# Association between alcohol consumption and telomere length

Jianqiang Li, Yu Guan and Xi Xu

Faculty of Information Technology,
Beijing University of Technology,
Beijing, 100124, China
and
Beijing Engineering Research Center for IoT Software and Systems,
Beijing, 100124, China
Email: lijianqiang@bjut.edu.cn
Email: guanyu0010@126.com
Email: gcaxuxi@163.com

Yan Pei*

School of Computer Science and Engineering,
The University of Aizu,
Aizuwakamatsu, 965-8580, Japan
Email: peiyan@u-aizu.ac.jp
*Corresponding author

Jason C. Hung

Department of Computer Science and Information Engineering,
National Taichung University of Science and Technology,
Taichung, Taiwan
Email: jhung@nutc.edu.tw

Weiliang Qiu

Channing Division of Network Medicine,
Brigham and Women's Hospital/Harvard Medical School,
Boston, MA 02115, USA
Email: stwxq@channing.harvard.edu

**Abstract:** Both telomere length and alcohol consumption have an important impact on biological age and carcinogenesis. Researchers have conducted many efforts to study the relationship between alcohol consumption and telomere length yet reached no consensus. In this paper, a meta-analysis is performed and relevant investigation results from previous literature are integrated. Twenty-one works of literature published between 2000 and 2016, which comprise 27 analyses with a total samples' size of 35,891, meet our screening conditions. Whether the relationship between alcohol consumption and telomere length is significant, this issue varies with

study type (cohort, case-control, or cross-sectional) and study population (Europe, Asia, American, or Australia). It is deduced by combined evidence that alcohol consumption is associated with telomere length (with Fisher's combined p-value = 3.52E-8 and Liptak's weighted p-value = 8.24E-3). In the future, the consistent standardised quantifications of alcohol consumption and telomere length will avail further aggregation of the evidence from various studies.

**Keywords:** age; alcoholism; cancer; meta-analysis; mitotic clock; telomere length; AC-TL; chromosome; apoptotic mechanism; telomere shortening; oxidation source; behavioural exposure.

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**Biographical notes:** Jianqiang Li received his BS in Mechatronics from the Beijing Institute of Technology, Beijing, China, in 1996, and MS and PhD in Control Science and Engineering from the Tsinghua University, Beijing, China in 2001 and 2004, respectively. He worked as a researcher in the Digital Enterprise Research Institute, National University of Ireland, Galway in 2004–2005. He worked in NEC Labs China as a researcher between 2005–2013 and in Department of Computer Science, Stanford University, as a Visiting Scholar in 2009–2010. He joined Beijing University of Technology, Beijing, China, in 2013. His research interests are in data mining, information retrieval, semantic web and big data. He has over 40 publications including one book, 10+ journal papers, and 37 international patent applications (19 of them have been granted in China, USA or Japan). He served as a PC members in multiple international conferences and organised the IEEE workshop on medical computing.

Yu Guan received her BS in Information Security from the Beijing University of Technology in 2016. Currently, she is a PhD student at the Faculty of Information Technology, Beijing University of Technology. Her research interests are big data and data mining applied to medical area.

Xi Xu received his BS from the Anhui University of Science and Technology in 2016, and MS from the Faculty of Information Technology, Beijing University of Technology in 2019. Currenlty, he is a PhD student at the Faculty of Information Technology, Beijing University of Technology. His research interests include data mining and machine learning, especially weakly supervised learning applied in medical field.

Yan Pei received his BE and ME from the Northeastern University, Shenyang, and PhD in Engineering from the Kyushu University, Fukuoka, Japan. He was a software engineer and the software project manager of Chinese and German IT industries for several years before entering academic society. He is currently working as an Associate Professor with the University of Aizu. His research interests include evolutionary computation, machine learning, and software engineering. He serves as the Chair and an organising committee member for many international conferences sponsored by the IEEE, ACM, and other international associations. He is also serving as an editor for

many international journals. He received several awards such as the Best Paper Awards from the ICGEC 2012, FC 2018, and FC 2019. He is a senior member of the IEEE SMC, IEEE CIS, and the Japanese Society for Evolutionary Computation.

Jason C. Hung is an Associate Professor of Department of Computer Science and Information Engineering at the National Taichung University of Science and Technology, Taiwan. His research interests include multimedia system, e-learning, affective computing, artificial intelligence and social computing. He received his BS and MS in Computer Science and Information Engineering from the Tamkang University, in 1996 and 1998, respectively. He also received his PhD in Computer Science and Information Engineering from the Tamkang University in 2001. He participated in many international academic activities, including the organisation of many international conferences. He is the Founder of International Conference on Frontier Computing. He served as the Vice Chair of IET Taipei LN. In 2014, he was elected as a Fellow of the Institution of Engineering and Technology (FIET). He was elected as the Vice Chair of IET Taipei LN in November 2014. From June 2015, he is the Editor-in-Chief of *International Journal of Cognitive Performance Support*.

Weiliang Qiu graduated from the University of British Columbia, Vancouver, BC, Canada and he received his Doctor of Statistics in 2004. He worked as an Assistant Professor at the Harvard Medical School and an Associate Biostatistician at the Channing Division of Network Medicine, Brigham and Women's Hospital from 2013 to 2018. His research interests include cluster analysis for genomic data analysis based on a mixture of Bayesian hierarchical models and the integration of different types of omics data with environmental information and lifestyle information for disease prevention, diagnosis, treatment, and prognosis. He has published more than 85 peer-reviewed papers.

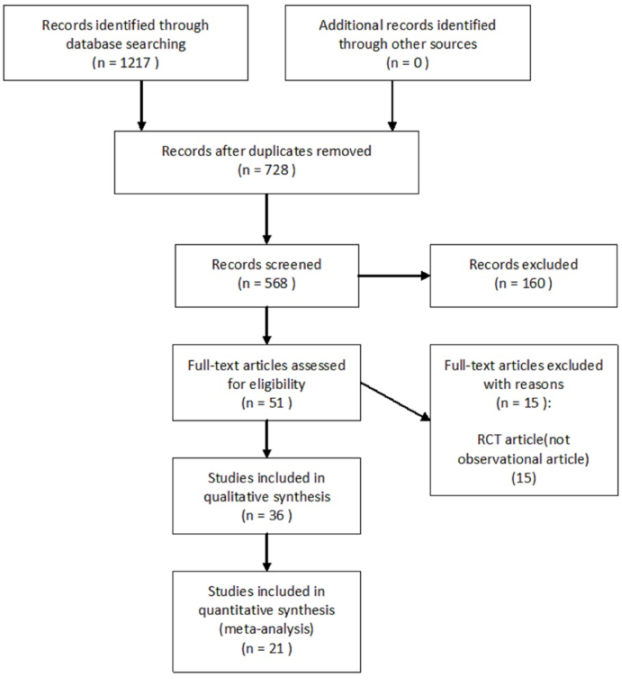
## 1 Introduction

Telomeres are the particular parts that locate at the end of both tails of the chromosome, which protect the ends from deterioration or fusion with neighbouring chromosomes (Raffa and Cenci, 2015; Wong and Collins, 2003). Those tails will become shorten during cell replications with time passing (Wong and Collins, 2003). The chromosomes will obtain unstable meanwhile the apoptotic mechanism will be activated by the cells immediately and the viability will be lost as soon as the telomere length (TL) is shortened to the critical length (Hayashi et al., 2015). The TL is therefore called as the 'mitotic clock' of the cell's lifespan since it reveals the cell's history of copy as well as the potential of replication (Wong and Collins, 2003). Defects in TL are associated with certain age-related diseases, cancers, and premature ageing syndromes (Blasco, 2005). Telomere shortening is known for having a probability that leads to genomic instability during the initial stage of tumorigenesis (Londono-Vallejo, 2008).

