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Gamma-glutamyltransferase and risk of future dementia in middle-aged to older Finnish men: A new prospective cohort study

Setor K. Kunutsor[a,*], Jari A. Laukkanen[b]

[a]School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, UK, USA

[b]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Finland.

***Corresponding author:**

Setor K. Kunutsor, School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, BS10 5NB, UK; Phone: +44-7539589186; Fax: +44-1174147924; Email: skk31@cantab.net

Abbreviations

BMI = body mass index; **CI =** confidence interval; **CHD** = coronary heart disease; **CRP** = C-reactive protein; **CVD** = cardiovascular disease; **FLI** = fatty liver index; **FPG** = fasting plasma glucose; **GGT =** gamma-glutamyltransferase; **HDL-C** = high-density lipoprotein cholesterol; **HR** = hazard ratio; **KIHD** = Kuopio Ischemic Heart Disease; **RDR** = regression dilution ratio; **SD** = standard deviation; **SBP** = systolic blood pressure

Abstract

INTRODUCTION: We assessed the association of gamma-glutamyltransferase (GGT) with risk of dementia.

METHODS: Serum GGT activity was assessed at baseline in the Kuopio Ischemic Heart Disease prospective cohort of 2415 relatively healthy men with good cognitive function. Correction was made for within-person variability in GGT levels.

RESULTS: During an average follow-up of 22 years, 219 new cases of dementia were recorded. Serum GGT was log-linearly associated with risk of dementia. The hazard ratio (HR) (95% CIs) for dementia per 1 standard deviation (SD) higher baseline $\log_e$ GGT values was 1.33 (95% CI: 1.14-1.55) after adjustment for several established and emerging risk factors. The corresponding HR was 1.52 (95% CI: 1.22-1.89) after correction for within-person variability.

DISCUSSION: GGT is positively, log-linearly, and independently associated with future risk of dementia in the general male population. Further research is needed to unravel the mechanistic pathways of GGT in the pathogenesis of dementia.

Keywords: Gamma-glutamyltransferase; Risk factor; Dementia

1. Background

Dementia is a vast public health problem and has been established as one of the major challenges of this century.[1] With the ageing global population, enormous resources will be required to care for those afflicted with the disease, thereby imposing a significant economic burden on health systems and society as a whole.[2] The global prevalence is expected to rise from 30 million in 2010 to 106 million in 2050.[2] Though there is a direct correlation between ageing and the incidence of dementia, the pathogenesis of dementia is not fully understood. A number of pathways have been implicated, notably including inflammation and oxidative stress.[3, 4] Several pharmacological agents exist for the treatment of dementia, but majority of these agents have not proved beneficial in modifying the course of the disease.[5] Though active research is underway to develop interventions that will slow down the disease progress,[6] there is an urgent need to develop strategies to prevent or delay disease onset. It has been projected that a delay by one year in both disease onset and progression will result in nearly 9.2 million fewer cases of the disease by 2050.[2]

Gamma-glutamyltransferase (GGT), a biomarker which is routinely used in clinical practice to help indicate potential hepatic or biliary disease, has been shown to be associated with a wide range of vascular disease outcomes.[7-9] Since vascular disease is associated with cognitive impairment and dementia,[10] serum levels of GGT might increase the risk of dementia. Given the pro-oxidant and pro-inflammatory properties of GGT[11] and similar pathways implicated for the development of dementia,[3, 4] we hypothesized that GGT will be associated with an increased risk of dementia. We therefore aimed to evaluate in detail the nature and magnitude of the prospective association of GGT with risk of dementia in a population-based cohort of 2415 apparently healthy men from eastern Finland. Repeat measurements of GGT were performed 4 and 11 years after baseline examinations in 900 participants to help quantify within-person variability in GGT values. In subsidiary analysis, we also assessed the association of GGT with the dementia subtype - Alzheimer’s disease.

2. Methods

This study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Appendix**).[12]

2.1. Study population

The study population consisted of a representative sample of men living in the city of Kuopio and its surrounding rural communities in eastern Finland. Subjects were participants in the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a longitudinal population-based study designed to investigate risk factors for CVD and other chronic diseases.[13] Participants were 42-61 years of age during baseline examinations performed between March 1984 and December 1989. Of 3433 potentially eligible and randomly selected men, 3235 were found to be eligible for the study. Of this number, 2682 (82.9 %) volunteered to participate, 186 did not respond to the invitation and 367 declined to give informed consent. The final cohort for the present analysis included 2415 men with no history of dementia at baseline and with non-missing information on serum GGT and covariates. The derivation of the analytic cohort is provided in **Figure 1**. The Research Ethics Committee of the University of Eastern Finland approved the study, and each participant gave written informed consent.

2.2. Ascertainment of outcomes

All dementia cases that occurred from study enrollment through 2012 were included. There were no losses to follow-up. In the KIHD study, all participants (using Finnish personal identification codes) are under continuous annual monitoring for incident dementia cases and cardiometabolic outcomes, including incident cases and deaths.[14] The sources of information on outcomes were based on a comprehensive review of hospital admission and discharge records, inpatient physician claims data, medico-legal reports, and by record linkage with the hospital coronary intervention, national hospital discharge and national

death registries. Incident coronary heart disease events were defined as nonfatal myocardial infarction, ischemic heart disease, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty according to ICD-9 codes or ICD-10 codes. For dementia screening and diagnosis, participants were first screened with tests of cognition, including the Mini-Mental State Examination and Geriatric Mental State[15] at baseline examination and every year. This was followed by further cognitive testing of screen-positives. Subjects suspected of having dementia were examined by neurologists, underwent neuropsychological testing, and magnetic resonance imaging of the brain. An independent committee of neurologists of the KIHD study, masked to clinical data, reviewed all potential cases of dementia to obtain a consensus on the diagnosis and aetiology. Participants with a diagnosis of dementia underwent another examination after one year to confirm the diagnosis.

