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REVIEW

Association between alcohol intake, mild cognitive impairment and progression to dementia: a dose–response meta-analysis

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Abstract

Background Mild cognitive impairment (MCI) is a cognitive state falling between normal aging and dementia. The relation between alcohol intake and risk of MCI as well as progression to dementia in people with MCI (PDM) remained unclear.

Objective To synthesize available evidence and clarify the relation between alcohol intake and risk of MCI as well as PDM.

Method We searched electronic databases consisting of PubMed, EMBASE, Cochrane Library, and China Biology Medicine disc (CBM) from inception to October 1, 2019. Prospective studies reporting at least three levels of alcohol exposure were included. Categorical meta-analysis was used for quantitative synthesis of the relation between light, moderate and heavy alcohol intake with risk of MCI and PDM. Restricted cubic spline and fixed-effects dose–response models were used for dose–response analysis.

Result Six cohort studies including 4244 individuals were finally included. We observed an unstable linear relation between alcohol intake (drinks/week) and risk of MCI (P linear = 0.0396). It suggested that a one-drink increment per week of alcohol intake was associated with an increased risk of 3.8% for MCI (RR, 1.038; 95% CI 1.002–1.075). Heavy alcohol intake (> 14 drinks/week) was associated with higher risk of PDM (RR = 1.76; 95% CI 1.10–2.82). And we found a nonlinear relation between alcohol intake and risk of PDM. Drinking more than 16 drinks/week (P nonlinear = 0.0038, HR = 1.42; 95% CI 1.00–2.02), or 27.5 g/day (P nonlinear = 0.0047, HR = 1.46; 95% CI 1.00–2.11) would elevate the risk of PDM.

Conclusion There was a nonlinear dose–response relation between alcohol intake and risk of PDM. Excessive alcohol intake would elevate the risk of PDM.

Keywords Alcohol · Mild cognitive impairment · Dementia · Dose–response · Meta-analysis

Introduction

Mild cognitive impairment (MCI) is a cognitive state falling between normal aging and dementia [1]. An estimated prevalence of MCI was 6.7–25.2% for ages 60–84 [2]. And progression to dementia in people with MCI (PDM) was

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conservatively estimated at 5–10% per year in a systematic review and meta-analysis [3]. As no evidence existed to support effective intervention or pharmacologic treatments for MCI [2, 4] and dementia [5, 6], finding the modifying factors of MCI and PDM might be a significant approach for prevention of cognitive dysfunction and dementia.

As a globally consumed beverage, alcohol intake was proved of a modifying factor of dementia in a dose–response meta-analysis [7]. The study found that modest alcohol intake (≤ 12.5 g/day) was associated with a reduced risk of dementia, while heavy drinking (≥ 23 drinks/week or ≥ 38 g/day) would significantly elevate the risk. However, whether it provided an appropriate alcohol intake of lower risk of MCI or PDM was far from clear. Although some studies explored the relation between alcohol intake and risk of MCI [8–10], and PDM [9, 11, 12], these studies should be interpreted more cautiously because of heterogeneous alcohol categories and units. And the results were not always consistent. For instance, Anttila found that participants drinking no alcohol or drinking frequently (> 1 time/month) at midlife were both twice as likely to have MCI in old age as those who drank infrequently (< 1 times/month) [8]. But Solfrizzi found no significant association between any levels of alcohol intake (< 1 drinks/day, 1–2 drinks/day, > 2 drinks/day) and risk of MCI versus abstainers [9]. And Koch found no significant association of any level (none, 0.1–0.9 drinks/week, 1.0–7.0 drinks/week, 7.1–14.0 drinks/week, > 14.0 drinks/week) of alcohol intake (drinks/week) and risk of PDM [12]. However, Solfrizzi suggested that up to 1 drink/day of alcohol or wine may decrease the risk of PDM [9]. Additionally, whether there was a dose–response relation between alcohol intake and risk of MCI or PDM remained unclear.

Therefore, we conducted this dose–response meta-analysis for comprehensively synthesizing available evidence, and the objectives of this meta-analysis were: (1) quantifying the relation between alcohol intake and risk of MCI; (2) quantifying the relation between alcohol intake and risk of PDM.