Despite that telomere shortening is natural in ageing, it is influenced by many other elements, such as paternal age at birth, ethnicity, gender, age, telomere maintenance

genes, and genetic mutations of telomere (Zglinicki et al., 2003). Mechanisms, such as inflammation and oxidative stress, can accelerate the telomere shortening process (Zglinicki et al., 2003). The TL is impacted by environmental, psychosocial, behavioural exposures and so on (Ornish et al., 2013). Being an oxidation source and a behavioural exposure (Wu and Cederbaum, 2006), alcohol exposure, or should we say, alcohol consumption (AC), therefore brings up an interesting subject about the investigation of its effect on TL.

**Figure 1** The flowchart of study selection




Notes: There were 1,217 records identified at the beginning and 21 studies were eligible after all the screenings.

Being one of the most global used recreational drugs, the International Agency for Research on Cancer (IARC) classified alcoholic drinks to be carcinogenic to humans, i.e., a group 1 carcinogen (Secretan et al., 2009). IARC identified AC as a cause of cancers of the pharynx, oral cavity, oesophagus, liver, larynx, colorectal, female breast, and as a probable cause of pancreatic cancer (Secretan et al., 2009; Bagnardi et al., 2015; Smyth et al., 2015). An estimation made by the World Health Organization reported that as of 2010 number of worldwide alcoholism reached 208 million (UNDESA, 2013). From the aspect of public health, AC is not only one of the top-three risk factor in the world, but also the greatest one in middle-income countries, which constitute nearly half of the world's population (World Health Organization, 2014). Moreover, AC deeply affects a person's life expectancy and it can prominently shorten itself by around ten years (Schuckit, 2014). Researchers have already made many efforts on this subject, but have not reached any consensus on association between the AC and the TL. Some researches indicated it to be significantly inverse (Pavanello et al., 2011; Aida

et al., 2011; Strandberg et al., 2012), i.e., the more alcohol consumed, the shorter TL. Some research works revealed it to be significantly positive. For instance, Liu et al. (2009) noticed the TL was significantly longer in ever drinkers compared to that in never drinkers for controls of gastric cancer in a paper published in 2009. Later, they illustrated the same association in hepatocellular carcinoma (HCC) patients in a paper published in Liu et al. (2011). Besides these research works, a few pieces of research discovered that there was not any association between AC and TL.

In this paper, a meta-analysis is conducted to facilitate the AC-TL association investigation. Through the initial database search, 1,217 records were identified. After eliminating duplicate records and conducting three rounds of screening, 21 articles published between 2000 and 2016 (including 27 analyses, with a total of 35,891 samples) met the screening criteria. The relevant information of 21 articles is extracted and analysed statistically. We calculated Fisher's combined p-value and Liptak's weighted p-value (weighted by sample size) and found a significant association between AC and TL (Fisher's combined p-value = 3.52E-8; Liptak's combined p-value = 8.24E-3). We identified two factors affecting the significance of the AC-TL association: study type (cohort study, case-control study, or cross-sectional study) and study population (American, Asian, Australian, or European). To the best of our knowledge, the present study is the first meta-analysis to aggregate evidence about the AC-TL association. We also expect the AC-TL association to be different among never drinkers, moderate drinkers, and heavy drinkers. However, inconsistent quantification of AC hinders the evaluation. In future studies of the AC-TL association, consistent quantifications of AC and TL are desired.

The rest of the paper is structured as follows. In Section 2 methods, we present the literature search strategy, selection criteria and the statistical analysis that we applied. In Section 3 results, the information obtained by the methods is introduced and the statistical analysis results are demonstrated. In Section 4 discussion and conclusions, some other interesting observations are discussed, besides, contributions and limitations of our work as well as potential future research directions are also discussed.

## 2 Methods

### *2.1 Literature search strategy and selection criteria*

This meta-analysis study provides a comprehensive account of investigation meanwhile systematic search of ten scientific databases. They include Nature, Google Scholar, Science Direct, PubMed, Wiley-Blackwell, Science Online, ProQuest, Chongqing VIP (http://lib.cqvip.com/), CNKI (Chinese National Knowledge Infrastructure, http://www.cnki.net/, https://en.wikipedia.org/wiki/CNKI), and Baidu Scholar (http://xueshu.baidu.com/). The last three are Chinese research databases among them. As a selection criterion, an article must meet the basic requirements as written in English or Chinese, full-text available, published or at least in the press between January 2000 and December 2016. Hence, the AC effect on health is generally manifested after a long period while randomised controlled trial, i.e., randomised clinical trials (RCTs) are mostly performed in a rather short period. Our focus will be only on observational studies in this meta-analysis.

### 2.2 First round of selection

In the selection of round one, we fix our keywords to be ‘telomere’, ‘alcohol’, and ‘ethanol’, while query scope is solely limited to title and abstract. That is, if it was detected in an abstract or a title of either the set (‘ethanol’ and ‘telomere’) or the set (‘alcohol’ and ‘telomere’), this paper will be selected in the next step.

### 2.3 Second round of selection

During the selection of round two, we firstly retain papers that are full-text available and then exclude those did not even mention anything between AC and TL. The remaining ones are further grouped according to the original studies’ types: observational study or random clinical trial.

### 2.4 Third round of selection

RCT studies are excluded in consideration of the fact that it generally takes a long period for the AC effect to be manifested on health, while RCTs are mostly performed in rather a short period. Papers with low document quality are simultaneously excluded in this third round of selection.

It is indispensable to evaluate the quality of documents before processing any data though criteria vary according to the type of article. For the quality of case-control studies and cohort studies, Newcastle-Ottawa Quality Assessment Scale (NOS) (Stang, 2010) is applied. For that of cross-sectional studies, the 11-item checklist that was suggested by the Agency for Healthcare Research and Quality (AHRQ) is adopted. When a study is evaluated by NOS scale, no more than one point for each numbered item can be stored within the categories of exposure (for case-control studies), selection and outcome (for cohort studies), and no more than two points for the category of comparability. The range of the NOS score is zero to nine (Stang, 2010). As stated in the AHRQ checklist, if an item was answered ‘YES’, the score of it is ‘1’; if ‘UNCLEAR’ or ‘NO’, then ‘0’. Article quality is assessed as follows: articles that are marked as 0–3 is assessed as low quality, 4–7 as moderate-quality, and 8–11 as high quality, respectively (Hu et al., 2015).

Particular test criteria are required for these three types of studies for passing the third round of selection. A cross-sectional study needs to have AHRQ $\geq$ 7, while a case-control study or a cohort study needs to have NOS scale $\geq$ 6. In Figure 1, we illustrate the procedure of study selection.

### 2.5 Extraction of relevant information

Twenty one articles pass all the selection steps and are screened out for further analysis. Information that is extracted for the current meta-analysis is as following: type of the study (cross-sectional, case-control, or cohort), whether the AC-TL association is significant (test statistics and p-values), country of the participants, ethnicity, age, sample size, gender, the population source, statistical models of the study, quantification of AC, as well as quantification of TL.

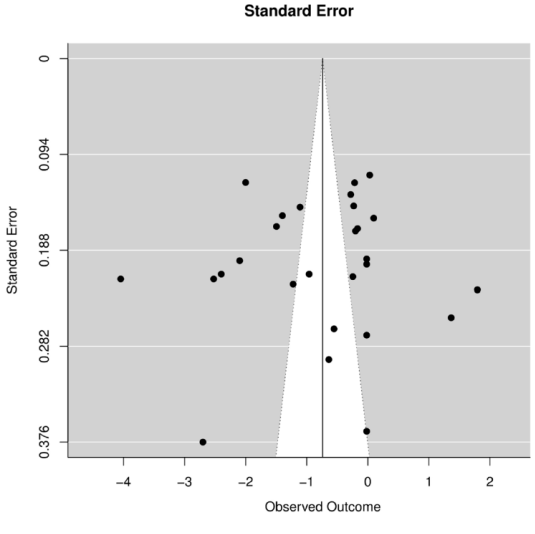
### 2.6 Classification of analyses

When a study compares TL between two different types of AC groups (e.g., social drinkers and alcoholics), it is marked as a case-control study. When it tests the association between baseline-measured AC and TL measured at the end of the follow-up, or when it tests the association between baseline-measured TL and TL measured at the end of the follow-up, it is regarded as a cohort study. When it evaluates the association between continuous AC and TL that both measured at the same time (e.g., at the end of follow-up or at baseline), it is labelled as a cross-sectional study.