2.3. Measurement of risk factors

Collection of blood specimens and the measurement of serum lipids, lipoproteins and glucose have been described previously.[16] Blood samples were taken between 08:00 and 10:00 hours. In addition to fasting, participants were instructed to abstain from drinking alcohol for at least 3 days and from smoking for at least 12 h prior to assessment. The serum samples were stored frozen at -80 °C for 0.2-2.5 years. Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany). Serum GGT activity was measured using the kinetic method (Thermo Fisher Scientific, Vantaa, Finland) and C-reactive protein (CRP) with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Repeat measurements of GGT were performed 4 years and 11 years after baseline examinations during a 22 year period in a random subset of participants. Smoking, alcohol consumption, blood pressure, use of medication, family histories, and baseline diseases were assessed by self-administered questionnaires as described previously.[16] Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory. Chronic disease diagnoses and medication use were checked during medical examinations by the internist. Body mass index (BMI)

was computed as the ratio of weight in kilograms to the square of height in metres. The energy expenditure of physical activity was assessed from a 12-month physical activity history modified from the Minnesota Leisure-Time Physical Activity Questionnaire[17] as described in detail previously.[18] Briefly, this detailed quantitative questionnaire deals with the most common leisure-time physical activities of middle-aged Finnish men (conditioning physical activity, e.g. walking, skiing, bicycling, swimming, rowing, ball games, etc and nonconditioning physical activity, e.g. crafts, repairs, building, gardening, hunting, fishing, etc) and enables the assessment of all components of physical activity. For each activity performed, participants were asked to record the frequency, average duration, and intensity. Energy expenditure was measured for each physical activity by multiplying the metabolic index of activity (in metabolic equivalent*hour/week) by body weight in kilograms. Adulthood socioeconomic status is a summary index that combines measures of income, education, occupation, occupational prestige, material standard of living, and housing conditions, all of which were assessed with self-reported questionnaires.[19] Diabetes was defined as a fasting plasma glucose of ≥ 7.0 mmol/l or clinical diagnosis of diabetes with dietary, oral, or insulin treatment, or according to self-reports. A history of coronary heart disease (CHD) was defined as either a previous myocardial infarction, ischemic heart disease, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, angina pectoris or the use of nitroglycerin for chest pain once a week or more frequently.

2.4. Statistical analysis

Values of skewed variables (GGT and CRP) were log-transformed to achieve approximately symmetrical distributions. We performed descriptive analyses summarising the baseline characteristics of the participants. Cross-sectional associations of GGT with various risk markers were assessed using linear regression models adjusted for age. Time-to-event analyses were conducted using Cox proportional hazard models after confirming assumptions of proportionality of hazards. To quantify and correct for within-person variability in levels of GGT, that is, the extent to which an individual's GGT measurements

vary around a long-term average level exposure ("usual levels"),[20] adjusted regression dilution ratios (RDRs) were estimated by regressing available repeat measurements on baseline values.[21] To characterize the shape of the association between GGT and risk of dementia, hazard ratios (HRs) were calculated within quartiles of baseline GGT values and plotted against mean GGT values within each quartile. Floating variances were used to calculate 95% confidence intervals for the log hazard ratio in each group, including the reference group, to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile)[26]. As the association showed a log-linear shape, HRs were calculated per 1 standard deviation (SD) higher $\log_e$ GGT values. The SD of baseline $\log_e$ GGT was 0.65 (equivalent to approximately 2-fold higher circulating GGT, as $e^{0.65}=1.92$). In subsidiary analyses, HRs were also calculated by quartiles defined according to the baseline distribution of serum GGT values. HRs were adjusted for age, BMI, systolic blood pressure (SBP,) prevalent CHD, smoking status, history of diabetes mellitus, use of medications (antihypertensive agents and lipid-lowering drugs), total cholesterol, high-density lipoprotein cholesterol (HDL-C), alcohol consumption, socio-economic status, physical activity, and CRP. We performed subgroup analyses using interaction tests to assess statistical evidence of any differences in hazards across levels/categories of pre-specified individual level characteristics, including age at survey, BMI, SBP, total cholesterol, CRP, history of diabetes, smoking status, and history of CHD. Sensitivity analyses included (i) excluding the first five years of follow-up to avoid including cases with prevalent but undetected impaired cognitive function; (ii) excluding participants with GGT values greater than three times the upper limit of normal, given that elevated levels of GGT is a common reason for liver disease work-up; and (iii) excluding participants with potential fatty liver disease using a validated predictive index – the fatty liver index (FLI). The FLI - a simple algorithm for predicting fatty liver - is based on BMI, waist circumference, triglycerides, and GGT, and has a diagnostic accuracy ranging from 0.72 to 0.84%.[22, 23] All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

3. Results

3.1. Baseline characteristics and correlates of gamma-glutamyltransferase

Table 1 summarizes baseline characteristics of the 2415 participants. The mean age of the participants was 53 (SD 5) years. Median (interquartile range) GGT value was 20 (15-33) U/L. During an average follow-up of 22 years, there were 219 new cases of dementia (annual rate 4.19/1,000 person-years at risk; 95% CI 3.67 to 4.79). Of the total number of dementia cases, 132 were cases due to Alzheimer's disease. Serum GGT values were weakly to moderately and positively correlated with physical measures (BMI, blood pressure, and physical activity) and with several lipid, metabolic, and inflammation markers (CRP). Weak inverse correlations were observed for age (r = -0.03) and HDL-C (r = -0.03). Baseline GGT values were higher in people with diabetes compared with people without diabetes, higher in current smokers compared with non-smokers, and higher in people on antihypertensive medication compared with people not on antihypertensive medication (**Table 2**).

