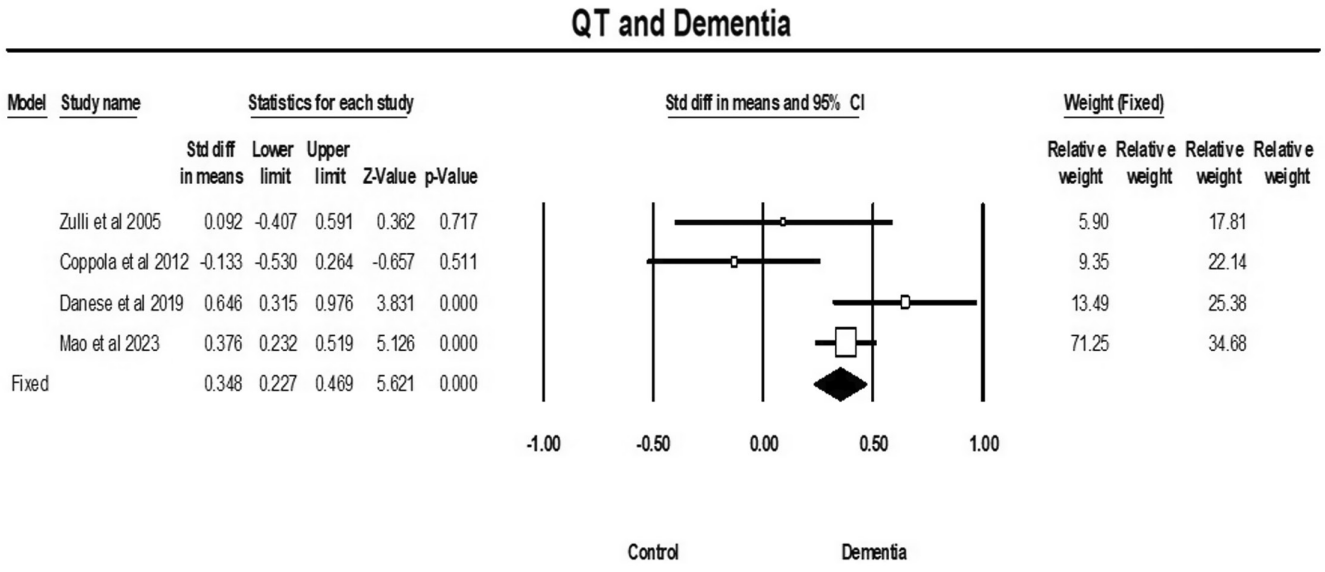

FIGURE 3 The Forest plot for QT interval in studies that examined it in patients with AD compared to a comparator–control group without cognitive impairment. The relative weight that each study contributed to the overall effect is shown.

memory, praxis, and executive functions severe and moderate disability.[22]

Two studies examined QTc variation, and both found a significantly greater amount of variation in patients with AD compared to either those with MCI or controls (Figure 5). Both studies measured QTc variation in the same way, specifically the difference between the maximal QTc and the minimum QTc on a 12 lead ECG.[6,21] The odds ratio for QT dispersion in AD was 3.712 ($P<0.001$) (fixed effects model) or 3.858 ($P=0.003$) (random effects model) when compared to the group with MCI. There was no heterogeniety between the two studies ($Q=2.292$, $P=0.130$; $I^2=56.371$, $Tau^2=0.071\pm0.177$). When compared to the control group, the odds ratio for QT dispersion in AD was 5.143 ($P<0.001$) (fixed effects model) or 6.358 ($P=0.019$) (random effects model). There was

