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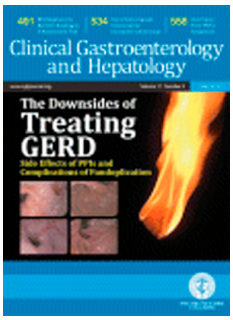
Published in:
Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association

DOI:
10.1016/j.cgh.2018.01.034

Publication date:
2018

Document version:
Accepted manuscript

Accepted Manuscript



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PII: S1542-3565(18)30103-4
DOI: 10.1016/j.cgh.2018.01.034
Reference: YJCGH 55670

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 21 January 2018

Please cite this article as: Wod M, Hallas J, Andersen K, García Rodríguez LA, Christensen K, Gaist D, Lack of Association Between Proton Pump Inhibitor Use and Cognitive Decline, *Clinical Gastroenterology and Hepatology* (2018), doi: 10.1016/j.cgh.2018.01.034.

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Running head: Proton pump inhibitors and cognitive decline

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Grant support: DG is partially supported by the Odense University Hospital.

Abbreviations: BMI: body mass index; DTR: Danish Twin Registry; H_2RA: Histamine-2 receptor antagonists; LSADT: Longitudinal Study of Aging Danish Twins; MADT: Middle-Aged Danish Twin study; PPI: proton pump inhibitors

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Disclosures: MW, KA, and KC reported no conflicts of interest. JH has participated in projects funded by Takeda with money payed to his employer. LAGR works for CEIFE, which has received funding from Bayer AG and AstraZeneca for research work unrelated to this project; LAGR has also received honoraria for serving on advisory boards for Bayer AG. DG reported receiving honoraria from AstraZeneca (Sweden) for participation as a coinvestigator on a research project.

Writing assistance: None.

Author contributions:

Study concept: DG.

Study design: MW, JH, KA, LAGR, KC, DG.

Acquisition of data: MW, KC and DG.

Analysis and interpretation of data: MW, JH, KA, LAGR, KC, DG.

Drafting of the manuscript: MW and DG.

Critical revision of the manuscript for important intellectual content: MW, JH, KA, LAGR, KC, DG.

Obtained funding: The project was carried out without funding.

Study supervision: DG.

Words (incl. figure/table legends, and references): 3,979 (max 4,000)

ABSTRACT

Background & Aims: Studies of association between use of proton pump inhibitors (PPI) and dementia have yielded conflicting results. We investigated the effects of PPIs on cognitive decline in a study of middle-aged and elderly twins in Denmark.

Methods: In a prospective study, we collected data from surveys of middle-aged individuals (46–67 years old; the Middle Aged Danish Twin study) and older individuals (the Longitudinal Study of Aging Danish Twins) who underwent cognitive assessments (a 5-component test battery) over a 10-year period (middle-age study, n=2346) or a 2-year period (longitudinal study of aging: n=2475). We determined cumulative use of PPIs 2 years prior study enrollment and during follow up, in defined daily doses (DDDs) of PPIs, using data from a nationwide prescription register. Multi-variable linear regression models were used to examine associations between cumulative PPI use and a composite score of cognitive function at baseline and decreases in scores during the follow-up periods.

Results: Use of PPIs before study enrollment was associated with a slightly lower mean cognitive score at baseline in the middle age study. The adjusted difference in mean score of individuals with high consumption of PPIs (≥400 DDD) was lower than that of non-users in the middle-age study (mean crude score for high PPI use, 43.4±13.1 vs for non-use, 46.8±10.2; adjusted difference of 0.69 points; 95% CI, –4.98 to 3.61). In the longitudinal study of aging twins, individuals with high consumption of PPI had higher adjusted scores than non-users (mean crude score for high PPI use, 35.2±10.8 vs for non-use, 36.2±11.1; adjusted difference of 0.95 points; 95% CI, –1.88 to 3.79). In analyses of cognitive decline, among individuals with high consumption of PPIs in the longitudinal study of aging, the adjusted mean difference between baseline score and follow-up score was lower than that of non-users (mean crude score for high PPI use at baseline, 36.6±10.1 and at follow up, 34.3±12.3 vs for non-use at baseline, 38.1±10.5 and at follow up, 37.6±11.3; adjusted difference of 1.22 points; 95% CI, –3.73 to 1.29). In the middle-age study, users with the highest consumption of PPIs (≥1600 DDD) had slightly less cognitive decline than non-users (baseline mean crude score for high PPI use, 43.4±10.1 and follow-up mean crude score, 41.3±9.7 vs baseline score of

49.1±10.2 for non-users and follow-up score of 46.3±9.9 for non-users; adjusted difference of 0.94 points; 95% CI, –1.63 to 3.50). No stated differences in scores between PPI users and non-users were significant.

Conclusion: In analyzing data from 2 large population-based studies of twins in Denmark, we found no association between PPI use and cognitive decline.

KEY WORDS: acid-related diseases; side-effects; treatment; epidemiology

INTRODUCTION

Proton pump inhibitors (PPI) are a class of drugs commonly used in the treatment of gastroesophageal reflux disease and the healing and prevention of gastroduodenal ulcers. PPI use has increased markedly in recent years.[1,2] In Denmark, 7.4% of all adults used PPIs in 2014.[2] The findings of two studies in Germany of a potential association between PPI use and increased risk of dementia[3,4] gave rise to concern,[5] particularly as these drugs are more frequently used among older individuals, where the risk of dementia is high. Although preclinical data lend some support to the hypothesis of a detrimental effect of PPI on cognition, e.g, through influencing β-amyloid levels in the brains of mice,[6] the evidence is equivocal.[7] To date, the results of epidemiological studies have also been inconclusive, with more recent studies pointing towards a null association between PPI use and dementia.[8,9] Current knowledge on the relationship between long-term PPI use and cognitive function, a predictor of the risk of dementia in later life,[10] is scant.[11] To investigate the association of long-term PPI use on changes in cognitive function over time, we utilized prospectively collected data from two large cohort studies conducted in Denmark where cognition was repeatedly assessed by trained interviewers , and information on PPI use was ascertained through a nationwide prescription register. As the cohorts were recruited among Danish twins, we also investigated the association between PPI use and cognition among twin-pairs discordant with regard to cognitive decline –a powerful design to study the effects of non-genetic and non-common environment exposures.[12]

METHODS

For the purposes of this study, we linked data from surveys of Danish twins with nationwide register data as described in the following. The study was approved by the Danish Data Protection Agency and Statistics Denmark's Scientific Board. According to Danish law, approval from an ethics board and informed consent are not required for register studies.