3.2. Correction for within-person variability

Repeat measurements of GGT taken 4 years and 11 years after baseline examinations over 22 years were available in a random sample of 900 participants. Overall, the regression RDR of $\log_e$ GGT, adjusted for age, was 0.69 (95% CI: 0.63 to 0.74), suggesting that the associations using one-off or baseline measurements of GGT with dementia could under-estimate the association by [(1/0.69)-1]*100 = 45%.

3.3. Gamma-glutamyltransferase and risk of dementia

Rates of dementia per 1000 person-years of follow-up across quartiles of GGT were 5.36 (95% CI: 4.17 to 6.89) for the fourth quartile, 4.37 (95% CI: 3.39 to 5.64) for the third quartile, 3.66 (95% CI: 2.68 to 4.99) for the second quartile, and 3.59 (95% CI: 2.78 to 4.64) for the first quartile. Cumulative hazard

curves demonstrated a greater risk of dementia among males in the top quartile of GGT levels compared to those in the bottom quartile (P = 0.01 for log-rank test; **Figure 2**). Baseline and usual GGT values were log-linearly associated with risk of dementia in analyses adjusted for age, BMI, SBP, history of CHD, smoking status, history of diabetes mellitus, use of antihypertensive agents and lipid-lowering drugs, alcohol consumption, socio-economic status, and physical activity (**Figure 3**). The age-adjusted HR per 1 SD change in baseline $\log_e$ GGT value was 1.44 (95% CI: 1.26 to 1.65; $P < 0.001$), which was somewhat attenuated following further adjustment for several established risk factors 1.32 (95% CI: 1.14 to 1.55; $P < 0.001$). The observed association did not change after further adjustment for CRP 1.33 (95% CI: 1.14 to 1.55; $P < 0.001$). The corresponding HRs per 1 SD change in usual $\log_e$ GGT values were 1.70 (95% CI: 1.40 to 2.07; $P < 0.001$), 1.51 (95% CI: 1.21 to 1.88; $P < 0.001$), and 1.52 (95% CI: 1.22 to 1.89; $P < 0.001$) respectively (**Table 3)**. The HRs remained consistent after further adjustment for incident coronary events (**Table 3)**.The significant associations were maintained in analyses by quartiles of the baseline distribution of GGT values. HRs were similar in analyses that excluded (i) the first five years of follow-up; (ii) participants with GGT values greater than three times the upper limit of normal; and (iii) participants with potential fatty liver disease (**Table 4**). The associations generally did not vary significantly by levels or categories of several clinically relevant characteristics and other risk markers, except for suggestion of effect modification by age (P for interaction = 0.032) and history of CHD (P for interaction = 0.046) (**Figure 4**). Significant positive associations were observed in older individuals (aged 54 years and above) and individuals with a history of CHD compared to non-significant associations in younger individuals and those without a history of CHD respectively (**Figure 4**).

In separate analyses for Alzheimer's disease, the positive association of GGT with Alzheimer's disease in age-adjusted analyses was attenuated upon further adjustment for several established risk factors (**Table 5**).

4. Discussion

4.1. Key findings

In this large-scale population of middle-aged to older Finnish men, we have for the first time assessed the shape, magnitude, independence, and specificity of the prospective association of both baseline and usual values of GGT with risk of dementia (including the specific outcome of Alzheimer's disease) in a single comprehensive investigation. In analyses adjusted for age and established risk factors, we observed an approximately log-linear association of GGT with risk of dementia. The association did not materially change on further adjustment for CRP and incident coronary events. Except for suggestion of effect modification by age and history of CHD, the overall findings remained consistent across several categories and levels of risk markers for dementia. There were more extreme results in studies conducted among older individuals, consistent with established evidence that increasing age is the most important risk factor for dementia.[24] A stronger association with people with a history of CHD was also demonstrated, also consistent with evidence that vascular disease is associated with increased risk of dementia.[10] The associations remained robust in several sensitivity analyses.

4.2. Possible explanations for findings

A growing body of evidence suggests that serum levels of GGT may be associated with a wide range of disease outcomes. Several prospective studies have demonstrated associations between GGT and risk of vascular and non-vascular outcomes.[7-9, 25-27] Several mechanisms have been postulated for these associations and these include the pro-inflammatory and pro-oxidant activities of GGT[11], as well as its direct involvement in atheromatous plaque formation.[28, 29] Though the pathogenesis of dementia has not been completely elucidated, mechanistic research provides strong support for inflammatory and oxidative processes.[3, 4, 30] Our results are therefore biologically plausible as GGT mediates these processes. Gamma-glutamyltransferase plays a major role in glutathione (the major thiol antioxidant in the body) metabolism, generating reactive oxygen species, which contribute to the aging process and

pathogenesis of age-related neurodegenerative diseases such as dementia.[31, 32] Additionally, elevated GGT levels are associated with atherosclerosis, which has also been implicated as an underlying link in the pathogenesis of dementia.[10]