Method

We had prospectively registered the protocols of this systematic review into two parts in PROSPERO (www.crd.york.ac.uk/prospero/): Part 1, association between alcohol intake and risk of MCI (CRD42019127261); part 2, association between alcohol intake and risk of PDM (CRD42019127367). We conducted the two part at the same time and reported in this systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [13].

Search strategy

We searched electronic databases [PubMed, EMBASE, Cochrane Library, and China Biology Medicine disc (CBM)] from inception to October 1, 2019 using the following key terms: ethanol, alcohol, drinking, mild cognitive impairment, preclinical dementia, etc. (full search strategy was available in Supplementary Text 1). No restrictions were imposed.

Eligibility criteria

Studies were included if the following criteria were met simultaneously: (1) was prospective cohort study; (2) the association between alcohol intake and risk of MCI or PDM had been investigated, and there was no restriction on the comorbidity at the baseline; (3) alcohol exposure was categorized into at least three levels which could be quantitated with no restriction on alcohol unit (frequency or quantity); (4) level-specific hazard ratio (HR) or relative risk (RR) associated with 95% confidence interval (CI) were reported. In addition, if multiple articles were published based on the same cohort, we chose that with a larger sample size or longer follow-up time. Studies were excluded if the full-text could not be obtained after we contacted the corresponding authors.

Study selection

Two reviewers independently examined all the titles and abstracts for preliminary inclusion based on pre-set eligibility criteria. Literatures that did not meet the inclusion criteria were excluded at this stage. Then, full-text of literatures left over were checked for final inclusion by two reviewers independently. Any dispute arising in the pairing process were resolved by consensus.

Data extraction and quality evaluation

Two reviewers extracted information into a standardized form independently. For each study, we extracted: (1) study characteristics: first author, publication year, study design, study area, duration of follow-up, loss to follow-up rate, sample size; (2) participants details: diagnostic criteria, age, gender; (3) details of exposure: method of assessing alcohol intake, alcohol categories and unit; (4) outcomes of each alcohol categories: number of events, adjusted confounders, effect size (RR, or HR with 95% CI). The extracted data were cross-checked by the two reviewers. The Newcastle-Ottawa Scale (NOS) tool [14] was used for risk of bias assessment of cohort studies by two review authors independently too.

The NOS contains eight items, categorized into 3 dimensions consisting of selection (4 items, 1 star each), comparability (1 item, up to 2 stars), and outcome (3 items, 1 star each) for cohort studies. We regarded research with scores of "0–3", "4–6" and "7–9" as "low", "medium", and "high" quality, respectively [15]. Any dispute arising in the pairing process were resolved by consensus.

Data analysis

Firstly, we conducted categorical meta-analysis with the same alcohol category. Specifically, we combined the risk estimates reflective of the same category in the same study using fixed-effect model and then those in different studies using random-effect model. The alcohol intake was predefined qualitatively as light (< 7 drinks/week), moderate (7–14 drinks/week), and heavy (> 14 drinks/week) based on previous study [7, 16]. The combined results for qualitative categories were compared to observe the variation trend of dementia risk based on alcohol dose.

Then, to conducted dose–response analysis, we assigned the median or mean alcohol intake for alcohol category to each corresponding RR/HR. When the median or mean intake was not reported, we assigned the midpoint of the upper and lower boundaries in each category as the median intake [17, 18]. As previous study reported, when the lowest or upper category was open-ended, we set the lower boundary to zero and assumed that the boundary had the same amplitude as the adjacent category [17, 18].

Since alcohol units used in included studies were unified, we used different pooled units for meta-analysis. We assumed that one drink contains 12 g as used in previous studies if studies did not report specific conversion criteria [7, 18, 19]. And according to previous study, the median frequency for individuals drinking at least 12 g/day was about five times a week [20]. Thus, we could mutually transform alcohol unit from frequency into quantity. Furthermore, one unit was regarded as 8 g and 0.67 drinks as previous study [21, 22].