Study Population and Data Linkage

The individuals in this study were identified among 9045 twins who participated in one of two population-based nationwide cohorts: The Longitudinal Study of Aging Danish Twins[13] (LSADT) and the Middle Age

Danish Twin study[14] (MADT). Both studies were conducted through the nationwide Danish Twin Registry (DTR), which has covered all twin cohorts in the country since 1870.[15] Each survey comprised multidimensional interviews conducted by trained interviewers. All participants provided informed consent, and the Danish Scientific Ethics Committees approved both studies.

For each twin participating in LSADT, we used survey information from baseline (biannual waves, 1997-2005) and the 2 year follow-up. For MADT participants, we used information collected at baseline in 1998 and at follow-up 10 years later. For further details, see **Supplementary Material**.

Data from DTR were linked with information from population-based registers at Statistics Denmark. This included information from the Danish National Prescription Register (Prescription Registry),[16] which holds information on all prescriptions for drugs dispensed at Danish community pharmacies since 1995 (see **Supplemental Material**).[16]

Assesment of Exposure to PPI

We used Prescription Register data to ascertain use of PPI among the twins. Each individuals cumulative use of PPI was calculated in defined daily doses[17] (DDD) as detailed in the Supplemental Material. Some PPIs are available without prescription in Denmark, but over-the-counter sales account for only 2% of the total volume.[18]

Assesment of cognitive functioning

Cognitive functioning at baseline and follow-up was assessed by a five-component test battery. The test included: a fluency test (number of animals named in one minute), forward digit span, backward digit span, immediate and delayed recall of a 12-item list. Based on this information a composite cognitive score was calculated as a *T*-score by standardising each single test to the mean and standard deviation of the values of the 45-49 year olds into a composite cognitive score, which was then linearly transformed to have a mean of 50 and a standard deviation of 10 in the youngest age group. This score has been used in a series of studies, and has been shown to be a valid, reliable and very age-sensitive measure of cognitive functioning with high internal consistency reliability.[19–21]

Co-variates

Self-reported and register-based data were used to classify participants with regard to a number of disorders, and drug use patterns as listed in the statistical analyses section, and detailed in the **Supplementary Methods** and **Supplementary Figure 1**.

Statistical analysis

Descriptive statistics were expressed as means (standard deviations) or medians (interquartile range) for continuous variables and numbers and proportions for categorical variables.

We performed analyses for the overall cohorts (individual-based analyses), and for twin pairs where both twins in a pair participated (within-pair analyses). In each of these approaches we assessed the association between PPI use and cognitive functioning in cross-sectional analyses and in longitudinal analyses.

Individual-based analyses

Comparisons of cognitive scores and PPI use were performed using multivariate linear regression. Outcome was cognitive score at baseline in cross-sectional analyses, and change in cognitive score from baseline to follow-up in the longitudinal analyses; negative values for each of these outcomes was indicative of participants on PPI attaining lower cognitive scores than non-users of PPI. All models were adjusted for age, sex, body mass index (BMI), smoking, alcohol use, education level, history of depression, neurological disorders (stroke, epilepsy, Parkinson's disease), thyroid disorders, hypertension, diabetes, use of drugs with possible acute effects on cognition (strong analgesics, anxiolytic, antipsychotic drugs, or antidepressants), and use of statins, oral steroids, postmenopausal hormone replacement therapy (HRT), low-dose aspirin, or nonsteroidal anti-inflammatory drugs as well as ever use of H_2RA. We adjusted for twin pair cluster effects (correlations) in all models in order to get unbiased confidence intervals. Cross-sectional analyses were also performed as stratified by age at baseline visit for both cohorts (below or above median age).

We performed supplementary analyses and tested for dose-response trend as outlined in the Supplementary Methods. Finally, prompted by recent reports,[11] we assessed the correlation between H_2RA use and cognitive function in separate post hoc analyses with this class of drugs as the main exposure adjusted for potential

confounders as described above and with the addition of PPI use (ever use (1+ prescriptions) vs. never use (0 prescriptions)) to the model.

Within-pair analyses

Depending on zygosity, twins share 50% (dizygotic) to 100% (monozygotic) of their genetic material. To adjust for genetic and shared environmental confounding, we performed intrapair analyses limited to same sex pairs in which at least one of the twins had received PPI during follow up. Among these twins we calculated the proportion (and corresponding 95% CI using the binomial distribution) of pairs in which the co-twin with the higher cumulative dose of PPI had the lowest cognitive score (cross-sectional analyses). For corresponding longitudinal analyses, we calculated the proportion of pairs with the largest decline in cognitive score. The null-hypothesis in all analyses was a proportion of pairs of 50%. The within-pair analyses are further detailed in the **Supplemental Material**.

Data were analysed using STATA (Version 13.1).

RESULTS

In all, baseline data on 7878 twins (MADT: n=4314; LSADT: n=3615) were available for cross-sectional analyses and 4821 participants for follow-up analyses (MADT: n=2346, LSADT: n=2475) (Fig. 1). Median age at baseline interview for MADT and LSADT were 56.6 (IQR 51.3-63.3) years and 75.4 (IQR 73.0-80.6) years, respectively. Cognitive scores did not differ between men and women in LSADT (36.1±11.1) versus 35.9±11.0); *P* >0.05) (**Supplementary Table 2**). In the MADT, men had lower cognitive score than women (46.0±10.2) versus 47.5±10.1); *P*<0.001). The cognitive scores of participants at baseline varied across strata of age in a predictable manner (**Supplementary Table 3**). A total of 262 (6%) of MADT twins and 299 (8.3%) of LSADT twins had used PPI in the 2-year period prior to baseline. Compared with non-exposed twins, participants with prebaseline use of PPI were slightly younger, did not differ in sex distribution, had attained a lower education level, and had slightly lower unadjusted mean composite cognitive scores at baseline in LSADT (34.5 vs 36.1; *P* <0.05), but not in MADT (45.6 vs 46.8; *P*>0.05) (Table 1). In general, participants with prebaseline PPI use had a higher prevalence of comorbidities, and a more frequent use of

medications other than PPI suggesting PPI users had a worse general health background status, compared with twins with no PPI use in the 2-year period prior to baseline.