4.3. Implications of findings

Our findings are relevant as they provide further insight on putative risk factors that may inform our understanding of neurodegenerative disorders. The results highlight a potential deleterious role of serum GGT levels on the risk of dementia. Till date, there is still no cure for dementia and only pharmacological and non-pharmacological agents exist to alleviate the cognitive and behavioural symptoms of the disease. Therefore, potential risk factors which may have causal or predictive relevance to dementia could help tailor preventive and therapeutic interventions. Dementia has a multifactorial aetiology and current evidence suggests inflammation and oxidative stress as major hallmarks in the pathogenesis of dementia. Given the role of GGT as both an inflammatory and oxidative mediator, there remains a possibility that lowering levels of GGT may decrease the risk of future dementia. Individuals with elevated GGT levels might benefit from nutritional and lifestyle modification (e.g., weight loss and physical activity[33]) that decrease GGT levels. Our findings are among the first in this research area and therefore is a topic for further investigation. Gamma-glutamyltransferase remains a promising though unproven strategy in the prevention of chronic diseases, therefore further research is warranted to investigate any potential therapeutic implications of GGT in dementia.

4.4. Strengths and limitations

Our study has several strengths. It is the first longitudinal study so far on the association between GGT and dementia. The large sample was selected to be a nationally representative population-based sample of middle-aged men, was well characterised, involved a high participation rate and there were no losses during follow-up, minimising the risk of selection bias. To obtain reliable data, baseline measurements of

GGT and other covariates were made in a relatively healthy cohort of middle-aged individuals with good cognitive function, therefore limiting any possibilities of reverse-causation bias. Participants have been prospectively monitored using established databases for hospital admissions including out-of-hospital outcome events, supplemented with reliable data on a comprehensive panel of lifestyle and biological markers to allow adequate adjustment for potential confounding, enabling reliable assessments of the associations. The mean follow-up period in this study was sufficiently long to ascertain the risk for dementia in the general population settings. Serial measurements of GGT made within a subset of individuals over time were available, enabling quantification of the extent of within-person variability over the long period of follow-up. However, studies are needed with repeat measurements of GGT in larger numbers of participants to assess GGT variability in greater detail. Our study also has some limitations. There might be the possibility of selection bias because about 17% of participants declined to participate in the study and 8% of eligible subjects did not have GGT measurements; however, this may be unlikely since potential participants for the KIHD study included men from an ethnically and genetically homogeneous population[13] and the number of participants without GGT measurements represented only a very small proportion of the total sample. In addition, as with most observational studies of this kind, it is not uncommon to record a small proportion of participants who decline to participate in the study. The participation rate was still rather high and the population representative. Our analyses focused on all types of dementia and Alzheimer's disease only, since reliable data for other specific dementia subtypes such as vascular dementia were not available. The KIHD study involved prolonged blood storage which could underestimate the associations, however, GGT is not known to be influenced by prolonged storage or repeated freeze-thaw cycles.[34] The KIHD study included only middle-aged to older Caucasian men and cannot necessarily be extrapolated to women, the young, elderly, and other ethnicities. Measurements of other liver function enzymes such as the aminotransferases were not made in the KIHD study, thus preventing comparisons of the separate and joint associations of these enzymes with dementia risk.

Though a comprehensive panel of confounders was taken into account to ensure the validity of our results, potential residual confounding due to errors in risk marker measurements and other unmeasured confounders (such as other liver enzymes and biliary and liver diseases) cannot be entirely ruled out in these analyses. However, in several sensitivity analyses, we excluded participants with GGT values greater than three times the upper limits of normal and participants with potential fatty liver disease as predicted by the FLI, thereby minimising potential bias due to undiagnosed liver disease such at baseline. In addition, we did not have complete genetic data, which precluded further analyses such as adjusting for the *APOE* gene (encoding apolipoprotein E), a major genetic risk factor for age-related cognitive decline and Alzheimer's disease.[35]

4.5. Conclusions

Available evidence suggests that GGT is positively, log-linearly, and independently associated with future risk of dementia over two decades in the general male population. Further research is needed to replicate these findings and help unravel the mechanistic pathways of GGT in the pathogenesis of dementia.