Restricted cubic spline and fixed-effects dose–response models were used for dose–response meta-analysis [23, 24]. Sensitivity analyses were performed to estimate the influence of alcohol unit transformation from frequency to quantity as well as the choice of statistic index between "HR" and "RR" on the synthesis results. Furthermore, we conducted sensitivity analysis by excluding one study at a time and to assess the influence of individual studies on the pooled estimate [18]. Egger test was used to assess publication bias if included studies were more than ten [25, 26]. The I^2 statistic was used to measure the heterogeneity among each studies [27]. $I^2 > 50\%$ and $p < 0.05$ was defined as a significant heterogeneity. All statistical analyses were conducted in Stata version 15.0 (Stata Corp, College Station, TX, USA), with two-tailed $p < 0.05$ for statistical significance.

Result

Literature search

The results of studies selection process were presented in a flow diagram (Fig. 1). We identified 3699 articles during initial electronic search, of which 2816 records were left after removing duplication. 2753 records were excluded after reviewing titles and abstracts, leaving 63 papers with full-text available. Finally, 57 papers were further excluded and a total of six studies were included [8–12, 28]. Titles of articles excluded after screen of the full-text were provided in supplement materials (Supplementary Table 1).

Study characteristics

In the included six studies, two studies explored the relation between alcohol intake and risk of MCI as well as PDM [9, 10]. Additionally, one studies were about alcohol intake and risk of MCI [8]. Three studies explored the relation between alcohol intake and risk of PDM [11, 12, 28]. Six studies were both prospective cohort studies published in English [8–12, 28]. In total, 2883 individuals with normal cognition and 260 incident MCI cases were included in Part 1, 1361 individuals with MCI and 430 incident dementia cases were included in Part 2. Diagnostic criteria to identify MCI and detailed operational procedures of included studies were different from each other. We summarized detailed criteria items and diagnostic procedures in Supplementary Table 2. Two studies did not report clear diagnostic procedures [11, 28]. One study [28] selected MCI individuals from two different cohort [29, 30] which used different diagnostic criteria for MCI, thus, we presented them separately. Three studies were conducted in the Europe [8, 9, 28], one study was conducted in China [11], one study was conducted in America [12] and one study was conducted in Australia [10]. Studies included in Part 1 were regarded as high quality (NOS score ≥ 7), while two studies [10, 11] were regarded as medium quality (scored 6) in Part 2. The characteristics of include studies were presented in Table 1. Specific scores for each item of NOS can be found in the supplement material (Supplementary Table 3).

Part 1: alcohol intake and risk of MCI

Categorical meta-analysis

Among the three included studies, two studies [9, 10] used drinks/day, and one used times/month [8] as alcohol