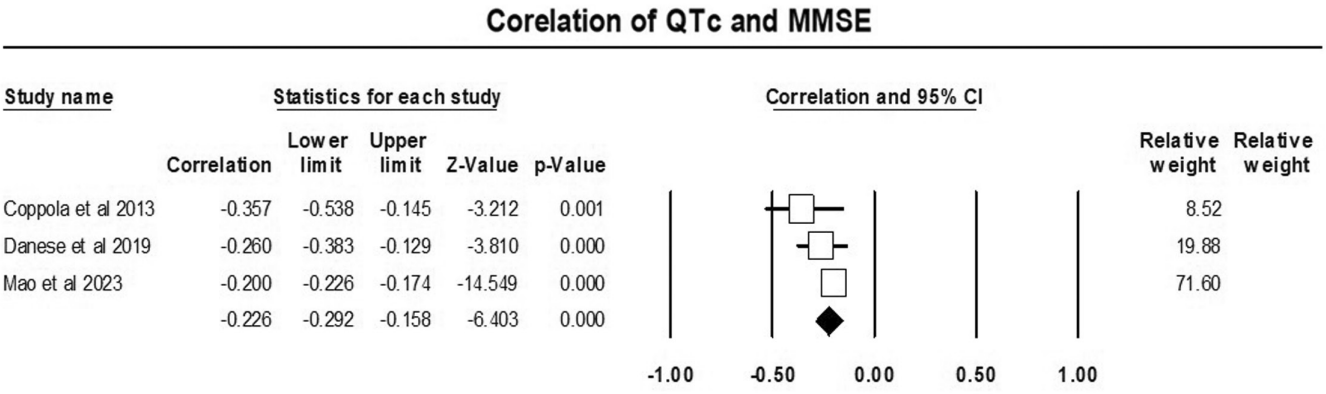

FIGURE 4 The Forest plot for the correlation between QTc, and the degree of cognitive impairment as detected on a MMSE.