Acknowledgments

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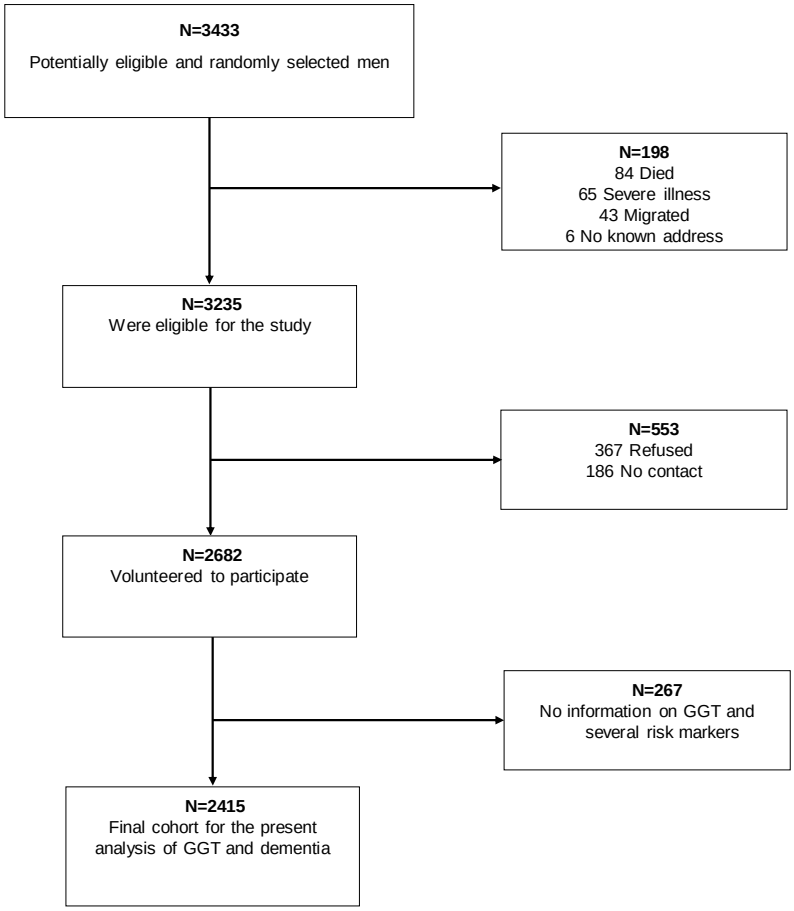
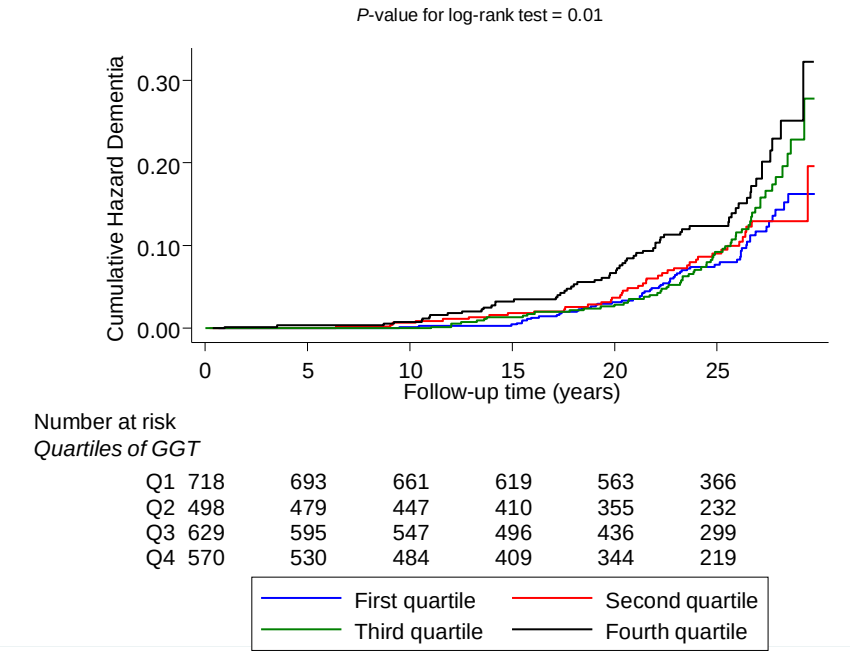
Figure Legends

Fig.1. Derivation of analytic sample



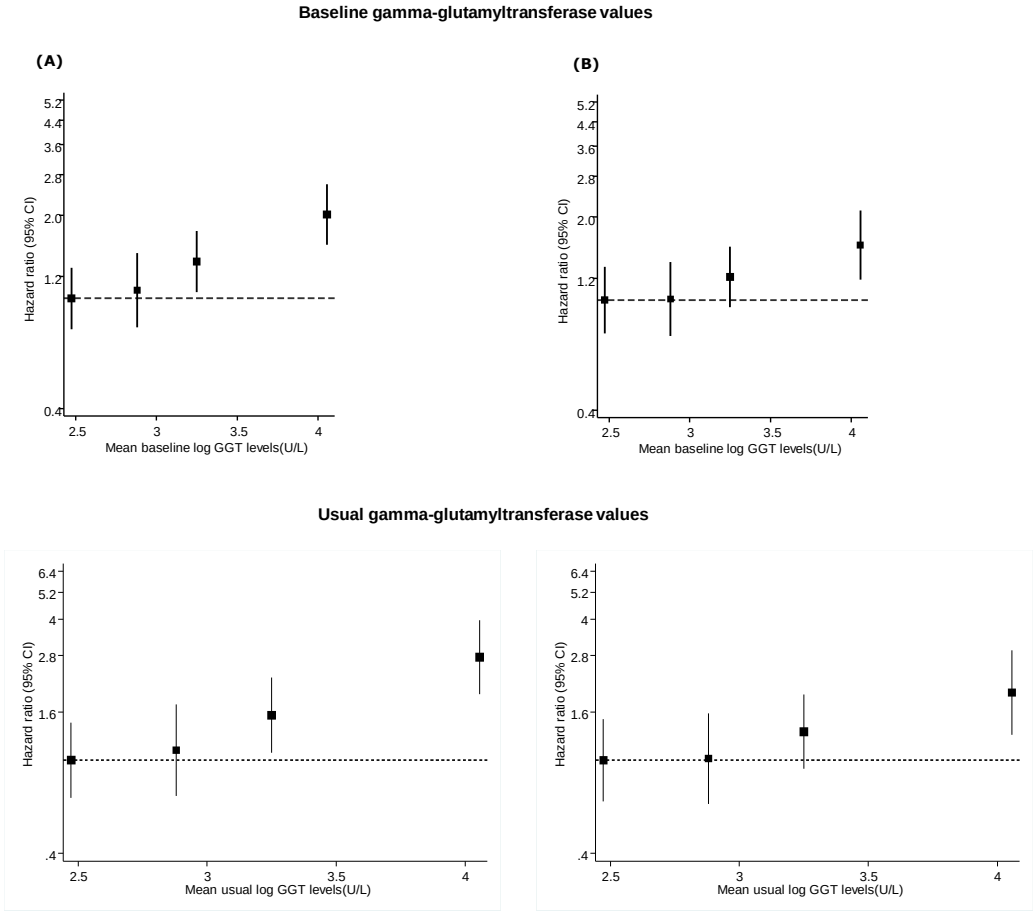
GGT, gamma-glutamyltransferase

Fig. 2. Cumulative hazard curves for dementia by quartiles of gamma-glutamyltransferase