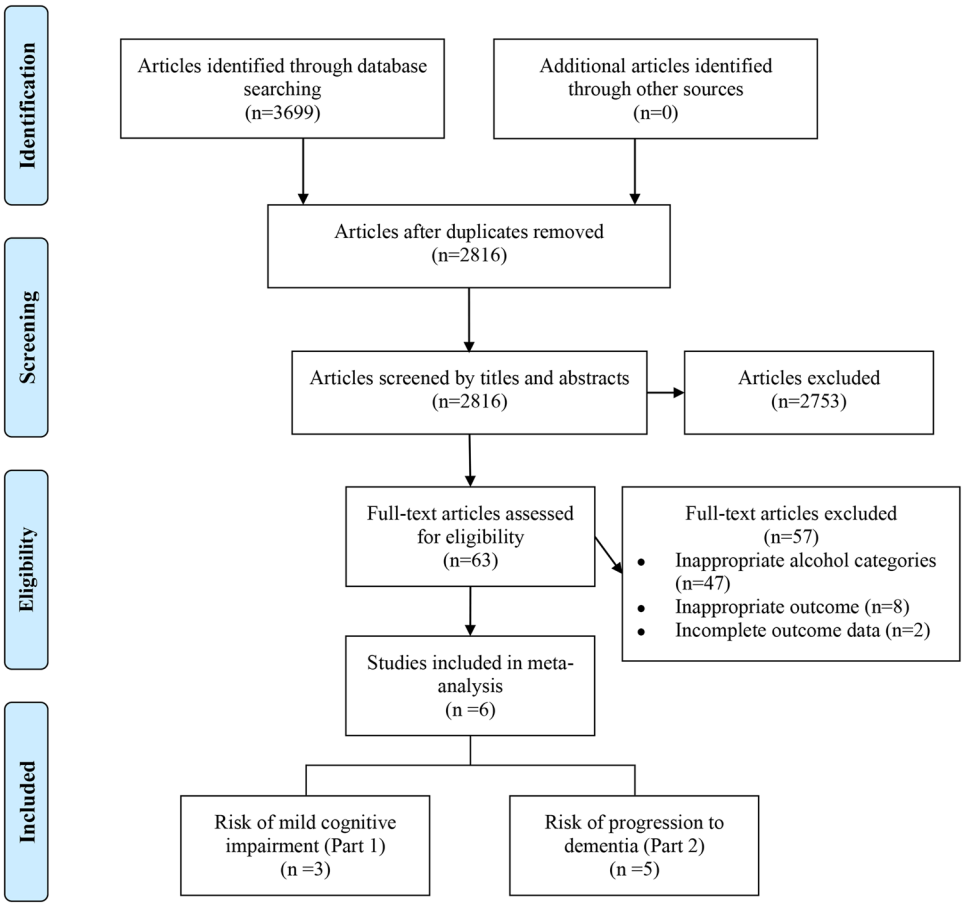

Fig. 1 Flow diagram of the literature search and study selection process

unit. When manually converted units of frequency (times/week) into quantity (drinks/week), the pooled results showed no significant association between risk of MCI and light alcohol intake (RR = 0.79; 95% CI 0.56–1.11; $I^2 = 0\%$) or moderate alcohol intake (RR = 1.43; 95% CI 0.85–2.42; $I^2 = 0\%$) (Fig. 2). Result was similar when not convert "times/week" into "drinks/week". As included studies were less than ten, we didn't perform analysis of publication bias.

Dose–response meta-analysis

We found a linear dose–response relation between alcohol intake (drinks/week) and risk of MCI when transforming alcohol unit from frequency into quantity [8–10] (P linear = 0.0396, Fig. 3a). It suggested that a one-drink increment per week in alcohol intake was associated with an increased risk of 3.8% for MCI (RR = 1.038; 95% CI 1.002–1.075). Sensitivity analysis showed that unit transformation from frequency into quantity did not influence the result. But we could not observe the relation when grams/day was used as pooled unit (P linear = 0.0521, Fig. 3b).

Part 2: Alcohol intake and risk of PDM

Categorical meta-analysis

The pooled RRs of risk of PDM for light, moderate, and heavy alcohol intake were 0.74 (95% CI 0.28–1.95; $I^2 = 63.4\%$), 0.85 (95% CI 0.51–1.41; $I^2 = 0\%$), and 1.76 (95% CI 1.10–2.82; $I^2 = 0\%$), respectively (Fig. 4). Only heavy alcohol intake seemed a significant risky association with PDM. Since included studies were less than ten, we did not perform analysis of publication bias.

Dose–response meta-analysis

Among five studies included in the dose–response analysis, three studies used drinks/day [9–11], one study used drinks/week [12], and one study used units/week [28] as alcohol unit. Two study reported specific conversion criteria for drink and gram [9, 11]. Thus, we used drinks/week and gram/day as pooled alcohol unit. We observed a nonlinear association between alcohol intake (drinks/week) and risk of PDM when pooling four studies using "HR" as statistic index [9, 11, 12, 28] (P nonlinear = 0.0038, Fig. 5a). We found that drinking more than 16 drinks/week (HR = 1.42;

Table 1 Baseline characteristics of studies included in the systematic review and meta-analysis