Cross-sectional analyses of cognitive score

Individual-based analyses

In MADT cohort, the adjusted difference in mean score of individuals with high prebaseline consumption of PPIs (≥400 DDD) was lower than that of non-users (mean crude score for high PPI use, 43.4±13.1 vs for non-use, 46.8±10.2; adjusted difference of 0.69 points; 95% CI, –4.98 to 3.61). In LSADT cohort, individuals with high prebaseline PPI consumption had higher adjusted scores than non-users (mean crude score for high PPI use, 35.2±10.8 vs for non-use, 36.2±11.1; adjusted difference of 0.95 points; 95% CI, –1.88 to 3.79). Overall, cumulative dose of PPI within two years before baseline participation did not influence attained composite cognitive scores in either cohort, i.e., LSADT, or MADT (Table 2). An exception, was a statistically significant difference in cognitive score among twins participating in LSADT who had been exposed to cumulative doses of 1-99 DDD of PPI and had lower cognitive scores compared with non-exposed twins (cognitive score difference -2.04; 95%CI, -3.51 to -0.56); this difference was slightly more pronounced among older twins (age ≥75.4 years: -3.15; 95%CI, -5.27 to -1.04). Composite cognitive scores for MADT participants in the younger group (<56.5 years) with cumulative dose of PPI of 200-399 DDD were also lower compared with the non-exposed reference group (mean difference in cognitive score: -6.79; 95% CI,
-10.38 to -3.19), albeit this measure was based on small numbers (n=6). Tests for trend were statistically non-significant (LSADT: $P = 0.23$; MADT: $P = 0.16$).

Within-pair analyses

There were 2693 intact twin pairs (i.e., both twins in pair participated) with data on cognitive score at baseline – of these 2083 were same sex pairs and 1800 of them did not differ with regard to PPI drug exposure, leaving 283 pairs for baseline intra-pair analyses (MADT: 146 pairs; LSADT: 137 pairs). Cumulative PPI use in the 2-year period prior to baseline did not influence cognitive score testing among twin pairs participating in LSADT, as measured by the proportion of twin pairs in which the twin exposed to

higher cumulative PPI dose at baseline also was the twin with the lowest composite cognitive score (79 of 137 pairs, 58%; 95%CI, 49% to 66%; *P* = 0.087). However, this result was influenced by increasing the magnitude of intrapair difference in cognitive score, particularly so for the top 25% (26 of 34 pairs, 76%; 95%CI, 59% to 89%; *P* = 0.003) (**Figure 2, panel A**). Corresponding analyses for MADT showed no material influence of cumulative PPI exposure on differences in cognitive score testing of the twin-pairs (proportions: overall 54%; 95%CI, 46% to 62%, *P* = 0.36; top 25%: 39%; 95%CI, 23% to 57%), *P* = 0.24) (**Figure 2, panel B**). Note that all of the above estimates were adjusted for age, and sex by design, and not for other variables included in the individual-based analyses.

Longitudinal analyses of decline in cognitive score

Individual-based analyses

Compared with the reference group, minor differences were observed in the difference in cognitive score in the twins exposed to PPI in the 2-year follow-up in LSADT, and none of these were statistically significant (Table 3). Among individuals with high consumption of PPIs in LSADT, the adjusted mean difference between baseline score and follow-up score was lower than that of non-users (mean crude score for high PPI use at baseline, 36.6±10.1 and at follow up, 34.3±12.3 vs for non-use at baseline, 38.1±10.5 and at follow up, 37.6±11.3; adjusted difference of 1.22 points; 95% CI, –3.73 to 1.29). In MADT, decline in cognitive scores of individuals exposed to PPI in the 10-year follow-up period was less pronounced from that of non-exposed individuals in all but one stratum (i.e., cumulative PPI dose of 800 DDD; adjusted delta-difference -1.69; 95%CI, -4.47 to 1.10). In MADT, users with the highest consumption of PPIs (≥1600 DDD) had slightly less cognitive decline than non-users (mean crude score for high PPI use at baseline 43.4±10.1 and at follow-up, 41.3±9.7 vs for non-use at baseline, 49.1±10.2 and at follow-up, 46.3±9.9; adjusted difference of 0.94 points; 95% CI, –1.63 to 3.50). Tests for trend were statistically non-significant (LSADT: *P* = 0.26; MADT: *P* = 0.20).

Within-pair analyses

Out of a total of 1296 intact twin pairs with data on cognitive score at baseline and follow-up, 1071 pairs were same sex; of these 743 pairs did not differ with regard to cumulative PPI exposure in the follow-up period. Thus, a total of 328 pairs were included in the follow-up within-pair analyses (MADT: 224; LSADT: 104).

The proportion of twin pairs in which the twin exposed to higher cumulative PPI dose at baseline also was the twin with the largest decline in composite cognitive score did not differ significantly from 50% (null hypothesis) (53 of 104 pairs, 51%; 95%CI, 41% to 61%; $P = 0.92$). Corresponding analyses restricted to twin pairs with differences in cognitive score belonging to the top 25% did not materially influence the proportion (11 of 26 pairs, 42%; 95%CI, 23% to 63%; $P = 0.56$) (**Figure 3, panel A**). Similar results were found in MADT (overall: 111 of 224 pairs, 50%; 95%CI, 43% to 56%, $P = 0.94$; top 25% with highest difference in cognitive score: 29 of 56 pairs, 52%; 95%CI, 38% to 65%, $P = 0.89$) (**Figure 3, panel B**). Supplementary analyses including pairs with more marked discordance with regard to PPI use (i.e., ≥100 DDD of PPI in 2-year follow-up in LSADT, and ≥500 DDD of PPI in 10-year MADT period) did not materially affect results on cognitive decline (**Supplementary Figure 2**). In analyses restricted to monozygotic twin pairs, the proportion of pairs where the twin exposed to the higher PPI dose also was the twin with largest decline in composite cognitive score was not higher than expected according to the null hypothesis (**Supplementary Figure 3**). Results of supplementary analyses are presented in Supplementary Material.

DISCUSSION

This study is the first to examine the association between long-term PPI use and cognitive decline in a population-based setting. Cognitive scores of more than 7,800 middle-aged and older Danish twins at baseline did not indicate an association with previous PPI use. Follow-up data on more than 4000 of these twins did not indicate that use of this class of drugs was correlated to cognitive decline. These findings were supported by results of within pairs analyses of twins discordant for cognitive scores (baseline) or cognitive decline (follow-up). The magnitude of estimates did not indicate any important association with cognitive function as measured through the composite score, and none of our adjusted estimates reported a statistically significant effect in the longitudinal analyses. In addition, there did not seem to be a clear dose-response

effect in any analyses. Overall, the results of this study do not indicate that long-term PPI use correlates with risk for cognitive decline.