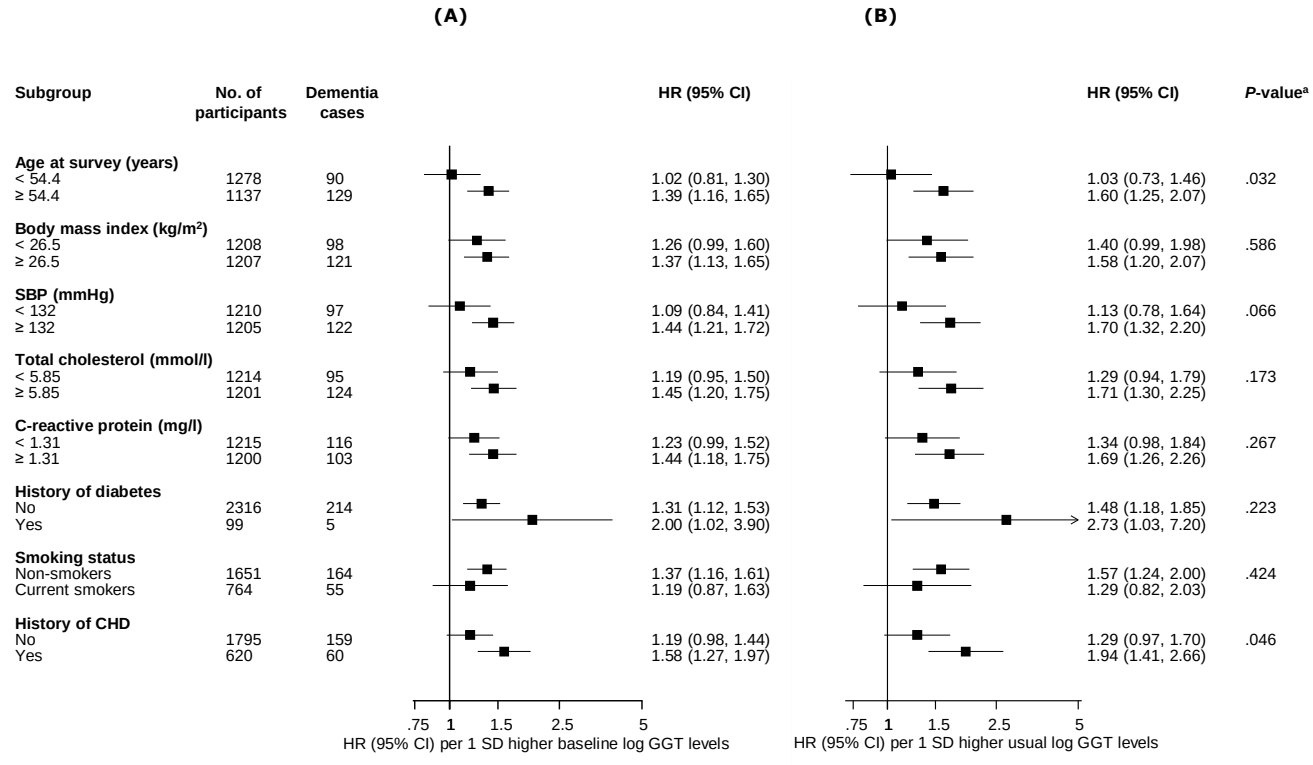
The median GGT level (IU/L) was 12.0 (range 11-14) for the lowest quartile; 18.0 (range 16-19) for the second quartile; 25.0 (range 23-29) for the third quartile; and 48 (range 40-72) for the top quartile; GGT, gamma-glutamyltransferase

Fig. 3. Hazard ratios for dementia, by quartiles of baseline and usual values of gamma-glutamyltransferase



A, adjusted for age; **B**, adjusted for age, body mass index, systolic blood pressure, history of coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity; GGT, gamma-glutamyltransferase

Fig. 4. Hazard ratios for baseline and usual values of gamma-glutamyltransferase and dementia risk by several participant level characteristics



A, baseline levels of GGT; **B**, usual levels of GGT; Hazard ratios were adjusted for age, body mass index, systolic blood pressure, history of coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity; CI, confidence interval; GGT, gamma-glutamyltransferase; HR, hazard ratio; SD, standard deviation; SBP, systolic blood pressure; *, *P*-value for interaction