Study	Study region	Sample size	Cases	Age at baseline (mean ± SD, year)	Sex (male %)	Follow-up (year)	Included	Alcohol categories	Adjusted confounders	NOS scores
Solfrizzi et al. [9]	Italy	1445	105	71.8 ± 5.0	56.40	3.5 (median)	Part 1[a]	None < 1drink/day 1–2 drink/day > 2 drink/day	Age, sex, education, coronary artery disease, hypertension, diabetes, stroke, smoking, total cholesterol	8
Anttila et al. [8]	Finland	1018	61	48.3 ± 4.8	37.92	23 (mean)	Part 1	Never < 1 time/month ≥ 2 times/month	Age, sex, education, follow up time, body mass index, total serum cholesterol, systolic blood pressure, diastolic blood pressure, smoking, history of myocardial	9
Lipnicki et al. [10]	Australia	420	94	NA	NA	6 (mean)	Part 1	Abstainer ≤ 1drink/day > 1drink/day	Age, sex, education	7
Solfrizzi et al. [9]	Italy	121	14	80.7 ± 15.3	49.59	3.5 (median)	Part 2[b]	None < 1drink/day 1–2 drink/day > 2 drink/day	Age, sex, education, cigarette pack-years, coronary artery disease, stroke, Type 2 diabetes, hypertension, total cholesterol, anxiolytics	9
Xu et al. [11]	China	176	66	67.8 ± 7.4	100	2 (max)	Part 2	Abstainers ≤ 2 drinks/day > 2 drinks/day	Sex	6
Reijs et al. [28]	Europe	346	114	70.6 ± 6.9	NA	NA	Part 2	None ≤ 14 units/week >14 units/week	Age, sex, education, center, diagnosis, social activity, physical activity, cognitive activity, smoking, alcohol consumption, sleep problems	7
Koch et al. [12]	America	473	195	NA	NA	NA	Part 2	Nondrinkers 0.1–0.9 drinks/week 1.0–7.0 drinks/week 7.1–14.0 drinks/week > 14.0 drinks/week	Age, sex, race/ethnicity, clinic site, education, social activity, smoking status, body mass index, lipid-lowering medication use, history of cardiovascular disease, diabetes, Center for Epidemiologic Studies Depression Scale score, treatment group assignment, and apolipoprotein E genotype	8
Lipnicki et al. [10]	Australia	245	41	NA	NA	6 (mean)	Part 2	Abstainer ≤ 1drink/day > 1drink/day	Age, sex, education	6