### 2.7 Statistical analysis

Meta-analysis acts as the standard approach to integrating independent researches evidence (DerSimonian and Laird, 1986), in which the evidence was pooled by using individual studies' weighted average test statistics. Nevertheless, applicable test statistics are still challenging to get for our present meta-analysis. In our included resource studies, separate statistical models according to distinct types are applied to test for the AC-TL association. We adopt general linear regression and t-test in case-control studies. We employ general linear regression and correlation analysis in the cohort and cross-sectional studies.

**Figure 2** Funnel plot of surrogate effect size and surrogate standard error




Note: The roughly symmetric funnel plot indicates no publication bias.

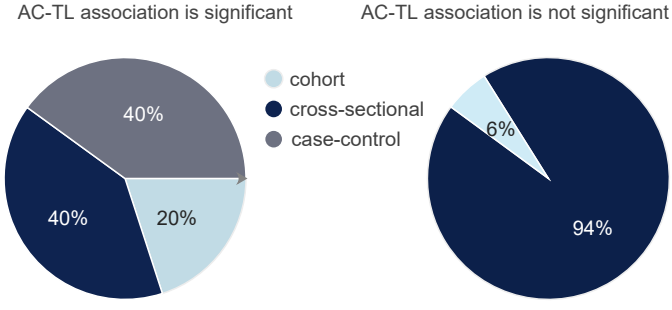
AC was sometimes considered to be a continuous variable in certain studies while otherwise to be categorical variables with diverse categorisations (e.g., four-, three-, or two-categories). The definitions of categories may still be diverse even if the number of categories is identical. For instance, one study defined three categories as 0–1, 2–4, >4 drink-units/day (Pavanello et al., 2011) while another defined three categories as 0, 1–19, ≥20 gram/day (Houben et al., 2011). Likewise, the TL measurements among

the 21 articles also varied. Mostly, TL was regarded as a continuous variable, apart from that, one categorised TL to quintiles (Cassidy et al., 2010), one categorised TL to quartiles (Weischer et al., 2014), two categorised TL to tertiles (Houben et al., 2011; Kozlitina and Garcia, 2012).

Interpretation diversities existing in different studies' test statistics thus revealed it is inappropriate to integrate test statistics. What is worse, some researches did not even report the test statistics values. Yet, it is delightful to notice that almost all the research reported sample sizes and p-values. Taking the calculation of the combined p-values and considering it to be the pooled evidence, a meta-analysis about the AC-TL association was finally able to be performed. AC and TL are claimed to be significantly associated if the combined p-value $< 0.05$. There are several proposed approaches for combining p-values and Fisher's method is adopted in our present study. Liptak's method (Won et al., 2010) is employed to utilise the sample sizes information. Fisher combines the p-values from several statistics. It defines a simple alternative hypothesis with the known expected effect of each test statistic and then determines the most powerful test for this alternation. With this method, the information of effect size can be utilised to obtain the optimal weight for Liptak's method of combining p-values.

Since statistical models for investigating the AC-TL association varied in separate studies, test statistics, as well as their accordingly standard errors of the effect sizes, were further missed. The potential publication bias plus heterogeneity among researches are unable to be accessed directly. In order to roughly assess heterogeneity in our present research, log10 (p-value) is adopted so that to surrogate each study's effect size, beside than that, the inverse of sample size is also adopted to surrogate the effect size's variance. log10 (Fisher's combined p-value) plus log10 (Liptak's combined p-value) are then adopted as the pooled effect size, respectively, to calculated $I^2$. The funnel plot is drawn to assess the publication bias roughly, applies the signed log10 (p-value) to surrogate the effect size, and the square root of the inverse of a sample size to be the standard error. The sign of the study's effect size is the same as the sign of the test statistic. The sign will be assumed as negative if the test statistic is missing (i.e., the higher AC, the shorter TL). A funnel plot is drawn by R package metafor.

**Figure 3** Parallel pie chart: The association between study type and AC-TL association (see online version for colours)




Notes: Type of the study and the significance of AC-TL association is revealed to be significantly relevant by Fisher's exact tests (p-value = 1.86E-3).

Fisher's exact test is employed in our present meta-analysis in order to check whether the below-listed factors influence the significance of the AC-TL association.

1 type of the study (cross-sectional, case-control, or cohort study)

2 goal of the article (whether an article's primary goal is to test the AC-TL association)

3 specificity of the sex (only on female, only on male, or on both sex)

4 categorisation of AC (having a category as never-drinker or not)

5 population of the study (European, Australian, Asian or American).

For binary factors (e.g., article goal), the hypergeometric distribution is directly used to obtain p-values of Fisher's exact test. For others, the p-values of Fisher's exact test are calculated by using the network designed by Mehta and Patel (1983) and improved by Clarkson et al. (1993). Besides, two-sample Wilcoxon rank-sum tests are carried out to verify whether the sample size and mean age will influence the AC-TL association. A test needs to have its two-sided p-value < 0.05 to be claimed as significant. R Version 3.4.2 or IBM SPSS Statistics Version 22.0 is adopted for all analyses.

## 3 Results

### *3.1 Basic information and the heterogeneity test results*

Twenty-one articles are obtained after all three rounds of screening.

In Table 1, we list these 21 articles' relevant information and their quality scores. For the convenience of using, we define some abbreviations in this table. StudyType indicates the type of the AC-TL association study, cS is a cross-sectional study, Co is a cohort study and C-C is a case-control study. PubYear indicates the publication year of the article. StudyDsgO (studyDesignOriginal) indicates the original study design of the article, cS is a cross-sectional study, L is a longitudinal study, C-C is a case-control study and nCC is nested case-control study. PA (primaryAnalyse) indicates if the primary goal of the study is to analyse and investigate the AC-TL association. sA (sigAssoc) indicates if the AC-TL association is significant (*$p < 0.05$). Sex indicates if the AC-TL association study is based on women-only (0) data, men-only (1) data, or based on both women and men (2) data. P-value represents for the p-value for testing the AC-TL association. testS represents for the test statistic. NA means not available (i.e., missing value). note1 is ($coef$ = –0.014)+/–($se$ = 0.046) for abstainer; –0.055+/–0.039 for moderate AC; –0.024+/–0.050 for high AC. note2 is meanDiff = 0.07. note3 is meanDiff = 0.04. nTotal means the total sample size in the AC-TL association study. meanAge indicates the mean age of subjects in the AC-TL association study. sND (seperateNonDrinker) indicates if the AC-TL association study includes a non-drinker category, N = no, Y = yes, NA = not available (i.e., missing value). contint indicates which continent the subjects were from.