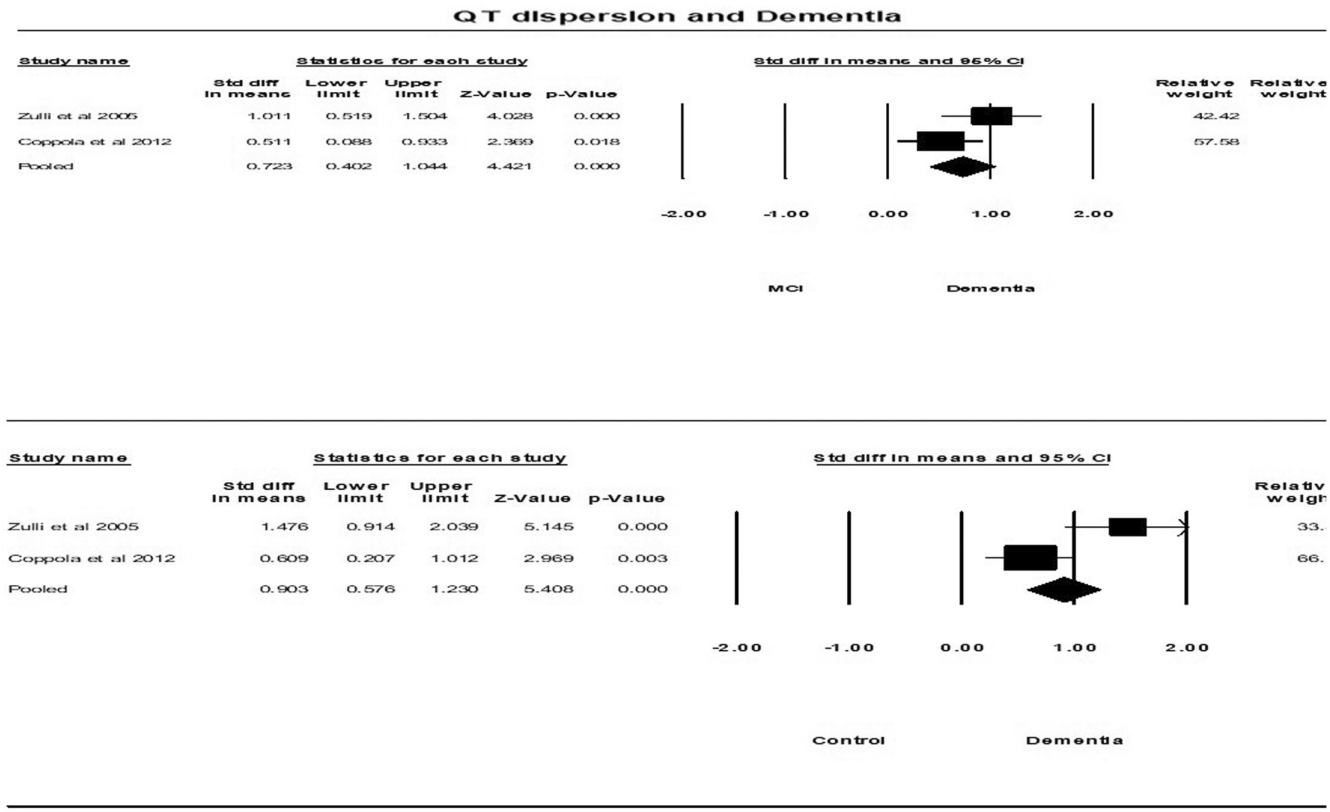

FIGURE 5 The Forest plot for QT dispersion in studies that examined it in patients with AD compared to a comparator group with MCI (upper panel) and a control group without cognitive impairment (lower panel). The relative weight that each study contributed to the overall effect is shown.

heterogeneity between the studies ($Q=6.037$, $P=0.014$; $I^2=83.436$, $Tau^2=0.314\pm0.532$). These findings are supported by a study of 63 healthy older adults, over 60 years of age, without dementia, in whom QT variability was significantly correlated with cognitive function as assessed by the Montreal Cognitive Assessment, executive composite score, non-executive composite score, and the digit symbol substitution test.[38]

Danese et al. evaluated all subjects with cognitive impairment with a structural brain imaging study (computed tomography or magnetic resonance imaging).[22] They reported a relationship between

the extent of the degenerative process and/or the "cerebral vascular load" and the QTc prolongation. The prevalence of alterations of QTc interval was higher in patients with Fazekas grade 2 and 3 than patients with Fazekas grade 0 and 1.[22] The results remained significant after excluding persons taking drugs that had the potential to produce QT prolongation.[22]

4 | DISCUSSION

This study has several important findings. First, there is an overall relationship between dementia and QT interval such that patients with dementia have a longer QT interval than individuals with MCI or individuals with no cognitive impairment. Second, QT prolongation correlates with the degree of cognitive impairment. Third, QT variability is increased in AD. Fourth, qualitative analysis identified several serious issues with the currently available data.

The finding of a significantly longer QT in AD supports the contention of a brain–heart connection in dementia. The mechanism by which this occurs remains to be defined. It has been speculated that the loss of cholinergic neurons in the brain, which occurs in AD, leads to a reduction in parasympathetic cardiac neuronal activation, that in turn prolongs the QT interval.[5,6] The effect of the parasympathetic nervous system on the QT interval, however, is not well defined.[11–13] Furthermore, it has been long accepted that any effect of the parasympathetic nervous system on cardiac repolarization is minimal.[14,15]

Using indirect assessment, to infer the role of the sympathetic and parasympathetic nervous system on the heart, several investigators concluded that patients with AD manifested a relatively hyper-sympathetic and hypo-parasympathetic state.[39–41] A hyper-sympathetic state would be expected to shorten the QT interval[12,15] rather than prolong it. The situation is more complex depending on the relative degree of sympathetic activation and parasympathetic withdrawal because various combinations of sympathetic and vagal tone can produce different ventricular electrophysiology effects at the same heart rate.[15,42] A reduction in both sympathetic and parasympathetic tone by trimethaphan, which interrupts sympathetic and parasympathetic nerve traffic to postganglionic autonomic neurones, produces a dose-dependent prolongation of QTc.[43] However, in any given state, the sympathetic or parasympathetic effects are dependent on the underlying sympathetic tone.[15] Thus, more investigation is necessary to tease out the precise mechanism by which AD produces QT prolongation.