[a]Part 1 association between alcohol intake and risk of MCI

[b]Part 2 association between alcohol intake and risk of PDM

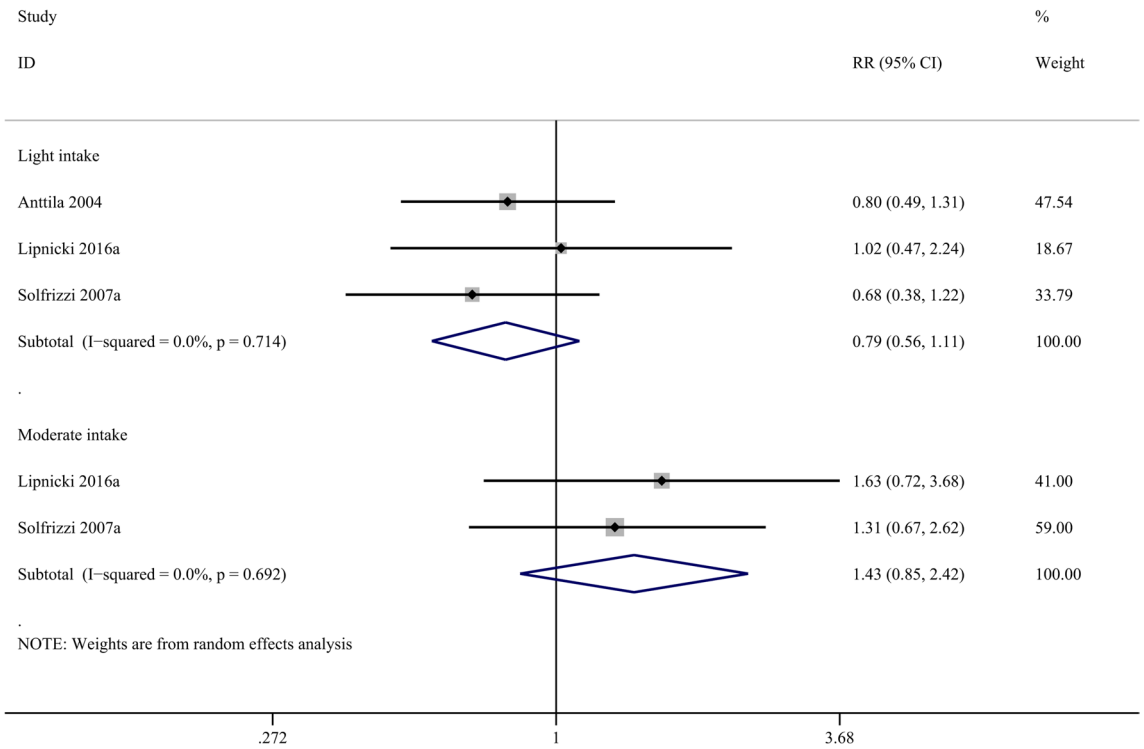

Fig. 2 Forest plot of relative risks (RRs) of MCI for different alcohol categories

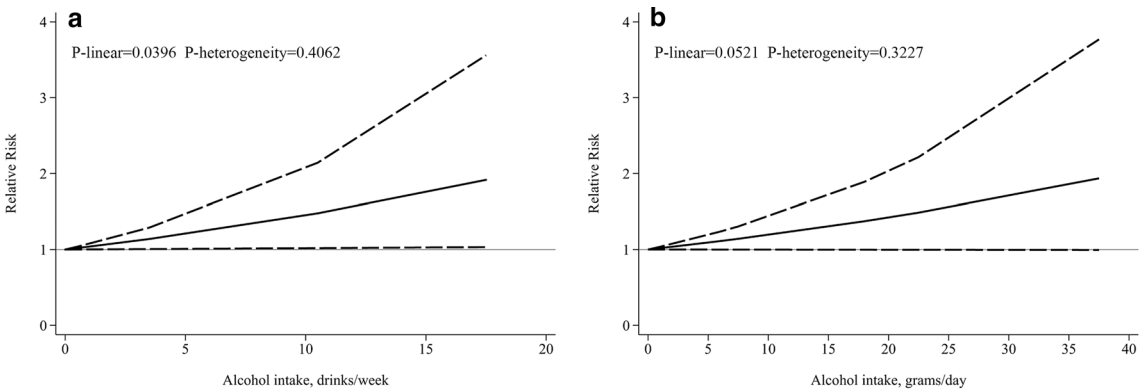

Fig. 3 Linear assciation between alcohol intake and risk of MCI (**a** using "drinks/week" as alcohol unit; **b** using "grams/day" as alcohol unit)

95% CI 1.00–2.02) would increase the risk of PDM. When pooled in grams/day, we also found a non-linear association between alcohol intake (grams/day) and risk of PDM (*P* nonlinear = 0.0047, Fig. 5b). We found that drinking more than 27.5 grams/day (HR = 1.46; 95% CI 1.00–2.11) would increase the risk of PDM.

Sensitivity analysis

We conducted sensitivity analysis by adding another one study using "RR" as statistic index to the model. We still observed a nonlinear associated between alcohol intake and risk of PDM. It suggested that drinking more than 17.5 drinks/week (RR = 1.42; 95% CI 1.00–2.05) would increase the risk of PDM (*P* nonlinear = 0.0061, Fig. 5c). When pooled in grams/day, it still suggested a risky threshold that was 30 g/day (RR = 1.47; 95% CI 1.00–2.16) (*P* nonlinear = 0.0059, Fig. 5d). Another sensitivity analysis suggested that when excluded Xu [11] or Koch [12], we could not observed a potential dose–response relation. Details of this sensitivity analysis was presented in supplement material (Supplementary Table 4).