The findings of two studies in Germany that suggested a possible link between PPI use and increased risk for dementia,[3,4] have not been replicated in other studies. Another study from Germany, based on primary care data reported a null association between PPI use and risk of dementia,[22] as did a more recent nationwide study from Finland, where PPI use of community-dwelling newly diagnosed patients with Alzheimer's dementia was compared to that of general population controls.[9] A follow-up study from the USA found that subjects taking PPIs on a regular or intermittent basis were slightly less likely to be diagnosed with mild cognitive impairment, or dementia, compared with non-users of PPIs.[8] The relationship of long-term PPI use with cognition has received less attention. A recent study, based on 13864 participants in the Nurse's Health Study, reported a null association between long-term PPI use and cognitive function assessed at a single point in time.[11] The present study results are in line with those from this US study and expand current knowledge on the relationship of PPI use and cognition after evaluating for the first time the lack of association between long-term use of PPPs and cognitive decline.

H_2RA use has also been reported to impact on cognition. While an early report raised the possibility of a protective effect of H_2RA use on risk of Alzheimer's dementia,[23] subsequent studies did not confirm it.[24–26] Lochhead et al recently reported poorer cognitive function associated with increasing duration of regular H_2RA.[11] Smaller cohort studies predating the publication from the Nurse's Health Study[11] reported increased incident cognitive impairment and cognitive decline among users of H_2RA, compared with non-users of these drugs.[27,28] In the present large study, we performed analyses on H_2RA use post hoc, prompted by the findings of a recent study.[11] Further, H_2RA use steeply declined in Denmark the past 18 years, as it has been largely replaced by use of PPIs. During the same period, H_2RA drugs have increasingly been purchased over the counter (OTC),[18] and information on these transactions is not available in the prescription registry. Yet, as expenses towards prescribed H_2RA are partially reimbursed in Denmark, we believe that chronic H_2RA use is likely captured by the prescription registry. However, these potential shortcomings should be born in mind, when assessing our finding of a lack of association between H_2RA use and cognitive decline.

This study has a number of strengths. We used a prescription registry to ascertain drug exposure, which eliminated recall bias. Importantly, for the years covered by the present study, the registry holds information on virtually all (98%) of PPI sold in Denmark.[18] Cognitive assessment at several points in time, enabling a valid measurement of cognitive decline over time, was performed by trained interviewers and based on a battery of recognized tests frequently utilized in epidemiological studies. By recruiting participants in a population-based setting we reduced selection forces faced by clinic-based studies. We were able to adjust for multiple confounders, including life-style, and education –information frequently not included in register-based studies on PPI use and dementia risk. As participants were twins, we could perform within-pair comparisons that provided control of genes and common intrauterine and childhood environment factors, factors that may influence cognitive decline.

A number of potential limitations need to be considered. While participation at baseline was generally high (≥70%), the participation rate in the follow-up of MADT was lower (62%). This finding may be associated with MADT follow-up being performed at research centres (i.e., involving transport), while all other study evaluations were performed at participants' homes. While we cannot rule out some degree of selection in study participation (particularly in MADT follow-up), we believe its impact on our findings to be minor. The follow-up wave of LSADT was performed 2 years after baseline, a time-frame that minimized concerns regarding attrition of the cohort, e.g., due to poor health, but, conversely, may have been too short to sufficiently capture long-term declining cognitive trajectories among elderly twins. Our prescription register data were left-censored, corresponding to the creation of the prescription register we used (1995). The impact of this on assessment of pre-baseline cumulative PPI use is probably negligible, as use of this class of drugs prior to 1995 was limited in Denmark.[18] In spite of these efforts, we cannot preclude the influence of insufficiently measured or unmeasured confounders on our results.

Conclusion

We conclude that there was no association between chronic PPI use and cognitive score or cognitive decline in this large population-based study of middle-aged and older twins Danish twins.

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LEGENDS

Figure 1. Flow-chart of selection of twins for study participation.

Figure 2. Baseline within-pair analysis. Proportion of pairs where the twin exposed to higher cumulative proton pump inhibitor dose at baseline also had lower cognitive score. Proportion estimates above 0.5 (red line) compatible with proton pump inhibitor use associated with larger decline in cognitive function. Proportions calculated for all twin pairs and stratified by the magnitude of intrapair difference in cognitive score; note that the strata are not mutually exclusive. *P*-values above each estimate.

Figure 3. Longitudinal within-pair analysis. Proportion of pairs where the twin exposed to higher cumulative proton pump inhibitor dose during follow-up declined more in cognitive score compared with co-twin. Proportion estimates above 0.5 (red line) compatible with proton pump inhibitor use associated with larger decline in cognitive function.
Proportions calculated for all twin pairs and stratified by the magnitude of intrapair difference in cognitive score; note that the strata are not mutually exclusive. *P*-values above each estimate.

Table 1. Baseline characteristics of study participants by prebaseline proton pump inhibitor use.

	LSADT-cohort		MADT-cohort	
	No PPI use	PPI use	No PPI use	PPI use
	n=3316	n=299	n=4001	n=262
Age, median (IQR) y	75.5 (72.5-80.3)	74.6 (71.9-79.5)	58.0 (52.4-63.2)	56.5 (51.2-62.3)
Men – no.(%)	1400 (42.2)	117 (39.1)	2039 (50.9)	136 (51.9)
Cognitive score, mean±SD	36.1±11.1	34.5±10.6	46.8±10.2	45.6±10.0
Education level[a] – no.(%)				
Low	1213 (36.7)	121 (40.6)	2096 (52.4)	148 (56.5)
Medium	1962 (59.4)	169 (56.7)	1421 (35.5)	86 (32.8)
High	128 (3.9)	8 (2.7)	484 (12.1)	28 (10.7)
Smoker[b] – no.(%)				
Current	1010 (30.6)	82 (27.5)	1592(39.8)	102 (38.9)
Former	1197 (36.2)	121 (40.6)	1028(25.7)	87 (33.2)
Never	1097 (33.2)	95 (31.9)	1379(34.48)	73 (27.9)
Alcohol[c], drinks per week – no.(%)				
0	1428 (43.7)	147 (50.3)	736 (18.5)	61 (23.4)
1-20	1623 (49.7)	127 (43.5)	2829 (70.9)	169 (64.8)
>21	214 (6.6)	18 (6.2)	423 (10.6)	31 (11.9)
Medical disorders[d] – no. (%)				
Depression	61 (1.1)	15 (5.0)	52 (1.3)	8 (3.1)
Neurological[e]	179 (8.0)	29 (9.7)	88 (2.2)	12 (4.6)
Thyroid	179 (2.4)	16 (5.4)	104 (2.6)	3 (1.1)
Hypertension	1526 (44.2)	187 (62.5)	839 (21)	93 (35.5)
Diabetes	220 (7.4)	25 (8.4)	116 (2.9)	9 (3.4)
Medication use[f] – no.(%)				
Histamine-2 receptor antagonists[g]	258 (0.1)	100 (0.3)	249 (0.1)	93 (0.4)
Low-dose aspirin[f]	742 (24.9)	92 (30.8)	225 (5.6)	36 (13.7)
Non-aspirin NSAIDs[f]	1964 (51.7)	221 (73.9)	2247 (56.2)	201 (76.7)