While the data are limited, there was a strong correlation between QTc and impaired cognitive function as assessed by MMSE.[6,22] The Mini Mental State Examination (MMSE) consists of 11 questions that assess five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. There was no reported relationship between the QT interval and cognition when cognition was assessed by the Stoop test.[37] The explanation for this apparent discrepancy may be due to the QTc formula used in that study, specifically the Hodges formula, a rarely used formula to adjust for the effect of heart rate on the QT interval.[37] Data from the same study supported the association of cardiac repolarization with cognitive impairment because JTc (QT interval minus the QRS duration) correlated with cognitive function[37] and JTc correlates well with several QTc formulae.[17,44]

There are few population-based studies that examined the relationship between QT interval and cognition. The results are discordant. In a sample of 839 older residents (mean age 81) from a geographically defined biracial community in Chicago, Illinois, USA, there was no correlation between QT interval and cognitive function.[45] Individuals had cognition testing using 17 measures of cognitive performance.[45] The results were correlated with data from a 12 lead ECG from which the QT interval was calculated from a linear transformation of the QT interval based on the RR interval.[45] A linear transformation is more accurate than formulae based on power functions such as QTcBZT.[44,46] In contrast, in the MIND CHINA study, 4886 dementia-free participants (age ≥ 60 years, 56.2% women) underwent a neuropsychological test battery to assess cognitive function.[36] Longer QT interval was significantly associated with lower global cognitive function and poorer executive function, "even among individuals without overt cardiovascular disease."[36] They did not appear to calculate QTc.[36]

A qualitative analysis of the studies reviewed herein, identified several issues. First, each of these studies briefly defined their method for measurement of QT interval from a 12 lead ECG from the start of QRS complex to the end of the T wave. The end of the wave was defined as the point of return to the isoelectric line.[6,21,22] The details of the method were usually not described, but in one study a ruler was used suggesting that the end of the T was defined simply as the intersection of the T wave and the TP segment. The current best approach to measurement of the QT interval involves defining the end of the T wave by drawing a tangent to the slope of the descending part of the T wave and marking its intersection with the T–P segment as the end of the T wave.[47] None of the studies reported that they used this method—the best practice way to measure the QT interval. Another issue is that almost all of the studies adjusted for the known effect of heart rate on the QT interval (heart rate corrected QT or QTc) used the Bazett formula. The Bazett formula has been seriously criticized as the poorest formula to adjust for effect of heart rate on the QT interval because it is not an accurate adjustment for heart rate across the heart rate range.[44,48,49] Importantly, QTcBZT overestimated the number of patients with prolonged QTc prolongation.[48]

There are several other issues that warrant discussion. First, the relationship between QT and AD was more evident between AD and individuals with MCI than with individuals without cognitive impairment (the control group). A metric defining a high-quality study is the provision of an extensive descriptions of the inclusion criteria for the control groups. In two of the three studies, details of the inclusion criteria for the control group are not provided. Another issue is existing studies did not explore the relationship of dementia and more detailed ECG analysis including QRS-T angle, spatial QRS-T angle, and T-wave morphology. This systematic review identified problems

with the utilization of a QT heart rate correction that is generally found to be poor in adjusting for the effect of heart rate on QT interval; issues with defining the inclusion criteria for the control group; conflicting data in population studies, and the lack of a strong electrophysiological basis for the original hypothesis linking AD and QT interval.

The mechanisms by which AD might prolong QTc is worthy of further discussion recognizing that this paper did not provide experimental evidence on this subject. QT prolongation may occur at several levels from the brain to the heart. QTc prolongation may be due to loss of brain tissue in specific areas. There are little data that correlated QTc with brain structure in AD. Danese et al. performed structural brain imaging studies (computed tomography or magnetic resonance imaging) on patients with cognitive impairment and found a relationship between the extent of the degeneration and/or the "cerebral vascular load" and the QTc prolongation.[22] Acute stroke that represents the loss of brain tissue is also associated with a prolonged QTc interval[50] and patients with a prolonged QTc interval are more likely to die within 90 days of their stroke, compared with patients without a prolonged QT interval.[50] In AD, an interaction at the level of the heart is possible. Type I membrane protein BACE1 (β-site APP-cleaving enzyme 1), which plays a detrimental role in AD, is also present in cardiac myocytes where it interacts with KCNQ1 (Kv7.1) proteins that form a homotetrameric channel, which produces a voltage-dependent K(+) current affecting cardiac repolarization.[51]