Among all the 21 articles, six of them performed more than one analyses, and the number of analyses that evaluated the AC-TL association was 44 in total. In Appendix Table A1, we summarise these 44 analyses' relevant information and their quality scores. Of the 44 analyses, the 27 independent ones are evaluated and the remaining 17 ones are discussed both in the discussion. As shown in Table 1, four of the 27 analyses are case-control studies (Pavanello et al., 2011; Aida et al., 2011; Liu et al., 2009, 2011),

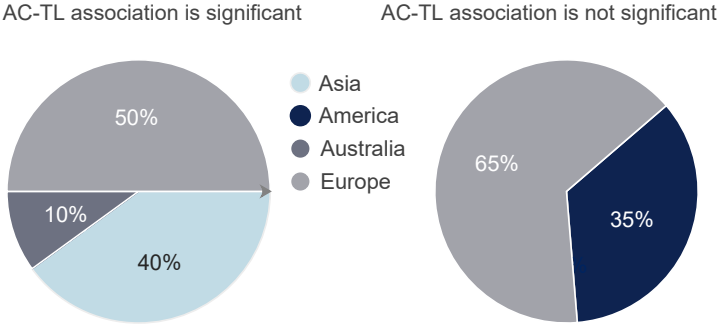
three are cohort studies (Strandberg et al., 2012; Weischer et al., 2014; Bendix et al., 2014), and other 20 are cross-sectional studies. While for the remaining 17 analyses, the number of case-control, cohort, and cross-sectional studies are ten, three and four, respectively.

Since statistical models for investigating the AC-TL association varied in separate studies, test statistics, as well as their accordingly standard errors of the effect sizes, were further missed, therefore the potential publication bias plus heterogeneity among studies were unable to be accessed directly. Surrogate test statistics, as well as surrogate standard errors, are hence adopted in our present study. The $I^2$ value is equal to 34.42 when we employ log10 (Fisher's combined p-value) to be the pooled effect size, illustrating small to medium heterogeneity. While the $I^2$ value is equal to 0 when we employ log10 (Liptak's combined p-value) to be the pooled effect size, illustrating small heterogeneity. The roughly symmetric funnel plot shown in Figure 2 indicates no publication bias.

### *3.2 Detailed observation based on varied factors*

As for primary goals, 11 of the 27 studies do primarily intended to discover the AC-TL association. Among that, number of cross-sectional, case-control, and cohort studies are seven (Pavanello et al., 2011; Strandberg et al., 2012; Cassidy et al., 2010; Latifovic et al., 2015; Qi et al., 2012; Weischer et al., 2014; Shin and Baik, 2016), two (Pavanello et al., 2011; Aida et al., 2011) and two Strandberg et al. (2012); Weischer et al. (2014), respectively. Primary goals of the other 16 studies varies from the association between mortality in humans and TL (Bendix et al., 2014) to the association between size of red blood cell and TL (Kozlitina and Garcia, 2012).

**Figure 4** Parallel pie chart: the association between continent and AC-TL association




Notes: The study population and the significance of AC-TL association are revealed to be significantly relevant, reported by Fisher's exact tests (p-value = 2.67E-3).

Among the 27 studies, when it comes to sex-specificity, numbers of male-only, female-only, and both-sex studies are eight (Pavanello et al., 2011; Strandberg et al., 2012; Fyhrquist et al., 2011; Houben et al., 2011; Mirabello et al., 2009; Bekaert et al., 2007), four (Cassidy et al., 2010; Fyhrquist et al., 2011; Qi et al., 2012; Bekaert et al., 2007) and 15 (Aida et al., 2011; Liu et al., 2009, 2011; Harris et al., 2006; Hou et al., 2009; Kozlitina and Garcia, 2012; Latifovic et al., 2015; Marcon et al., 2012; Starnino

et al., 2016; Weischer et al., 2014; Bendix et al., 2014; Mather et al., 2010; Shin and Baik, 2016), respectively. When it comes to the AC categorisation, there were nine studies that reported a category as non-alcohol drinkers (Pavanello et al., 2011; Aida et al., 2011; Liu et al., 2009, 2011; Hou et al., 2009; Houben et al., 2011; Latifovic et al., 2015; Shin and Baik, 2016), while two did not contain this information (Fyhrquist et al., 2011). When it comes to study population, sources were based on Australian [one study (Mather et al., 2010)], Asian [four studies (Aida et al., 2011; Liu et al., 2009, 2011; Shin and Baik, 2016)], American [six studies (Cassidy et al., 2010; Kozlitina and Garcia, 2012; Latifovic et al., 2015; Mirabello et al., 2009; Starnino et al., 2016; Qi et al., 2012)], and European [the last 16 studies (Pavanello et al., 2011; Strandberg et al., 2012; Fyhrquist et al., 2011; Harris et al., 2006; Hou et al., 2009; Houben et al., 2011; Marcon et al., 2012; Bekaert et al., 2007; Weischer et al., 2014; Bendix et al., 2014)]. Among the 27 articles, range of samples size is from 50 (Aida et al., 2011) to 5,862 (Qi et al., 2012), the minimum and maximum mean-age is 35 (Latifovic et al., 2015) and 79 year old (Harris et al., 2006), while range of p-value is from 9.00E-5 to 0.962.

Among the 27 studies, ten of them showed significant AC-TL associations (i.e., p-value < 0.05). The Liptak's combined p-value of the 27 studies is 8.76E-3 and the Fisher's combined p-value is 5.75E-8.

Four of the 20 (20%) cross-sectional studies, all four case-control studies, and two of the three cohort studies showed the AC-TL associations to be significant. The relationship between AC-TL association versus study type was illustrated with a cross-table as Table A2 and a parallel pie chart as Figure 3. Type of the study and the significance of AC-TL association was revealed to be significantly relevant by Fisher's exact tests (p-value = 1.86E-3).

For all the studies, 5 out of the 16 ones from Europe, the only one from Australia and all four from Asia revealed the AC-TL association to be significant, while all the six ones from USA reported the AC-TL association to be non-significant. The relationship between continent versus AC-TL association was illustrated with a cross-table in Appendix as Table A3 and a parallel pie chart as Figure 4. The study population and the significance of AC-TL association were revealed to be significantly relevant, reported by Fisher's exact tests (p-value = 2.67E-3).

### *3.3 The statistically irrelevant factors*

None of the below-listed factors is found to be relevant with the significance of AC-TL association: whether a study's primary goal is to detect the AC-TL association or not, if a study is on account of female-only, male-only or both-sex, or if a study has a category of AC as never-drinker. P-values are 0.22, 0.39 and 0.09 separately. Associations between each of these factors and AC-TL association are illustrated with cross-tables in Appendix as Tables A4, A5 and A6, respectively.

Neither the total number of sample size nor the mean-age is reported to be relevant to the significance of AC-TL association, shown by Wilcoxon rank-sum tests, with the p-values as 0.51 and 0.11 separately. In Appendix, Figures A1 and A2 demonstrate the relationships between these elements and the AC-TL association in parallel boxplots.