Statins[f]	89 (3.4)	10 (3.3)	91 (2.3)	12 (4.6)
Hormonal replacement therapy[f]	337 (0.3)	54 (18.1)	652 (16.3)	69 (26.3)
Oral Steroids[f]	455 (15)	62 (20.7)	419 (10.5)	55 (21)
Strong analgesics[f]	250 (5.1)	51 (17.1)	151 (3.8)	26 (9.9)
Antipsychotic drugs[f]	113 (2.4)	20 (6.7)	53 (1.3)	8 (3.1)
Benzodiazepines[f]	336 (6.3)	58 (19.4)	207 (5.2)	46 (17.6)
Hypnotics & sedatives[f]	566 (10.3)	68 (22.7)	204 (5.1)	25 (9.5)
Antidepressants	194 (4.3)	40 (13.4)	165 (4.1)	25 (9.5)

Abbreviations: IQR, interquartile range; LSADT, Longitudinal Study of Aging Danish Twins; MADT, Middle-aged Danish Twin study NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; PPI: proton pump inhibitor; SD, standard deviation.

[a]Information on educational level was missing in 14 subjects participating in LSADT and none in MADT.
[b]Information on smoking habits was missing in 13 subjects participating in LSADT and 2 in MADT.
[c]Information on alcohol use was missing in 58 subjects participating in LSADT and 14 in MADT.
[d]Physician diagnosed.
[e]Epilepsy, stroke, or Parkinson's disease.
[f]Defined as at least one filled prescription for the drug in question in the 2-year period preceding baseline.
[g]Defined as at least one filled prescription at any time preceding baseline (data available from 1995 onwards).

Table 2. Difference in mean composite cognitive score at baseline of individuals exposed to proton pump inhibitors compared with non-exposed individuals in two cohorts of Danish twins. Negative values indicate that exposed individuals attained lower cognitive scores than non-exposed individuals.

LSADT-cohort		Total		< 75.4[a] years		≥ 75.4[a] years
Cumulative dose of PPI[b], DDD	n	Cognitive score difference (95% CI)[c]	n	Cognitive score difference (95% CI)[c]	n	Cognitive score difference (95% CI)[c]
0	3316	Reference[d]	1639	Reference[d]	1677	Reference[d]
1-99	185	-2.04 (-3.51;-0.56)	100	-1.25 (-3.27;0.78)	85	-3.15 (-5.27;-1.04)
100-199	34	-0.26 (-3.44;2.91)	23	-0.62 (-4.58;3.35)	11	0.70 (-4.68;6.08)
200-399	36	-1.61 (-4.3;1.07)	19	-2.2 (-5.73;1.32)	17	-0.79 (-4.87;3.29)
≥400	44	0.95 (-1.88;3.79)	26	1.16 (-3.01;5.33)	18	-0.15 (-3.89;3.59)
MADT-cohort		Total		< 56.5* years		≥ 56.5* years
Cumulative dose of PPI[b], DDD	n	Cognitive score difference (95% CI)[c]	n	Cognitive score difference (95% CI)[c]	n	Cognitive score difference (95% CI)[c]
0 (reference)	4001	Reference[d]	2023	Reference[d]	1978	Reference[d]
1-99	173	0.84 (-0.53;2.22)	76	0.43 (-1.77;2.63)	97	1.12 (-0.62;2.87)
100-199	39	-2.15 (-4.78;0.49)	15	-3.44 (-7.31;0.43)	24	-1.19 (-4.73;2.35)
200-399	22	-3.03 (-6.2;0.13)	6	-6.79 (-10.38;-3.19)	16	-1.38 (-5.26;2.5)
≥400	28	-0.69 (-4.98;3.61)	11	-0.85 (-7.79;6.09)	17	-0.45 (-5.94;5.05)

Abbreviations: DDD, defined daily dose; LSADT, Longitudinal Study of Aging Danish Twins; MADT, Middle-aged Danish Twin study; PPI, proton pump inhibitor.

[a]Median age at baseline for entire cohort as cut-off value.

[b]Calculated according to prescription register data for 2 year period preceding baseline.

[c]Adjusted for age, sex, education level, body mass index, smoking, alcohol use, physician diagnosed history of depression, neurological disorders (stroke, epilepsy, Parkinson's disease), thyroid disorders, hypertension, diabetes and, based on prescription register data (6-month period prior to baseline); use of statins, oral steroids, hormone replacement therapy, low-dose aspirin, nonsteroidal anti-inflammatory drug and medications that may impair cognition (strong analgesics, anxiolytic, antipsychotic drugs, or antidepressants) and ever use of histamine-2 receptor antagonists. The inference was adjusted for twin pair cluster effects.

[d]Mean±SD cognitive scores for the reference groups:
LSADT: <75.4 years: 39.2±10.6; ≥75.4 years: 32.8±10.6; MADT: <56.5 years: 48.6±10.2; ≥56.5 years: 44.9±9.8.

Table3. Decline in composite cognitive score during follow-up for individuals exposed to proton pump inhibitors compared to non-exposed individuals. Negative values indicate that exposed individuals had larger decline in cognitive score than non-exposed individuals.

LSADT-cohort		Δdifference in cognitive score[a] (95% CI)	
Cumulative dose of PPI[b] during follow-up, DDD	N	Unadjusted	Adjusted[c]
0	2210	Reference[d]	Reference
1-99	147	-0.93(-2.4;0.53)	-0.36(-1.83;1.1)
100-199	29	1.26(-2.18;4.69)	1.10(-2.54;4.74)
200-399	42	1.05(-1.24;3.33)	1.38(-1.04;3.8)
≥400	47	-1.84(-4.33;0.66)	-1.22(-3.73;1.29)
MADT-cohort		Δdifference in cognitive score (95% CI)	
Cumulative dose of PPI[b] during follow-up, DDD	N	Unadjusted	Adjusted[c]
0	1727	Reference[e]	Reference
1-99	322	-0.63(-1.66;0.39)	0.16(-1.05;1.37)
100-199	75	-0.52(-2.32;1.28)	0.48(-1.79;2.75)
200-399	65	-0.27(-2.22;1.68)	0.87(-1.4;3.13)
400-799	55	-0.62(-2.91;1.66)	1.13(-1.59;3.84)
800-1,599	51	-2.67(-5.08;-0.26)	-1.69(-4.47;1.1)
≥1,600	51	0.66(-1.54;2.87)	0.94(-1.63;3.5)

Abbreviations: DDD, defined daily dose; LSADT, Longitudinal Study of Aging Danish Twins; MADT, Middle-aged Danish Twin study; PPI, proton pump inhibitor.