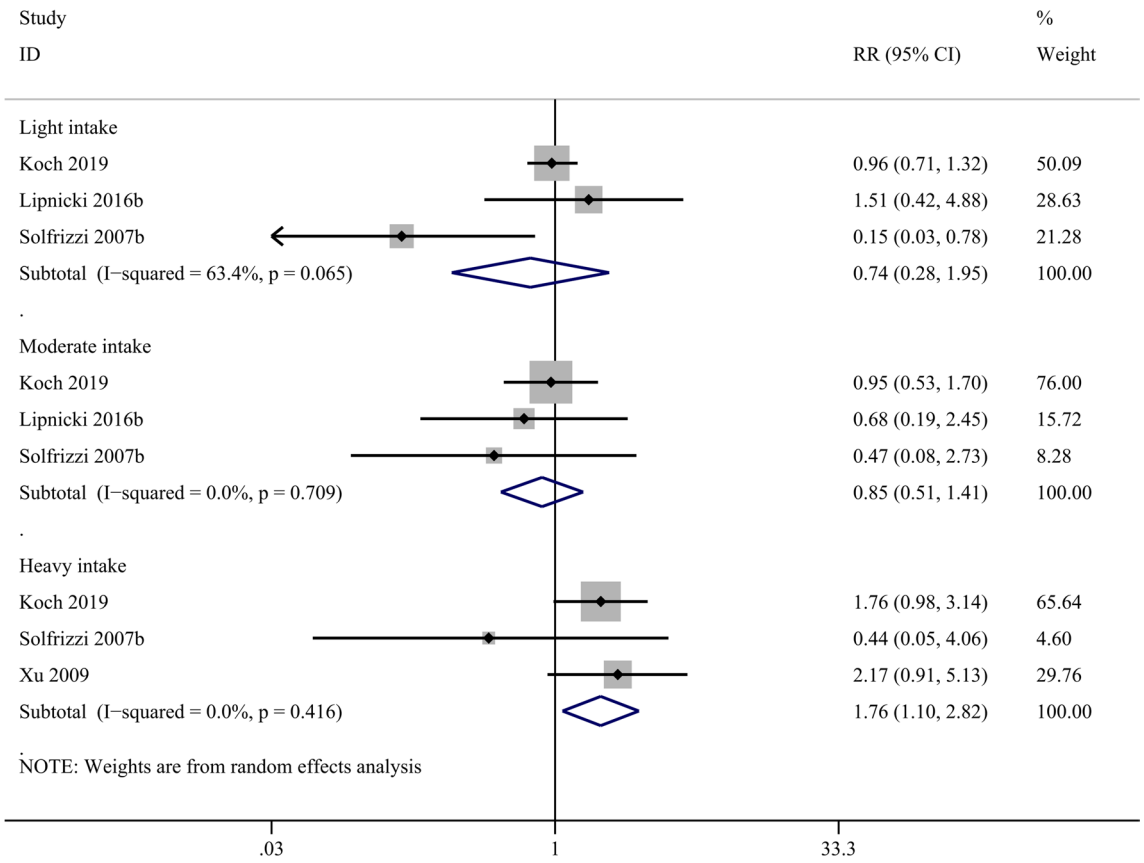

Fig. 4 Forest plot of relative risks (RRs) of PDM for different alcohol categories

Discussion

In this meta-analysis, we systematically evaluated the relation between alcohol intake and the risk of MCI and PDM for the first time. We found a potential linear relation that alcohol drinking might increase the risk of MCI although the association seemed to be instable. Furthermore, it suggested that there was also a potential nonlinear relation between alcohol intake and risk of PDM. Excessive alcohol intake (more than 16 drinks/week or 27.5 g/day) would elevate the risk of PDM. But the relation was not robust too.

Earlier studies about alcohol drinking and cognition defined cognitive impairment in terms of performance in a variety of neuropsychological tests and did not validate it by any clinical or diagnostic concepts [31]. The different measures of cognitive impairment defined based on psychometric made it difficult to compare different studies and to determine the relevance of cognitive impairment in participants' lives [8]. For instance, some prospective studies found that alcohol intake may improve the cognitive performance measured by Cognitive Abilities Screening Instrument (CASI) [32], the modified Telephone Interview for Cognitive Status (TICS-m) [33], and psychomotor speed and flexibility tests [34]. Furthermore, one study reported a *U* shape association that nondrinkers and heavy drinkers had the lowest CASI scores, while moderate drinkers had better cognitive performance [35] which was consistent with Launer 1998 based on Mini-Mental State Examination (MMSE) [36]. Nevertheless, one study found that alcohol intake was related to lower cognitive performance in a dose–response manner, even at low levels [37]. The concept of MCI takes into account both psychometric and clinical aspects, and so it may be considered to signify a clinically relevant entity itself [8, 38]. Identifying MCI could well be to help engage people in clinical research and offer pragmatic advice on life style and health modifications, which undoubtedly have a beneficial effect on cognitive performance and prevention of dementia.