Data on QT variability were presented herein for several reasons. First, studies that examined the relationship between QT variability and AD consistently showed an association.[6,21] Second, there is an association between QT variability and cognitive function.[37] Third, in other neurologic conditions associated with loss of brain tissue such as stroke,[51] QT variability is increased.[52,53] Fourth, variability of a biological factor is a meaningful factor as exemplified by the importance of variability of blood pressure and other cardiovascular risk factors in cardiovascular risk prediction.[28,29]

QT variability on a 12 lead ECG was consistently increased in AD.[6,21] QT variability in AD has been attributed to several factors. First, it is associated with an increased prevalence of silent myocardial ischemia in AD and MCI[54] Second, QT variability has also been found in brain loss situations such as stroke[52,55] and is directly related to the size of the lesion rather than to the localization or type of stroke.[55] Third, comorbidities, including coronary artery disease, drug effects, and interpersonal differences may account for an element of QT variability[56] and may be an explanation for why some cardiac conditions do not show a relationship between QT variability and cardiac mortality.[57,58] Fourth, an imbalance in the autonomic nervous system contributes to QT interval variability.[15,59] An important perspective is the concept summarized by Vrinceanu et al. that degeneration in the prefrontal cortex, which is involved in cognition and autonomic function[38,60] produces simultaneous loss of both autonomic regulation and cognition, especially executive functions.[38] A "neurovisceral integration model" has been proposed in which cognition, autonomic function, and emotional regulation are interconnected and include the prefrontal cortex.[60]

4.1 | Study limitations

There are a number of limitations of this study that warrant discussion. The nature of meta-analysis is its dependency on the available published literature. The strength of the conclusions is based on the validity of each study. The available data rely on mean results from each study and do not utilize individual data from all studies. Second, the small number of studies in this field was likely disproportionately influenced by one of the studies with the largest sample size. Third, the kinds of dementia could not be separately analyzed. One large study had only 25% with AD and the rest had a variety of neurodegenerative conditions.[22] However, different kinds of dementias frequently co-exist, so that even in the studies that included "only' AD," there was likely a mixture of other kind of dementias as well. Fourth, a formal assessment of the quality of studies in this meta-analysis could not be done. Ranking scales would rank the quality of these as low because of the absence of randomization or an intervention group but more importantly because of the limited information on the selection of the control groups.[61]

In summary, this meta-analysis concluded that patients with dementia have a longer QT interval than individuals with MCI or those without cognitive impairment. It further concluded that QT prolongation correlates with the degree of cognitive impairment. In addition, QT variability was increased in AD. This study focuses attention on the need to understand the determinants of aging-associated QT prolongation that appear important for understanding aging-induced dementia and mortality.

AUTHOR CONTRIBUTION

The author is responsible for conceptualization, data analysis, and writing the manuscript.

FUNDING INFORMATION

There was no sponsor or any contribution from a sponsor.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

ORCID

Simon W. Rabkin https://orcid.org/0000-0001-8923-1152

REFERENCES

1. Rabkin SW. Arterial stiffness: detection and consequences in cognitive impairment and dementia of the elderly. *J Alzheimers Dis*. 2012;32:541-549. doi:10.3233/JAD-2012-120757
2. Finsterer J, Wahbi K. CNS-disease affecting the heart: brain-heart disorders. *J Neurol Sci*. 2014;345:8-14. doi:10.1016/j.jns.2014.07.003
3. Vaccarino V, Shah AJ, Mehta PK, et al. Brain-heart connections in stress and cardiovascular disease: implications for the