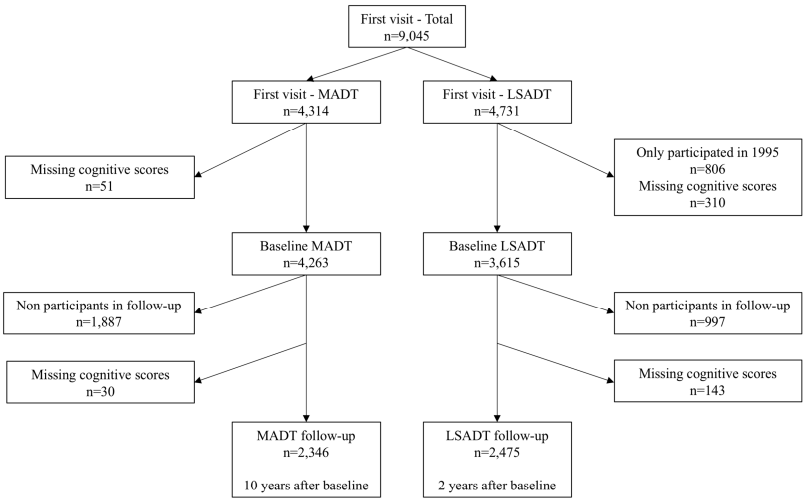
[a]The decline observed in subjects not exposed to PPI during follow-up has been subtracted (Δdifference in cognitive score); follow-up took place 2 years after intake for LSADT and after 10 years for MADT.

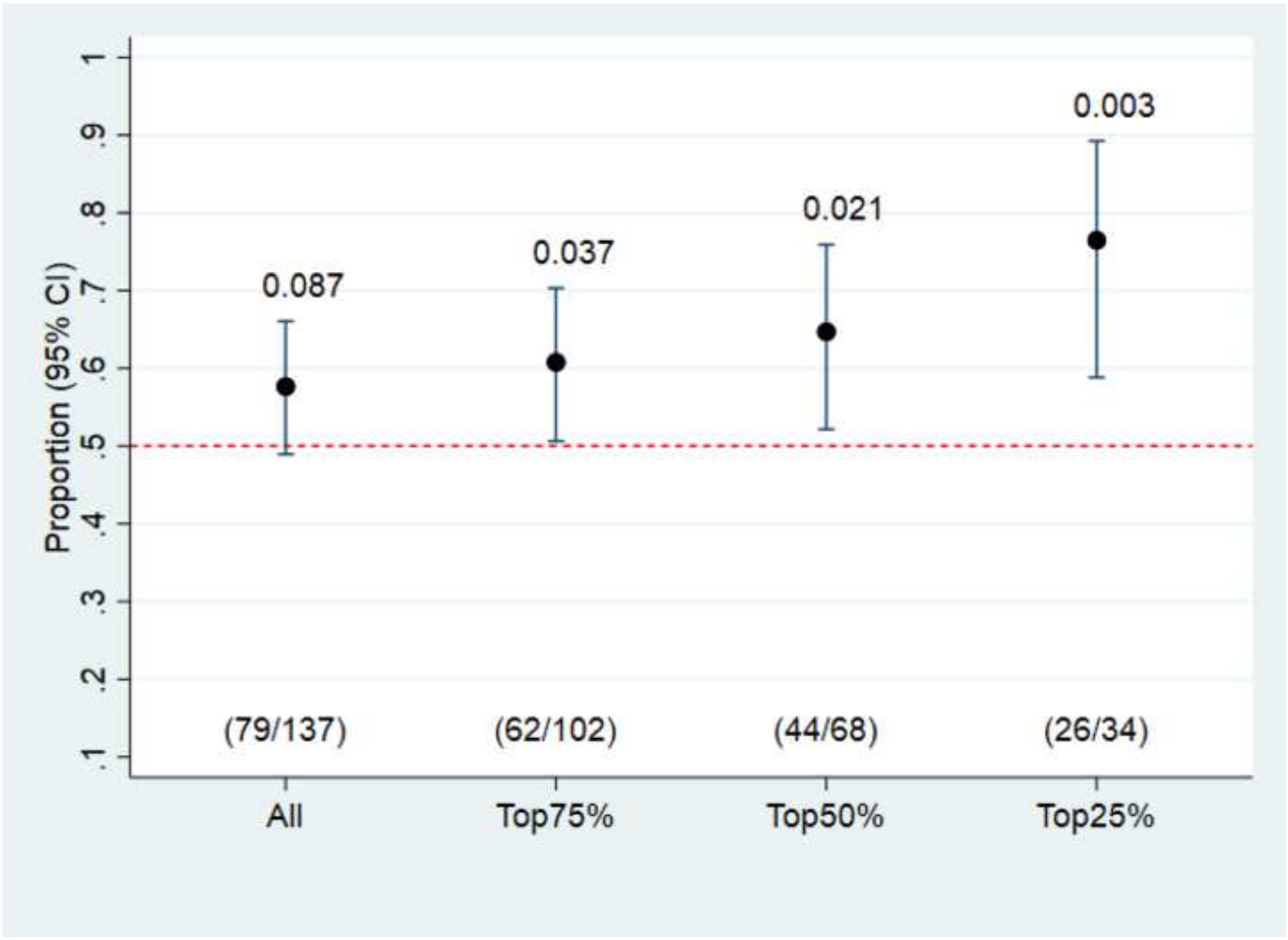
[b]Calculated based on prescription register data.