Table 1. Baseline participant characteristics

	Overall (N=2415) Mean (SD) or n (%)	Without Dementia (N=2196) Mean (SD) or n (%)	With Dementia (N=219) Mean (SD) or %	*P*-value
Log_e GGT (U/L)	3.13 (0.65)	3.12 (0.64)	3.22 (0.73)	0.044
Questionnaire/Prevalent conditions				
Age at survey (years)	53.2 (5.0)	53.0 (5.1)	55.8 (3.3)	< 0.0001
Alcohol consumption (g/week)	75.6 (136.5)	74.7 (137.6)	84.1 (125.6)	0.335
History of diabetes	99 (4.1)	68 (4.1)	14 (10.3)	0.155
Current smokers	764 (31.6)	515 (31.3)	62 (45.6)	0.030
History of CHD	620 (25.7)	334 (20.3)	57 (41.9)	0.540
Use of anti-hypertensives	542 (22.4)	287 (17.5)	38 (27.9)	0.007
Medication for dyslipidemia	16 (0.7)	11 (0.7)	0 (0.0)	0.694
Physical measurements				
BMI (kg/m^2)	26.9 (3.6)	26.9 (3.6)	27.1 (3.4)	0.253
SBP (mmHg)	134 (17)	134 (17)	135 (16)	0.475
DBP (mmHg)	89 (11)	89 (11)	89 (10)	0.369
Physical activity (kj/day)	1545 (1482)	1547 (1509)	1521 (1180)	0.802
Lipid markers				
Total cholesterol (mmol/l)	5.92 (1.09)	5.89 (1.09)	6.09 (1.05)	0.015
HDL-C (mmol/l)	1.30 (0.30)	1.29 (0.30)	1.36 (0.35)	0.002
Log_e triglycerides (mmol/l)	0.12 (0.51)	0.12 (0.51)	0.13 (0.52)	0.804
Metabolic and inflammatory markers				
Fasting plasma glucose (mmol/l)	5.37 (1.28)	5.38 (1.32)	5.22 (0.85)	0.088
Serum creatinine (µmol/1)	89.6 (20.8)	89.7 (21.4)	88.6 (13.0)	0.442
Log_e CRP (mg/l)	0.34 (0.97)	0.35 (0.97)	0.26 (0.97)	0.211

BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyltransferase

HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure

Table 2. Cross-sectional correlates of gamma-glutamyltransferase

	Pearson correlation r (95% CI)†	Percentage difference (95% CI) in GGT levels per 1 SD higher or compared to reference category of correlate‡
Log_e GGT (U/L)	-	-
Questionnaire/Prevalent conditions		
Age at survey (years)	-0.03 (-0.07, 0.01)	-2% (-5, 1)
Alcohol consumption (g/week)	0.29 (0.26, 0.33)***	21% (18, 24)***
History of diabetes		
No	-	Ref
Yes	-	55% (36, 76)***
Smoking status		
Other	-	Ref
Current	-	6% (-0, 12)
History of CHD		
No	-	Ref
Yes	-	18% (12, 26)***
Use of anti-hypertensives		
No	-	Ref
Yes	-	28% (20, 36)***
Medication for dyslipidemia		
No	-	Ref
Yes	-	17% (-15, 62)
Physical measurements		
BMI (kg/m^2)	0.34 (0.31, 0.38)***	25% (22, 28)***
SBP (mmHg)	0.23 (0.19, 0.26)***	16% (13, 19)***
DBP (mmHg)	0.23 (0.19, 0.27)***	16% (13, 19)***
Physical activity (kj/day)	0.03 (-0.01, 0.07)	2% (-1, 5)***
Lipid markers		
Total cholesterol (mmol/l)	0.10 (0.06, 0.14)***	7% (4, 9)***
HDL-C (mmol/l)	-0.03 (-0.07, 0.01)	-2% (-4, 1)
Log_e triglycerides (mmol/l)	0.26 (0.22, 0.30)***	19% (16, 22)***
Metabolic and inflammatory markers		
Fasting plasma glucose (mmol/l)	0.20 (0.16, 0.24)***	14% (11, 17)***
Serum creatinine (µmol/1)	-0.00 (-0.04, 0.04)	-0% (-3, 3)
Log_e C-reactive protein (mg/l)	0.26 (0.23, 0.30)***	19% (16, 22)***

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; GGT, gamma-glutamyltransferase; SD, standard deviation; SBP, systolic blood pressure; asterisks indicate the level of statistical significance: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$, †Pearson correlation coefficients between log_e GGT and the row variables; ‡, Percentage change in GGT levels per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean GGT levels for the category versus the reference) adjusted for age

Table 3. Associations of baseline and usual values of gamma-glutamyltransferase with dementia

	Events/Total	Model 1		Model 2		Model 3		Model 4	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Baseline GGT									
Per 1 SD increase in $\log_e$ GGT	219 / 2415	1.44 (1.26 to 1.65)	< 0.001	1.32 (1.14 to 1.55)	< 0.001	1.33 (1.14 to 1.55)	< 0.001	1.33 (1.14 to 1.55)	< 0.001
Quartile 1	59 / 718	Ref		Ref		Ref		Ref	
Quartile 2	40 / 498	1.07 (0.72 to 1.60)	0.742	1.01 (0.67 to 1.52)	0.962	1.01 (0.67 to 1.53)	0.949	1.00 (0.66 to 1.51)	0.991
Quartile 3	59 / 629	1.36 (0.95 to 0.95)	0.098	1.21 (0.83 to 1.76)	0.313	1.22 (0.84 to 1.77)	0.306	1.21 (0.83 to 1.77)	0.319
Quartile 4	61 / 570	2.01 (1.40 to 2.88)	< 0.001	1.58 (1.05 to 2.37)	0.027	1.59 (1.06 to 2.39)	0.027	1.58 (1.05 to 2.38)	0.030
Usual GGT									
Per 1 SD increase in $\log_e$ GGT	219 / 2415	1.70 (1.40 to 2.07)	< 0.001	1.51 (1.21 to 1.88)	< 0.001	1.52 (1.22 to 1.89)	< 0.001	1.51 (1.21 to 1.89)	< 0.001
Quartile 1	59 / 718	Ref		Ref		Ref		Ref	
Quartile 2	40 / 498	1.10 (0.61 to 1.99)	0.742	1.01 (0.56 to 1.85)	0.962	1.02 (0.56 to 1.87)	0.949	1.00 (0.55 to 1.82)	0.991
Quartile 3	59 / 629	1.57 (0.92 to 2.67)	0.098	1.33 (0.77 to 2.30)	0.313	1.34 (0.77 to 2.32)	0.306	1.32 (0.76 to 2.28)	0.319
Quartile 4	61 / 570	2.79 (1.65 to 4.74)	< 0.001	1.96 (1.08 to 3.56)	0.027	1.98 (1.08 to 3.61)	0.027	1.93 (1.07 to 3.50)	0.030