**Table 1** The information of the 27 independent studies

| *Study type* | *Paper* | *Pub year* | *Study DsgO* | *PA* | *sA* | *Sex* | *P-value* | *testS* | *nTotal* | *Mean age* | *sND* | *contint* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| cS | Harris et al. (2006) | 2006 | cS | No | No | 2 | 0.962 | NA | 185 | 79.1 | N | Europe |
| cS | Bekaert et al. (2007) | 2007 | L | No | No | 0 | 0.682 | –7.453 | 1291 | 45.9 | N | Europe |
| cS | Bekaert et al. (2007) | 2007 | L | No | No | 1 | 0.63 | –8.033 | 1,218 | 46.1 | N | Europe |
| cS | Hou et al. (2009) | 2009 | nCC | No | No | 2 | 0.06 | NA | 416 | 65.5 | Y | Europe |
| cS | Mirabello et al. (2009) | 2009 | C-C | No | No | 1 | 0.799 | 0.006 | 1,661 | 64 | N | USA |
| cS | Houben et al. (2011) | 2010 | L | No | No | 1 | 0.28 | NA | 203 | 78.47 | Y | Europe |
| cS | Mather et al. (2010) | 2010 | cS | No | Yes | 2 | 0.008 | –0.155 | 646 | 56.75 | N | Australia |
| cS | Cassidy et al. (2010) | 2010 | cS | Yes | No | 0 | 0.59 | NA | 2,284 | 58.86 | N | USA |
| cS | Fyhrquist et al. (2011) | 2011 | L | No | No | 0 | 0.962 | NA | 668 | 65 | NA | Europe |
| cS | Fyhrquist et al. (2011) | 2011 | L | No | No | 1 | 0.962 | NA | 603 | 63 | NA | Europe |
| cS | Pavanello et al. (2011) | 2011 | C-C | Yes | Yes | 1 | 0.003 | NA | 457 | 41 | Y | Europe |
| cS | Strandberg et al. (2012) | 2012 | L | Yes | No | 1 | 0.11 | –0.08 | 499 | 75.7 | N | Europe |
| cS | Kozlitina and Garcia (2012) | 2012 | L | No | No | 2 | 0.526 | NA | 3,157 | 50 | N | USA |
| cS | Qi et al. (2012) | 2012 | cS | Yes | No | 0 | 0.93 | 0.001 | 5,862 | 58.7 | N | USA |
| cS | Marcon et al. (2012) | 2012 | cS | No | No | 2 | 0.962 | –0.006 | 56 | 56 | N | Europe |
| cS | Bendix et al. (2014) | 2014 | L | No | No | 2 | 0.078 | –0.001 | 2,214 | 55 | N | Europe |
| cS | Weischer et al. (2014) | 2014 | L | Yes | Yes | 2 | 0.01 | NA | 4,576 | 54.25 | N | Europe |
| cS | Latifovic et al. (2015) | 2015 | cS | Yes | No | 2 | 0.57 | note1 | 477 | 35 | Y | USA |
| cS | Stamino et al. (2016) | 2016 | L | No | No | 2 | 0.23 | –1.205 | 132 | 45.34 | N | USA |
| cS | Shin and Baik (2016) | 2016 | cS | Yes | Yes | 2 | 0.04 | NA | 1,771 | 57.23 | Y | Asia |
| Co | Strandberg et al. (2012) | 2012 | L | Yes | Yes | 1 | 0.004 | –0.13 | 499 | 46.7 | N | Europe |
| Co | Bendix et al. (2014) | 2014 | L | No | Yes | 2 | 0.032 | –0.001 | 1,356 | 44.7 | N | Europe |
| Co | Weischer et al. (2014) | 2014 | L | Yes | No | 2 | 0.61 | –0.154 | 4,535 | 54.25 | N | Europe |
| C-C | Liu et al. (2009) | 2009 | C-C | No | Yes | 2 | 0.016 | note2 | 378 | 53 | Y | Asia |
| C-C | Pavanello et al. (2011) | 2011 | C-C | Yes | Yes | 1 | 0.00009 | NA | 457 | 38 | Y | Europe |
| C-C | Aida et al. (2011) | 2011 | C-C | Yes | Yes | 2 | 0.002 | NA | 50 | 67.25 | Y | Asia |
| C-C | Liu et al. (2011) | 2011 | C-C | No | Yes | 2 | 0.043 | note3 | 240 | 50.5 | Y | Asia |

## 4 Discussion and conclusions

In our research, evidence from the existing relevant observational studies was summarised in order to conduct a meta-analysis on the AC-TL relationship as well as to further detect elements that may influence the significance of this association. 21 articles passed all the screenings and were eligible to be included in the present meta-analysis, consisting of 44 studies of the AC-TL association. In brief, AC-TL association is significant according to the pooled evidence of the 27 independent studies (with the Liptak's combined p-value = 8.24E-3 and Fisher's combined p-value = 3.52E-8). Study population (p-value = 2.67E-3) as well as study type (p-value = 1.86E-3) are found to be significantly related to the AC-TL association significance. The AC-TL association remained significant even if all the 44 studies were used and the dependency among them were ignored (with Liptak's combined p-value = 3.57E-5 and Fisher's combined p-value = 1.11E-16).

Whether or not having a category of AC labelled as 'never drinker' is found to be significantly related to the AC-TL association significance (p-value = 0.026) when only the 20 cross-sectional studies and the four case-control studies were considered. Among them, four cross-sectional studies, as well as all the four case-control studies, reported the AC-TL association as significant. According to our observation, among all the 20 cross-sectional studies only five had an AC category as never-drinker, while in all four case-control studies the controls are never drinkers. We hence speculated that the influence of study type on the AC-TL association significance might because of the comparison between ever drinkers versus never drinkers. In Appendix, Figure A3 and Table A7 separately adopted the parallel pie chart and the cross-table to demonstrate the relationships between if a study has a category of AC as never-drinker versus the AC-TL association. The relationship kept being significant between the study population versus the AC-TL association significance (p-value = 0.012) even after we regrouped the study population to be 23 non-Asia studies versus four Asian studies, for the fact that there is only one study from Australia. In Appendix, Figure A4 and Table A8 separately adopted the parallel pie chart and the cross-table to demonstrate the relationships between if the study population was Asian versus the AC-TL association. The fact that the population of all the four studies is Asian revealed significant AC-TL association thus is intriguing and leads to interesting investigations.

It is noteworthy that although there is no significant correlation between sex-specificity versus the AC-TL association significance, all four female-only studies do reveal the AC-TL associations to be non-significant (p-value = 0.3948). To confirm whether this observation is accidental or not, more female-only studies are warranted.

Cohort study (longitudinal study) is theoretically better than a case-control study or cross-sectional study since the cohort study is able to infer if heavy AC shortens TL. Despite that, challenges still exist for cohort studies as following (Bendix et al., 2014).

1 it is difficult to ensure the procedure are the same when measuring TL at the end of a long-time follow-up and when at the very beginning baseline

2 similar to the blood storage method at the two-time points

3 whether or not that TL technically behaves the same at the two-time points is hard to guarantee.

Another potentially important factor in the AC-TL association is genetics. Subjects that carrying the common ADH1B*1/*1 (rs1229984) genotype were reported to more intend to abuse alcohol as well as exhibiting shorter TL (Pavanello et al., 2011). Only among the carriers of the mutant alleles (CT and TT) of ALDH2 (rs2074356), a large amount of AC was found to be inversely correlated with leukocyte TL (Shin and Baik, 2016). Researches above implied that genetics makes a helpful difference in identifying subtypes of subjects that have significant AC-TL associations. Certain studies merely gave upper or lower borders of p-values. For example, one study reported that the p-value < 0.001 while accessing the influence of interaction between AC and ADH1B genotypes on TL among 255 controls (Pavanello et al., 2011). For another four studies it reported p-values < 0.0001 (Pavanello et al., 2011). Another research reported p-value > 0.05 (Harris et al., 2006). When we calculated Liptak's weighted p-value and Fisher's combined p-value, we set p-value = 0.0009 when a study claims its p-value < 0.001, set p-value = 0.00009 for the four studies with p-value < 0.0001, and set p-value = 0.962 (the upper boundary of p-value among all the 44 studies) for the study with p-value > 0.05.

A few studies reported mean-age merely for each subject groups [e.g., for each TL tertile (Houben et al., 2011)]. Average of these groups' means was taken when whether or not age would influence the AC-TL association significance was investigated. Among all the 21 articles, six of them embodied more than one study that explored the AC-TL association. Among the 27 studies, Pavanello et al. (2011) embodied one cross-sectional study plus one case-control study, Bekaert et al. (2007) and Fyhrquist et al. (2011) both include one female-only study and one male-only study. For Weischer et al. (2014), Bendix et al. (2014) and Strandberg et al. (2012), each of them included one cohort study, and one cross-sectional study. The AC-TL association significance in diverse kinds of analyses within the same paper is assumed to be independent.