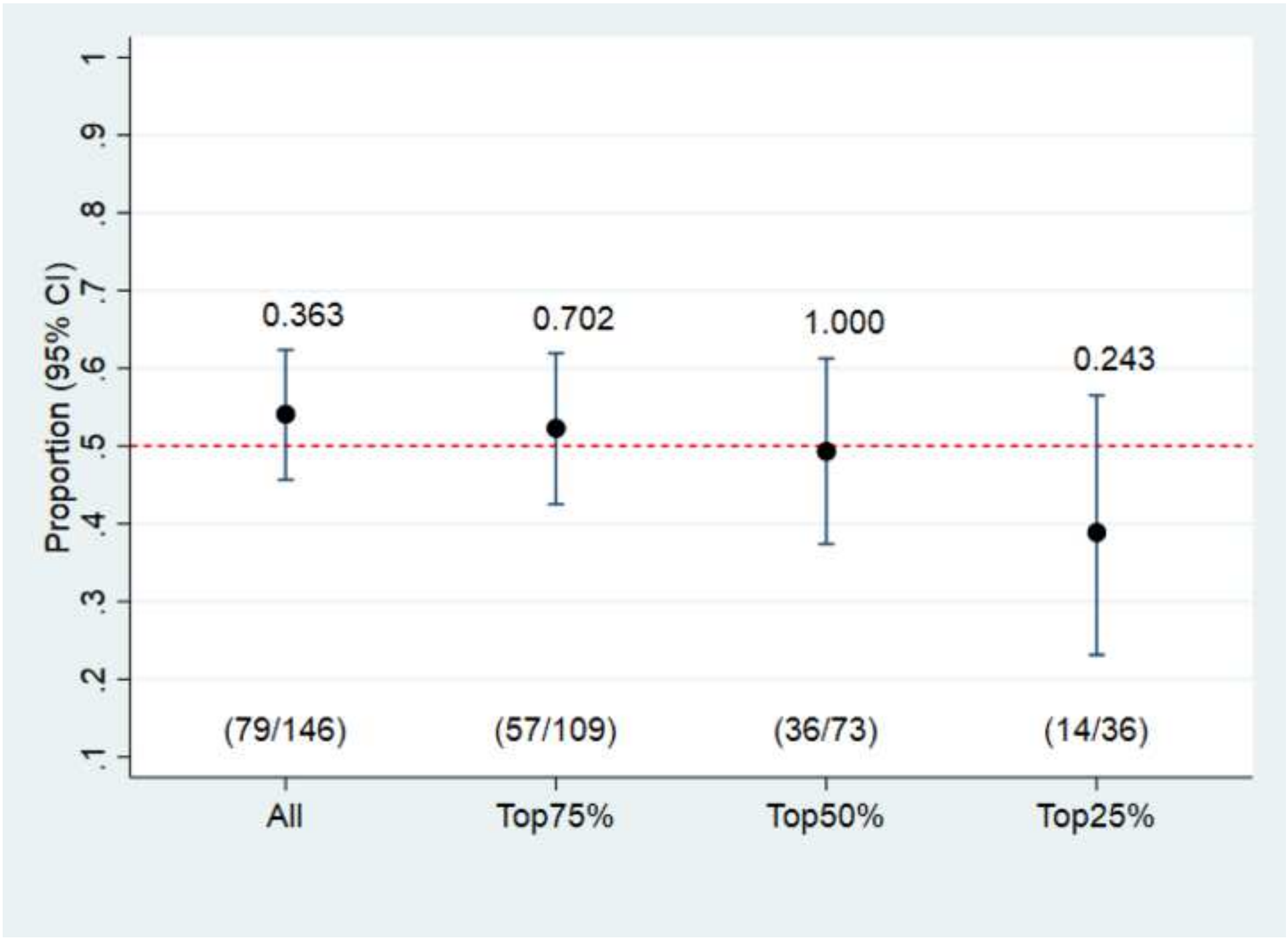
[c]Adjusted for age, sex, education level, body mass index, smoking, alcohol use, physician diagnosed history of depression, neurological disorders (stroke, epilepsy, Parkinson's disease), thyroid disorders, hypertension, diabetes and based on prescription register data, use of medication with possible chronic effect (statins, oral steroids, hormone replacement therapy, low-dose aspirin, nonsteroidal anti-inflammatory drugs) (<>500DDD during follow-up) and medications that may impair cognitive function (6-month period prior to intake) (strong analgesics, anxiolytic, antipsychotic drugs, or antidepressants) and ever use of histamine-2 receptor antagonists. The inference was adjusted for twin pair cluster effects.

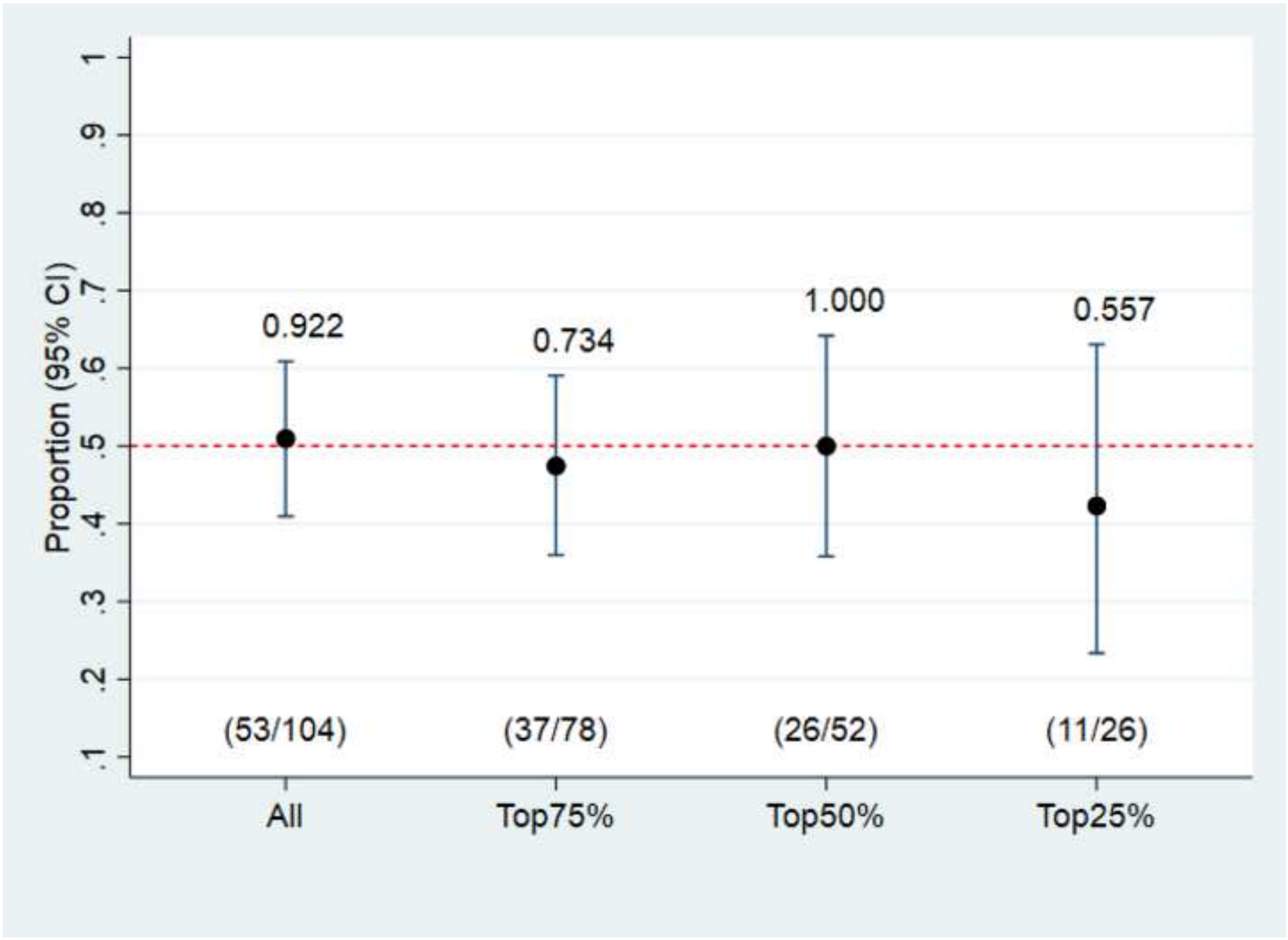
[d]Difference in unadjusted cognitive score between baseline and follow-up after 2 years in twins not exposed to proton pump inhibitors, LSADT: -0.52 (95% CI, -0.85;-0.19).