cardiac patient. *Atherosclerosis*. 2021;328:74-82. doi:10.1016/j.atherosclerosis.2021.05.020
4. Degerskar ANW, Englund EM. Cause of death in autopsy-confirmed dementia disorders. *Eur J Neurol*. 2020;27:2415-2421. doi:10.1111/ene.14450
5. Royall DR, Gao J-H, Kellogg DLJ. Insular Alzheimer's disease pathology as a cause of "age-related" autonomic dysfunction and mortality in the non-demented elderly. *Med Hypotheses*. 2006;67:747-758. doi:10.1016/j.mehy.2005.10.036
6. Coppola L, Mastrolorenzo L, Coppola A, et al. QT dispersion in mild cognitive impairment: a possible tool for predicting the risk of progression to dementia? *Int J Geriatr Psychiatry*. 2013;28:632-639. doi:10.1002/gps.3870
7. Lehéricy S, Hirsch EC, Hersh LB, Agid Y. Cholinergic neuronal loss in the globus pallidus of Alzheimer disease patients. *Neurosci Lett*. 1991;123:152-155. doi:10.1016/0304-3940(91)90918-j
8. Boissière F, Lehéricy S, Strada O, Agid Y, Hirsch EC. Neurotrophin receptors and selective loss of cholinergic neurons in Alzheimer disease. *Mol Chem Neuropathol*. 1996;28:219-223. doi:10.1007/BF02815225
9. Martinez JL, Zammit MD, West NR, Christan BT, Bhattacharyya A. Basal forebrain cholinergic neurons: linking down syndrome and Alzheimer's disease. *Front Aging Neurosci*. 2021;13:703876. doi:10.3389/fnagi.2021.703876
10. Kapa S, Venkatachalam KL, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: an elegant interaction and emerging concepts. *Cardiol Rev*. 2010;18:275-284. doi:10.1097/CRD.0b013e3181ebb152
11. Kautzner J, Hartikainen JEK, Heald S, Camm AJ. The effects of reflex parasympathetic stimulation on the QT interval and QT dispersion. *Am J Cardiol*. 1997;80:1229-1232. doi:10.1016/s0002-9149(97)00648-6
12. Magnano AR, Holleran S, Ramakrishnan R, Reiffel JA, Bloomfield DM. Autonomic nervous system influences on qt interval in normal subjects. *J Am Coll Cardiol*. 2002;39:1820-1826. doi:10.1016/s0735-1097(02)01852-1
13. Annila P, Yli-Hankala A, Lindgren L. Effect of atropine on the QT interval and T-wave amplitude in healthy volunteers. *Br J Anaesth*. 1993;71:736-737. doi:10.1093/bja/71.5.736
14. Martins JB, Zipes DP. Effects of sympathetic and vagal nerves on recovery properties of the endocardium and epicardium of the canine left ventricle. *Circ Res*. 1980;46:100-110. doi:10.1161/01.res.46.1.100
15. Abildskov JA. Neural mechanisms involved in the regulation of ventricular repolarization. *Eur Heart J*. 1985;6(Suppl D):31-39. doi:10.1093/eurheartj/6.suppl_d.31
16. Rabkin SW. Assessment of the QT interval in right bundle branch block. *Acta Cardiol*. 2023;78:672-679. doi:10.1080/00015385.2022.2066778
17. Tang JKK, Rabkin SW. Determination of the QT interval in left bundle branch block: development of a novel formula. *Can J Cardiol*. 2019;35:855-865. doi:10.1016/j.cjca.2019.02.014
18. Straus SMJM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47:362-367. doi:10.1016/j.jacc.2005.08.067
19. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation*. 1991;83:1888-1894. doi:10.1161/01.cir.83.6.1888
20. Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology*. 2011;22:660-670. doi:10.1097/EDE.0b013e318225768b