The large difference remains for the TL quantifications among the 27 studies. 16 studies quantified TL as ratio or proportion. Among the 16 analyses, one adopted normalised telomere-to-centromere ratio (NTCR) (Aida et al., 2011) and other 15 adopted T/S (the relative telomere to single-copy gene) ratio (Pavanello et al., 2011; Liu et al., 2009, 2011; Cassidy et al., 2010; Hou et al., 2009; Latifovic et al., 2015; Mirabello et al., 2009; Starnino et al., 2016; Weischer et al., 2014; Bendix et al., 2014; Mather et al., 2010; Shin and Baik, 2016). One evaluated TL by terminal restriction fragment (TRF) (Marcon et al., 2012). One evaluated TL with Z-score of T/S ratio (Qi et al., 2012). Two used the logarithm of TL (Fyhrquist et al., 2011; Shin and Baik, 2016). Three divided TL into four (Weischer et al., 2014) or three categories (Houben et al., 2011; Kozlitina and Garcia, 2012). Nine employed kb (kilobase) as the unit of TL. The large difference existing for the quantification of TL brought great difficulties aggregating data and interpreting results. In the future, it is very helpful if we build standard guidance on the TL quantification.

Similarly, a large difference exists for the AC quantifications among the 27 studies. 23 studies assessed AC on a continuous scale as alcoholic beverages perday (Pavanello et al., 2011; Qi et al., 2012; Weischer et al., 2014), beverages per week (Liu et al., 2009; Harris et al., 2006; Latifovic et al., 2015; Starnino et al., 2016; Bekaert et al., 2007; Bendix et al., 2014; Mather et al., 2010), g (grams) per day (Liu et al., 2011; Cassidy et al., 2010; Houben et al., 2011; Kozlitina and Garcia, 2012; Marcon et al., 2012; Mirabello et al., 2009; Shin and Baik, 2016), and g per week (Strandberg et al., 2012). Among them, a standard alcoholic beverage is multifarious from 12 g alcohol,

1.5 oz. liquor, 5 oz. wine (1 glass), to 12 oz. beer (1 bottle). One study assessed AC as total drink-years (total years of alcohol use * yearly frequency) (Hou et al., 2009). Other analyses applied categorised AC. One described an ever-drinker as a person who drinks at least one serving of liquor (1.5 oz.), wine (4 oz.), or beer (12 oz.) per month for at least six months, while an analysis classified AC with four categories: non-drinker, <10, 10–29, and >29 years of drinking alcohol (Hou et al., 2009). Two studies used the natural logarithm of AC (Bekaert et al., 2007). Three reported nothing about the AC quantifications (Aida et al., 2011; Fyhrquist et al., 2011). In the future, it is very helpful if we build standard guidance on the AC quantification.

Of all the 27 main studies included in our present meta-analysis, 15 gave test statistic values, and four of which described positive AC-TL associations (Liu et al., 2009, 2011; Mirabello et al., 2009; Qi et al., 2012). That is, the more AC, the longer the TL. Two of the four positive associations are statistically significant (Liu et al., 2009, 2011). Liu et al. (2009) brought a potential explanation for this significant positive association: drinking alcohol activates telomere in target tissues. They also reported that the possibility of accidental discovery is unable to be ruled out since the size of each subgroup is limited Liu et al. (2009). Liu et al. (2009) mentioned nothing about how they defined the 'ever-drinkers' category. Further, inspection is expected to evaluate the differences of the AC-TL association among heavy-, moderate- and never-drinkers.

Despite that telomere shortening is natural in ageing, it is influenced by many other elements, such as paternal age at birth, ethnicity, gender, age, telomere maintenance genes, genetic mutations of telomere, inflammation and oxidative stress, environmental, psychosocial, behavioural exposures and so on. Defects in TL are associated with certain age-related diseases, cancers, and premature ageing syndromes. Alcohol drinks, being an oxidation source, a behavioural exposure, and one of the most global used recreational drugs, has been identified as a cause of many kinds of cancers. Both telomere shortening and heavy alcohol drinking are related to cancer and are important to public health.

All in all, although the massive difference exists in AC and TL quantification methods hindered us from using meta-analysis and aggregating the relevant evidence. Our research still managed to aggregate the p-values of 27 relevant analyses with a total sample size as 35,891 and revealed the AC-TL association to be significant on the basis of Liptak's weighted p-value plus Fisher's combined p-value. Factors like study type (cohort, cross-sectional, or case-control study), population (European, Asian, or American), and gender of the subject, may influence the AC-TL association. To the best of our knowledge, our present study is the first meta-analysis to aggregate evidence about the AC-TL association, it not only preliminarily obtained an association but also demonstrated the feasibility and validity of this research direction.

In the future, if the AC and TL quantifications can be standardised meanwhile both beneficial and deteriorating effects of AC to human health are taken into consideration. It is beneficial for scientists to disclose the true relationship between AC and TL. And that result can be applied to many fields varied from public health, molecular biology, epidemiology to cancer study.

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## Appendix

**Table A1** The information of the 44 analyses in the 21 articles

| *studytype* | *firstAuthor* | *publishYear* | *studyDesignOriginal* | *primaryAnalysis* | *sigAssoc* | *bothSex* | *p-value* | *testStat* | *nTotal* | *meanAge* | *sepNonDrinker* | *continent* | *qualityEvaluationTool* | *studyQuality* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| crossSectional | Harris | 2006 | Cross-sectional | No | No | Both | 0.962 | NA | 185 | 79.1 | N | Europe | AHRQ | 10/11 |
| crossSectional | Bekaert | 2007 | Longitudinal study | No | No | Women only | 0.682 | –7.453 | 1291 | 45.9 | N | Europe | NOS | 8/9 |
| crossSectional | Bekaert | 2007 | Longitudinal study | No | No | Men only | 0.63 | –8.033 | 1218 | 46.1 | N | Europe | NOS | 8/9 |
| crossSectional | Hou | 2009 | Case-control study | No | No | Both | 0.06 | NA | 416 | 65.5 | Y | Europe | NOS | 7/9 |
| crossSectional | Mirabello | 2009 | Nested case-control study | No | No | Men only | 0.799 | 0.006 | 1661 | 64 | N | USA | NOS | 9/9 |
| crossSectional | Houben | 2010 | Longitudinal study | No | No | Men only | 0.28 | NA | 203 | 78.47 | Y | Europe | NOS | 8/9 |
| crossSectional | Mather | 2010 | Cross-sectional | No | Yes | Both | 0.008 | –0.155 | 646 | 56.75 | N | Australia | AHRQ | 9/11 |
| crossSectional | Cassidy | 2010 | Cross-sectional | Yes | No | Women only | 0.59 | NA | 2284 | 58.86 | N | USA | AHRQ | 7/11 |
| crossSectional | Fyhrquist | 2011 | Longitudinal study | No | No | Women only | 0.962 | NA | 668 | 65 | NA | Europe | NOS | 8/9 |
| crossSectional | Fyhrquist | 2011 | Longitudinal study | No | No | Men only | 0.962 | NA | 603 | 63 | NA | Europe | NOS | 8/9 |
| crossSectional | Pavanello | 2011 | Case-control study | Yes | Yes | Men only | 0.003 | NA | 457 | 41 | Y | Europe | NOS | 6/9 |
| crossSectional | Pavanello | 2011 | Case-control study | Yes | No | Men only | 0.92 | NA | 200 | 38 | Y | Europe | NOS | 6/9 |
| crossSectional | Pavanello | 2011 | Case-control study | Yes | No | Men only | 0.55 | NA | 257 | 44 | Y | Europe | NOS | 6/9 |
| crossSectional | Strandberg | 2012 | Longitudinal study | Yes | No | Men only | 0.11 | –0.08 | 499 | 75.7 | N | Europe | NOS | 7/9 |
| crossSectional | Kozlitina | 2012 | Longitudinal study | No | No | Both | 0.526 | NA | 3157 | 50 | N | USA | NOS | 6/9 |
| crossSectional | Sun | 2012 | Cross-sectional | Yes | No | Women only | 0.93 | 0.001 | 5862 | 58.7 | N | USA | AHRQ | 9/11 |
| crossSectional | Marcon | 2012 | Cross-sectional | No | No | Both | 0.962 | –0.006 | 56 | 56 | N | Europe | AHRQ | 8/11 |
| crossSectional | Bendix | 2014 | Longitudinal study | No | No | Both | 0.717 | –0.0001 | 1762 | 44.7 | N | Europe | NOS | 8/9 |
| crossSectional | Bendix | 2014 | Longitudinal study | No | No | Both | 0.078 | –0.001 | 2214 | 55 | N | Europe | NOS | 8/9 |
| crossSectional | Weischer | 2014 | Longitudinal study | Yes | No | Both | 0.1 | NA | 4576 | 54.25 | N | Europe | NOS | 7/9 |
| crossSectional | Weischer | 2014 | Longitudinal study | Yes | Yes | Both | 0.01 | NA | 4576 | 54.25 | N | Europe | NOS | 7/9 |