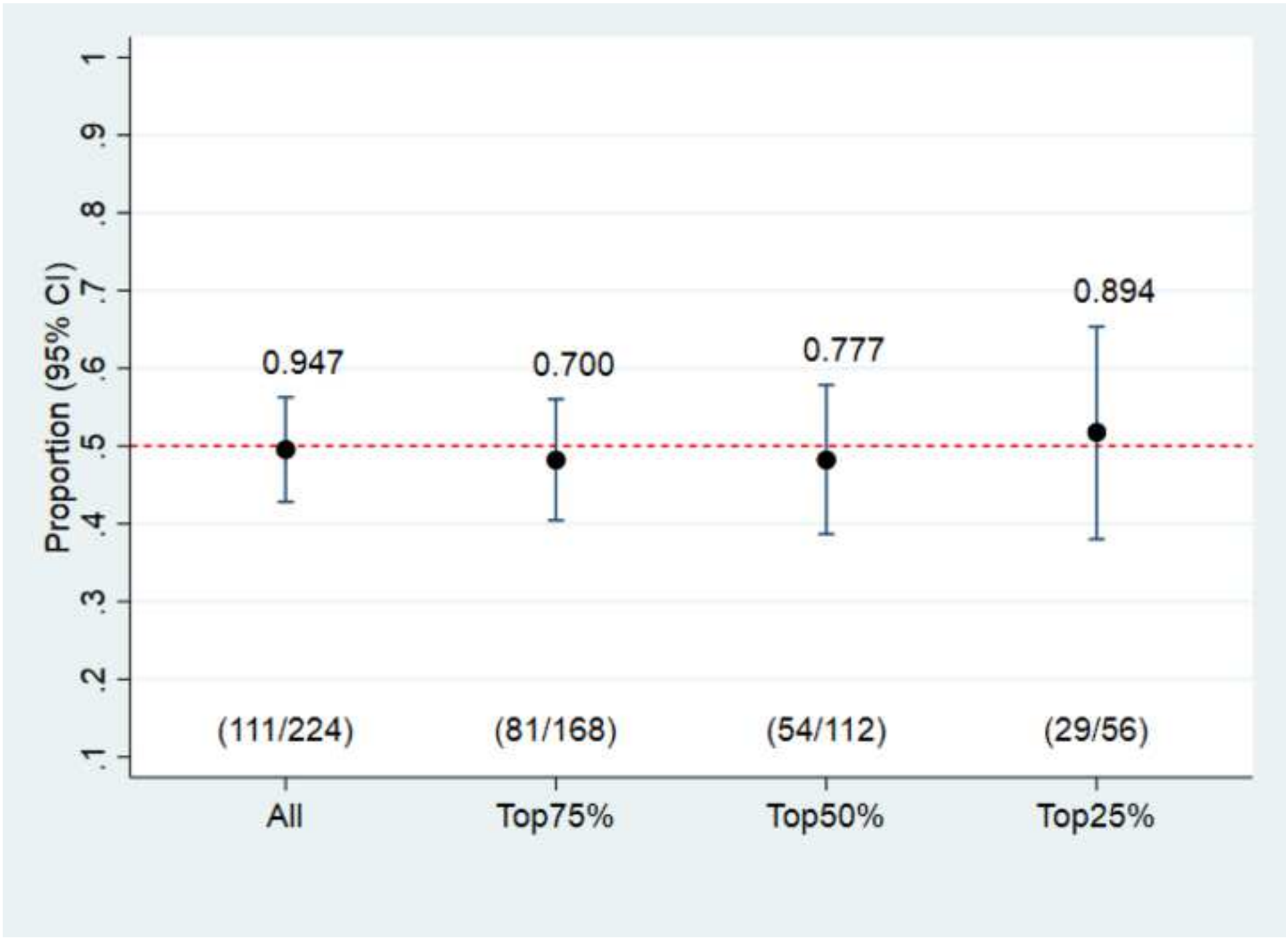
[e]Difference in unadjusted cognitive score between baseline and follow-up after 10 years in twins not exposed to proton pump inhibitors, MADT: -2.80 (95% CI, -3.19;-2.41).




Proportion (95% CI)
.1
.2
.3
.4
.5
.6
.7
.8
.9
1
0.087
0.037
0.021
0.003
(79/137)
(62/102)
(44/68)
(26/34)
All
Top75%
Top50%
Top25%


Proportion (95% CI)
.1
.2
.3
.4
.5
.6
.7
.8
.9
1
0.363
0.702
1.000
0.243
(79/146)
(57/109)
(36/73)
(14/36)
All
Top75%
Top50%
Top25%


Proportion (95% CI)
.1
.2
.3
.4
.5
.6
.7
.8
.9
1
0.922
0.734
1.000
0.557
(53/104)
(37/78)
(26/52)
(11/26)
All
Top75%
Top50%
Top25%


Proportion (95% CI)
.1
.2
.3
.4
.5
.6
.7
.8
.9
1
0.947
0.700
0.777
0.894
(111/224)
(81/168)
(54/112)
(29/56)
All
Top75%
Top50%
Top25%