21. Zulli R, Nicosia F, Borroni B, et al. QT dispersion and heart rate variability abnormalities in Alzheimer's disease and in mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:2135-2139. doi:10.1111/j.1532-5415.2005.00508.x
22. Danese A, Federico A, Martini A, et al. QTc prolongation in patients with dementia and mild cognitive impairment: neuropsychological and brain imaging correlations. *J Alzheimers Dis*. 2019;72:1241-1249. doi:10.3233/JAD-190632
23. Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. *J Am Coll Cardiol*. 1995;25:746-752. doi:10.1016/0735-1097(94)00446-W
24. Elming H, Holm E, Jun L, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. *Eur Heart J*. 1998;19:1391-1400. doi:10.1053/euhj.1998.1094
25. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. QTc dispersion predicts cardiac mortality in the elderly: the Rotterdam study. *Circulation*. 1998;97:467-472. doi:10.1161/01.cir.97.5.467
26. Rautaharju PM. Why did QT dispersion die? *Card Electrophysiol Rev*. 2002;6:295-301. doi:10.1023/a:1016397529393
27. Malik M, Acar B, Gang Y, Yap YG, Hnatkova K, Camm AJ. QT dispersion does not represent electrocardiographic interlead heterogeneity of ventricular repolarization. *J Cardiovasc Electrophysiol*. 2000;11:835-843. doi:10.1111/j.1540-8167.2000.tb00061.x
28. Parati G, Stergiou GS, Dolan E, Bilo G. Blood pressure variability: clinical relevance and application. *J Clin Hypertens (Greenwich)*. 2018;20:1133-1137. doi:10.1111/jch.13304
29. Lee S-H, Kim MK, Rhee E-J. Effects of cardiovascular risk factor variability on health outcomes. *Endocrinol Metab (Seoul)*. 2020;35:217-226. doi:10.3803/EnM.2020.35.2.217
30. Haidich AB. Meta-analysis in medical research. *Hippokratia*. 2010;14:29-37.
31. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
32. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097. doi:10.1371/journal.pmed.1000097
33. Mao M, Wang C, Hou T, et al. Ventricular electrocardiographic signatures associated with dementia and plasma Alzheimer's disease biomarkers in older adults: a population-based study. *J Alzheimers Dis*. 2023;94:1515-1526. doi:10.3233/JAD-230056
34. Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart*. 1920;7:353-370. doi:10.1111/j.1542-474X.1997.tb00325.x
35. Rabkin SW, Cheng XB. Nomenclature, categorization and usage of formulae to adjust QT interval for heart rate. *World J Cardiol*. 2015;7:315-325. doi:10.4330/wjc.v7.i6.315
36. Wang C, Mao M, Han X, et al. Associations of cardiac ventricular repolarization with serum adhesion molecules and cognitive function in older adults: the MIND-China study. *J Alzheimers Dis*. 2023;92:273-283. doi:10.3233/JAD-220874
37. Zonneveld MH, Noordam R, van der Grond J, et al. Ventricular repolarization is associated with cognitive function, but not with cognitive decline and brain magnetic resonance imaging (MRI) measurements in older adults. *J Clin Med*. 2020;9:911. doi:10.3390/jcm9040911
38. Vrinceanu T, Lagacé-Lavoie G, Kaushal N, et al. Mind the rhythm: ECG QT dispersion and cognition in healthy older adults. *Front Psychol*. 2020;11:566341. doi:10.3389/fpsyg.2020.566341
39. Wang SJ, Liao KK, Fuh JL, et al. Cardiovascular autonomic functions in Alzheimer's disease. *Age Ageing*. 1994;23:400-404. doi:10.1093/ageing/23.5.400