GGT, gamma-glutamyltransferase; 1 standard deviation higher $\log_e$ GGT was approximately equivalent to two-fold higher GGT levels.
Model 1: Adjusted for age
Model 2: Model 1 plus body mass index, systolic blood pressure, history of coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity
Model 3: Model 2 plus C-reactive protein
Model 4: Model 3 plus incident coronary heart disease as a time-dependent covariate

Table 4. Hazard ratios for dementia with exclusion of first five years of follow-up, participants with GGT values greater than three times the upper limit of normal, and participants with potential fatty liver disease

	Events/Total	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Excluding the first five years of follow-up	217 / 2297	1.42 (1.24 to 1.63)	< 0.001	1.31 (1.12 to 1.53)	0.001	1.32 (1.13 to 1.54)	< 0.001	1.31 (1.13 TO 1.54)	0.001
Excluding participants with GGT values greater than three times the upper limit of normal	218 / 2414	1.41 (1.23 to 1.63)	< 0.001	1.30 (1.11 to 1.53)	0.001	1.31 (1.12 to 1.53)	0.001	1.30 (1.11 to 1.53)	0.001
Excluding participants with potential fatty liver disease	217 / 2404	1.44 (1.25 to 1.65)	< 0.001	1.32 (1.14 to 1.54)	< 0.001	1.33 (1.14 to 1.55)	< 0.001	1.33 (1.14 to 1.55)	< 0.001

GGT, gamma-glutamyltransferase; hazard ratios were modelled per 1 standard deviation higher $\log_e$ GGT (approximately equivalent to two-fold higher GGT levels)
Model 1: Adjusted for age
Model 2: Model 1 plus body mass index, systolic blood pressure, history of coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity
Model 3: Model 2 plus C-reactive protein
Model 4: Model 3 plus incident coronary heart disease as a time-dependent covariate

Table 5. Associations of baseline and usual values of gamma-glutamyltransferase with Alzheimer's disease

	Events/Total	Model 1		Model 2		Model 3		Model 4	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Baseline GGT									
Per 1 SD increase in $\log_e$ GGT	132 / 2415	1.34 (1.11 to 1.60)	0.002	1.22 (0.99 to 1.50)	0.061	1.24 (1.01 to 1.53)	0.042	1.24 (1.01 to 1.53)	0.045
Quartile 1	41 / 718	Ref		Ref		Ref		Ref	
Quartile 2	21 / 498	0.80 (0.47 to 1.36)	0.412	0.74 (0.43 to 1.26)	0.261	0.76 (0.44 to 1.29)	0.308	0.75 (0.44 to 1.28)	0.288
Quartile 3	37 / 629	1.22 (0.78 to 1.90)	0.383	1.05 (0.66 to 1.67)	0.828	1.08 (0.68 to 1.73)	0.735	1.08 (0.68 to 1.72)	0.748
Quartile 4	33 / 570	1.60 (1.01 to 2.54)	0.045	1.20 (0.71 to 2.02)	0.487	1.25 (0.74 to 2.11)	0.408	1.24 (0.73 to 2.09)	0.428
Usual GGT									
Per 1 SD increase in $\log_e$ GGT	132 / 2415	1.52 (1.17 to 1.98)	0.002	1.33 (0.99 to 1.80)	0.061	1.37 (1.01 to 1.85)	0.042	1.37 (1.01 to 1.85)	0.045
Quartile 1	41 / 718	Ref		Ref		Ref		Ref	
Quartile 2	21 / 498	0.72 (0.33 to 1.57)	0.412	0.64 (0.29 to 1.40)	0.261	0.66 (0.30 to 1.46)	0.308	0.65 (0.30 to 1.43)	0.288
Quartile 3	37 / 629	1.34 (0.70 to 2.58)	0.383	1.08 (0.55 to 2.13)	0.828	1.13 (0.57 to 2.24)	0.735	1.12 (0.57 to 2.20)	0.748
Quartile 4	33 / 570	2.00 (1.02 to 3.93)	0.045	1.31 (0.61 to 2.82)	0.487	1.39 (0.64 to 3.00)	0.408	1.36 (0.63 to 2.92)	0.428

GGT, gamma-glutamyltransferase; 1 standard deviation higher $\log_e$ GGT was approximately equivalent to two-fold higher GGT levels.
Model 1: Adjusted for age
Model 2: Model 1 plus body mass index, systolic blood pressure, history of coronary heart disease, smoking status, history of diabetes, use of medications (antihypertensive agents and lipid-lowering drugs), total cholesterol, high-density lipoprotein cholesterol, alcohol consumption, socio-economic status, and physical activity
Model 3: Model 2 plus C-reactive protein
Model 4: Model 3 plus incident coronary heart disease as a time-dependent covariate