Notes: N = no, Y = yes, NA = not available (i.e., missing value), studytype indicating the study type of the AC-TL association, firstAuthor indicating the last name of the first author, publishYear indicating the article publication year, studyDesignOriginal indicating the original study design of the article, primaryAnalysis indicating if the primary goal of the study is to investigate the AC-TL association, sigAssoc indicating if the AC-TL association is significant ($*p < 0.05$), bothSex indicating if the AC-TL association study is based on women-only data, men-only data, or based on both women and men data, pvalue is the p-value for testing the AC-TL association, testStat test statistic, nTotal is the number of total sample size in the AC-TL association study, meanAge mean age of subjects in the AC-TL association study, sepNonDrinker indicating if the AC-TL association study includes a non-drinker category, continent indicating which continent the subjects were from.

**Table A1** The information of the 44 analyses in the 21 articles (continued)

| *studytype* | *firstAuthor* | *publishYear* | *studyDesignOriginal* | *primaryAnalysis* | *sigAssoc* | *bothSex* | *p-value* | *testStat* | *nTotal* | *meanAge* | *sepNonDrinker* | *continent* | *qualityEvaluationTool* | *studyQuality* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| crossSectional | Latifovic | 2015 | Cross-sectional | Yes | No | Both | 0.57 | (coef = –0.014)+/–(se = 0.046) for abstainer; –0.055+/–0.039 for moderate AC; –0.024+/–0.050 for high AC | 477 | 35 | Y | USA | AHRQ | 9/11 |
| crossSectional | Starnino | 2016 | Longitudinal study | No | No | Both | 0.23 | –1.205 | 132 | 45.34 | N | USA | NOS | 9/9 |
| crossSectional | Shin | 2016 | Cross-sectional | Yes | Yes | Both | 0.04 | NA | 1771 | 57.23 | Y | Asia | AHRQ | 10/11 |
| cohort | Strandberg | 2012 | Longitudinal study | Yes | Yes | Men only | 0.004 | –0.13 | 499 | 46.7 | N | Europe | NOS | 7/9 |
| cohort | Bendix | 2014 | Longitudinal study | No | Yes | Both | 0.032 | –0.001 | 1356 | 44.7 | N | Europe | NOS | 8/9 |
| cohort | Bendix | 2014 | Longitudinal study | No | Yes | Both | 0.005 | –0.001 | 1356 | 55 | N | Europe | NOS | 8/9 |
| cohort | Bendix | 2014 | Longitudinal study | No | Yes | Both | 0.014 | –0.001 | 1356 | 44.7 | N | Europe | NOS | 8/9 |
| cohort | Weischer | 2014 | Longitudinal study | Yes | No | Both | 0.61 | –0.154 | 4535 | 54.25 | N | Europe | NOS | 7/9 |
| cohort | Weischer | 2014 | Longitudinal study | Yes | No | Both | 0.73 | –1.12 | 4381 | 54.25 | N | Europe | NOS | 7/9 |
| case-control | Liu | 2009 | Case-control study | No | Yes | Both | 0.01 | meanDiff = 0.05 | 396 | 53 | Y | Asia | NOS | 8/9 |
| case-control | Liu | 2009 | Case-control study | No | Yes | Both | 0.016 | meanDiff = 0.07 | 378 | 53 | Y | Asia | NOS | 8/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | Yes | Men only | 0.00009 | NA | 457 | 38 | Y | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | Yes | Men only | 0.00009 | –8.98 | 251 | 41 | Y | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | Yes | Men only | 0.00009 | –8.98 | 206 | 41 | Y | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | Yes | Men only | 0.00009 | 0.35 | 404 | 41 | Y | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | No | Men only | 0.054 | 0.159 | 149 | 38 | N | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | Yes | Men only | 0.0009 | 0.34 | 255 | 44 | N | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | No | Men only | 0.793 | 0.01 | 400 | 41 | Y | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | No | Men only | 0.649 | 0.04 | 149 | 38 | N | Europe | NOS | 6/9 |
| case-control | Pavanello | 2011 | Case-control study | Yes | No | Men only | 0.729 | 0.02 | 251 | 44 | N | Europe | NOS | 6/9 |
| case-control | Aida | 2011 | Case-control study | Yes | Yes | Both | 0.002 | NA | 50 | 67.25 | Y | Asia | NOS | 6/9 |
| case-control | Aida | 2011 | Case-control study | No | No | Both | 0.109 | NA | 50 | 67.25 | Y | Asia | NOS | 6/9 |
| case-control | Liu | 2011 | Case-control study | No | Yes | Both | 0.043 | meanDiff = 0.04 | 240 | 50.5 | Y | Asia | NOS | 8/9 |

Notes: N = no, Y = yes, NA = not available (i.e., missing value), studytype indicating the study type of the AC-TL association, firstAuthor indicating the last name of the first author, publishYear indicating the article publication year, studyDesignOriginal indicating the original study design of the article, primaryAnalysis indicating if the primary goal of the study is to investigate the AC-TL association, sigAssoc indicating if the AC-TL association is significant (*$p < 0.05$), bothSex indicating if the AC-TL association study is based on women-only data, men-only data, or based on both women and men data, pvalue is the p-value for testing the AC-TL association, testStat test statistic, nTotal is the number of total sample size in the AC-TL association study, meanAge mean age of subjects in the AC-TL association study, sepNonDrinker indicating if the AC-TL association study includes a non-drinker category, continent indicating which continent the subjects were from.

**Table A2** Cross table: the relationship between study type and the significance of the AC-TL association

| *AC-TL association* / *Study type* | *Significant* | *Not significant* | *Total number* | *Ratio* |
|---|---|---|---|---|
| Cohort study | 2 | 1 | *3* | *66.70%* |
| Case-control study | 4 | 0 | *4* | *100%* |
| Cross-sectional study | 4 | 16 | *20* | *20.00%* |
| Total number | *10* | *17* | *27* | *37.00%* |

Notes: Type of the study and the significance of AC-TL association was revealed to be significantly relevant by Fisher's exact tests (p-value = 1.86E-3) (ratio is the ratio of number of studies with significant AC-TL association to the number of total studies).

**Table A3** Cross table: the relationship between continent and the significance of the AC-TL association

| *AC-TL association* / *Continent* | *Significant* | *Not significant* | *Total number* | *Ratio* |
|---|---|---|---|---|
| USA | 0 | 6 | *6* | *0.00%* |
| Asia | 4 | 0 | *4* | *100%* |
| Australia | 1 | 0 | *1* | *100%* |
| Europe | 5 | 11 | *16* | *31.30%* |
| Total number | *10* | *17* | *27* | *37.00%* |

Notes: The study population and the significance of AC-TL association were revealed to be significantly relevant, reported by Fisher's exact tests (p-value = 2.67E-3) (ratio is the ratio of number of studies with significant AC-TL association to the number of total studies).