40. de Vilhena Toledo MA, Junqueira LFJ. Cardiac sympathovagal modulation evaluated by short-term heart interval variability is subtly impaired in Alzheimer's disease. *Geriatr Gerontol Int*. 2008;8:109-118. doi:10.1111/j.1447-0594.2008.00456.x
41. Aharon-Peretz J, Harel T, Revach M, Ben-Haim SA. Increased sympathetic and decreased parasympathetic cardiac innervation in patients with Alzheimer's disease. *Arch Neurol*. 1992;49:919-922. doi:10.1001/archneur.1992.00530330041013
42. Frederiks J, Swenne CA, Kors JA, et al. Within-subject electrocardiographic differences at equal heart rates: role of the autonomic nervous system. *Pflugers Arch*. 2001;441:717-724. doi:10.1007/s004240000487
43. Diedrich A, Jordan J, Shannon JR, Robertson D, Biaggioni I. Modulation of QT interval during autonomic nervous system blockade in humans. *Circulation*. 2002;106:2238-2243. doi:10.1161/01.cir.0000035241.76918.6c
44. Rabkin SW, Szefer E, Thompson DJS. A new QT interval correction formulae to adjust for increases in heart rate. *JACC Clin Electrophysiol*. 2017;3:756-766. doi:10.1016/j.jacep.2016.12.005
45. Lucas BP, Mendes de Leon CF, Prineas RJ, Bienias JL, Evans DA. Relation of cardiac ventricular repolarization and global cognitive performance in a community population. *Am J Cardiol*. 2010;106:1169-1173. doi:10.1016/j.amjcard.2010.06.031
46. Rautaharju PM, Zhang Z-M. Linearly scaled, rate-invariant normal limits for QT interval: eight decades of incorrect application of power functions. *J Cardiovasc Electrophysiol*. 2002;13:1211-1218. doi:10.1046/j.1540-8167.2002.01211.x
47. Postema PG, Wilde AAM. The measurement of the QT interval. *Curr Cardiol Rev*. 2014;10:287-294. doi:10.2174/1573403x10666140514103612
48. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc*. 2016;5:1-10. doi:10.1161/JAHA.116.003264
49. Andršová I, Hnatkova K, Šišáková M, et al. Influence of heart rate correction formulas on QTc interval stability. *Sci Rep*. 2021;11:14269. doi:10.1038/s41598-021-93774-9
50. Stead LG, Gilmore RM, Bellolio MF, et al. Prolonged QTc as a predictor of mortality in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2009;18:469-474. doi:10.1016/j.jstrokecerebrovasdis.2009.02.006
51. Agsten M, Hessler S, Lehnert S, et al. BACE1 modulates gating of KCNQ1 (Kv7.1) and cardiac delayed rectifier KCNQ1/KCNE1 (IKs). *J Mol Cell Cardiol*. 2015;89:335-348. doi:10.1016/j.yjmcc.2015.10.006
52. Mulcahy J, Johnson P, James M. Electrocardiogram QT interval increases in acute stroke. *Cerebrovasc Dis*. 2010;29:178-180. doi:10.1159/000262315
53. Lederman YS, Balucani C, Lazar J, Steinberg L, Gugger J, Levine SR. Relationship between QT interval dispersion in acute stroke and stroke prognosis: a systematic review. *J Stroke Cerebrovasc Dis*. 2014;23:2467-2478. doi:10.1016/j.jstrokecerebrovasdis.2014.06.004
54. Zulli R, Nicosia F, Borroni B, et al. Increased prevalence of silent myocardial ischaemia and severe ventricular arrhythmias in untreated patients with Alzheimer's disease and mild cognitive impairment without overt coronary artery disease. *Clin Neurol Neurosurg*. 2008;110:791-796. doi:10.1016/j.clineuro.2008.05.002
55. Afsar N, Fak AS, Metzger JT, Van Melle G, Kappenberger L, Bogousslavsky J. Acute stroke increases QT dispersion in patients without known cardiac diseases. *Arch Neurol*. 2003;60:346-350. doi:10.1001/archneur.60.3.346
56. Kors JA, van Herpen G, van Bemmel JH. QT dispersion as an attribute of T-loop morphology. *Circulation*. 1999;99:1458-1463. doi:10.1161/01.cir.99.11.1458
57. Glancy JM, Garratt CJ, Woods KL, de Bono DP. QT dispersion and mortality after myocardial infarction. *Lancet*. 1995;345:945-948. doi:10.1016/s0140-6736(95)90697-5
58. Spargias KS, Lindsay SJ, Kawar GI, et al. QT dispersion as a predictor of long-term mortality in patients with acute myocardial infarction and clinical evidence of heart failure. *Eur Heart J*. 1999;20:1158-1165. doi:10.1053/euhj.1998.1445
59. Mine T, Shimizu H, Hiromoto K, et al. Beat-to-beat QT interval variability is primarily affected by the autonomic nervous system. *Ann Noninvasive Electrocardiol*. 2008;13:228-233. doi:10.1111/j.1542-474X.2008.00225.x
60. Thayer JF, Lane RD. Claude Bernard and the heart–brain connection: further elaboration of a model of neurovisceral integration. *Neurosci Biobehav Rev*. 2009;33:81-88. doi:10.1016/j.neubiorev.2008.08.004
61. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603-605. doi:10.1007/s10654-010-9491-z

How to cite this article: Rabkin SW. Relationship between Alzheimer dementia and QT interval: A meta-analysis. *Aging Med*. 2024;7:214-223. doi:10.1002/agm2.12291