**Table A4** Cross table: the relationship between a study's primary goal and the significance of the AC-TL association

| *AC-TL association* / *Factor* | *Significant* | *Not significant* | *Total number* | *Ratio* |
|---|---|---|---|---|
| Primary goal is to test for AC-TL association | 4 | 12 | *16* | *25.00%* |
| Primary goal is not to test for AC-TL association | 6 | 5 | *11* | *54.55%* |
| Total number | *10* | *17* | *27* | *37.00%* |

Notes: Whether a study's primary goal is to detect the AC-TL association or not and the significance of AC-TL association were not found to be relevant (p-values = 0) (ratio is the ratio of number of studies with significant AC-TL association to the number of total studies).

**Table A5** Cross table: the relationship between gender of a study's participants and the significance of the AC-TL association

| *AC-TL association* / *Gender* | *Significant* | *Not significant* | *Total number* | *Ratio* |
|---|---|---|---|---|
| Men only | 3 | 5 | *8* | *37.50%* |
| Women only | 0 | 4 | *4* | *0.00%* |
| Both sex | 7 | 8 | *15* | *46.67%* |
| Total number | *10* | *17* | *27* | *37.00%* |

Notes: If a study is on account of female-only, male-only or both-sex and the significance of AC-TL association were not found to be relevant (p-values = 0.39) (ratio is the ratio of number of studies with significant AC-TL association to the number of total studies).

**Table A6** Cross table: the relationship between whether a study has an AC category as never-drinker and the significance of the AC-TL association

| *AC-TL association* / *Factor* | *Significant* | *Not significant* | *Total number* | *Ratio* |
|---|---|---|---|---|
| A study has an AC category as never-drinker | 6 | 3 | *9* | *66.67%* |
| A study does not have an AC category as never-drinker | 4 | 12 | *16* | *25.00%* |
| NA | 0 | 2 | *2* | *0.00%* |
| Total number | *10* | *17* | *27* | *37.00%* |

Notes: If a study has a category of AC as never-drinker and the significance of AC-TL association were not found to be relevant (p-values = 0.09) (ratio is the ratio of number of studies with significant AC-TL association to the number of total studies).

**Table A7** Cross table: the relationship between whether a study has an AC category as never-drinker and the significance of the AC-TL association (cohort study excluded)

| *AC-TL association* / *Factor* | *Significant* | *Not significant* | *Total number* | *Ratio* |
|---|---|---|---|---|
| A study has an AC category as never-drinker | 6 | 3 | *9* | *66.67%* |
| A study does not have an AC category as never-drinker | 2 | 11 | *13* | *25.00%* |
| NA | 0 | 2 | *2* | *0.00%* |
| Total number | *8* | *16* | *24* | *33.33%* |

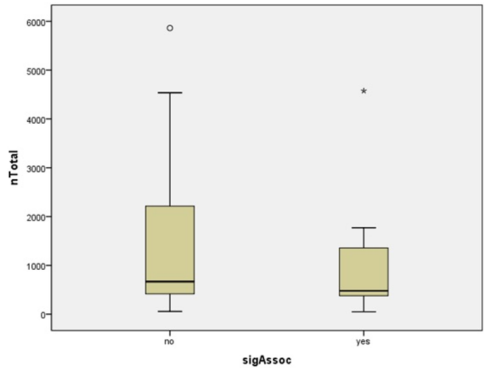
Notes: Whether or not having a category of AC labelled as 'never drinker' is found to be significantly related to the AC-TL association significance (p-value = 0.026) when only the 20 cross-sectional studies and the four case-control studies were considered (ratio is the ratio of number of studies with significant AC-TL association to the number of total studies).

**Table A8** Cross table: the relationship between whether the population of a study was Asian and the significance of the AC-TL association

| *Factor* \ *AC-TL association* | *Significant* | *Not significant* | *Total number* | *Ratio* |
|---|---|---|---|---|
| Asian | 4 | 0 | *4* | *100%* |
| Non-Asian | 6 | 17 | *23* | *26.09%* |
| Total number | *10* | *17* | *27* | *37.00%* |

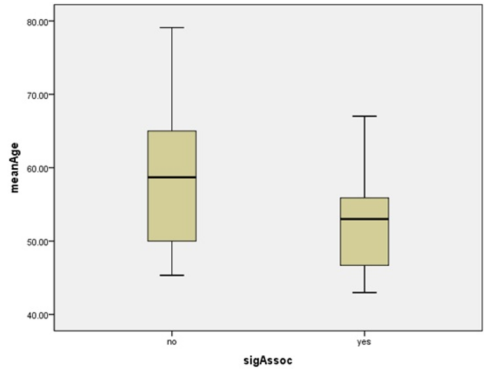
Notes: The relationship kept being significant (p-value = 0.012) after we regrouped the study population to be 23 non-Asia studies versus four Asian studies, for the fact that there is only one study from Australia (ratio is the ratio of number of studies with significant AC-TL association to the number of total studies).

**Figure A1** Parallel boxplots of the relationship between total number of sample size and AC-TL association (see online version for colours)



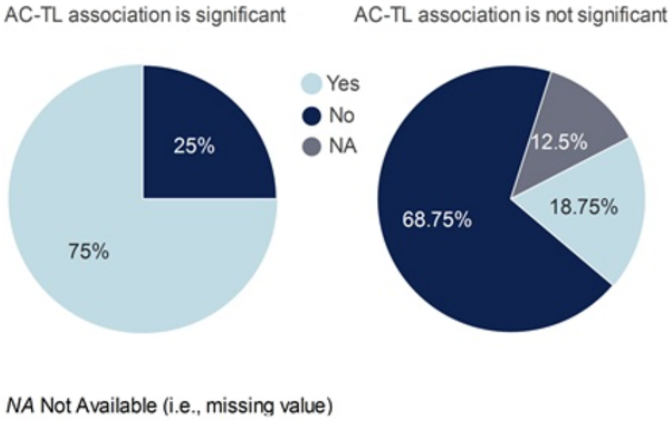

Notes: The total number of sample size and the significance of AC-TL association were not found to be relevant, shown by Wilcoxon rank-sum tests (p-value = 0.51).

**Figure A2** Parallel boxplots of the relationship between mean age and AC-TL association (see online version for colours)



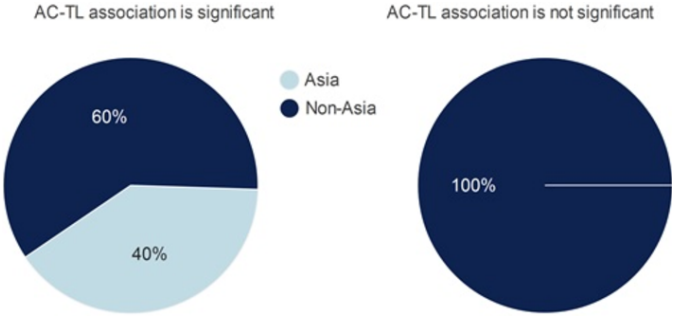

Notes: The mean age and the significance of AC-TL association were not found to be relevant, shown by Wilcoxon rank-sum tests (p-value = 0.11).

**Figure A3** Parallel pie chart: the relationship between whether a study has an AC category as never-drinker and the AC-TL association (no cohort) (see online version for colours)




Notes: Whether or not having a category of AC labelled as 'never drinker' is found to be significantly related to the AC-TL association significance (p-value = 0.026) when only the 20 cross-sectional studies and the four case-control studies were considered.

**Figure A4** Parallel pie chart: the relationship between whether the population of a study was Asian and the AC-TL association (see online version for colours)




Notes: The relationship kept being significant (p-value = 0.012) after we regrouped the study population to be 23 non-Asia studies versus four Asian studies, for the fact that there is only one study from Australia.