A significant number of studies have considered the relation between alcohol intake and risk of MCI and PDM. However, the results might be confused. Some prospective studies found that alcohol intake was associated with a reduced risk for MCI [39, 40]. In the contrast, other studies did not find a protective effect of alcohol for MCI [9, 10, 41]. One study found alcohol drinking was not related to risk of PDM [42]. However, another research revealed that light–moderate alcohol drinker (defined as consuming no more than two drinks a day for at least 6 months) was a risk

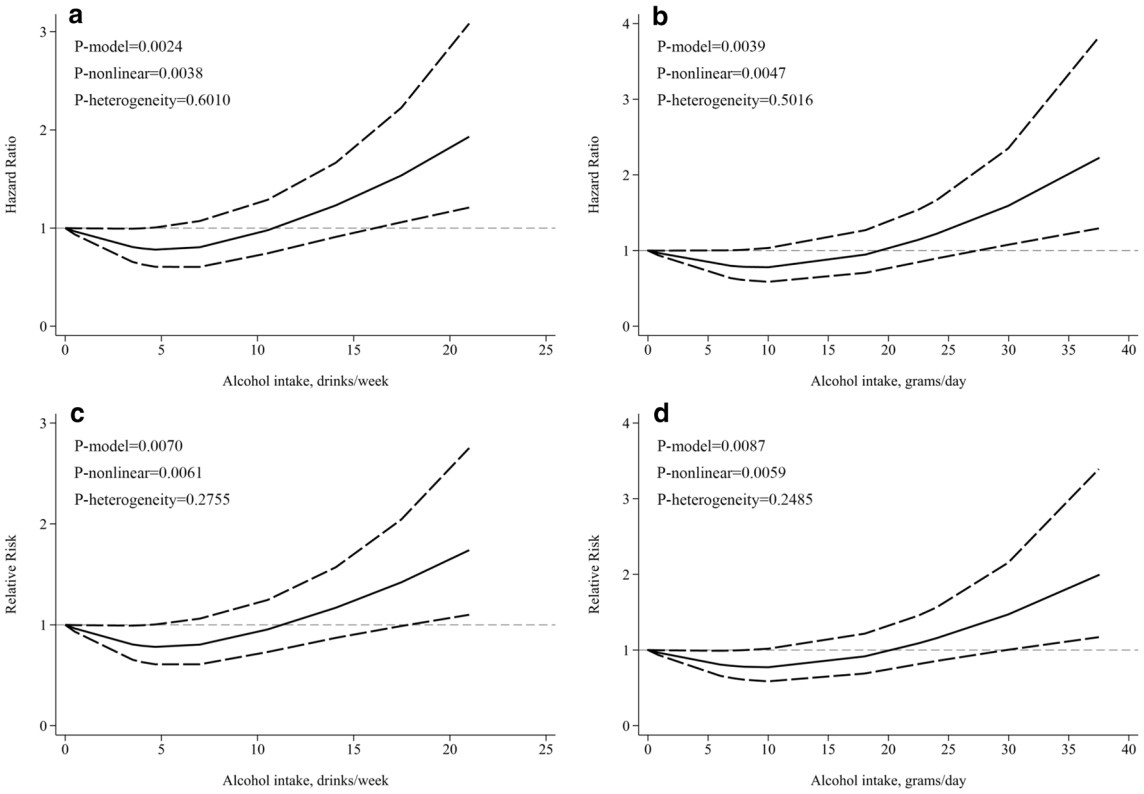

Fig. 5 Non-linear association of alcohol intake and risk of PDM (**a** using "drinks/week" as alcohol unit and "hazard ratio" as statistic index; **b** using "grams/day" as alcohol unit and "hazard ration" as statistic index; **c** sensitivity analysis when unsing "drinks/week" as alcohol unit; **d** sensitivity analysis when using "grams/day" as alcohol unit)

factor for PDM [43]. As noticed in the above studies, alcohol drinking was often used as a confounding factor when the researchers explored another target potential factor. And then alcohol drinking was always defined in different variable forms artificially. And the most common is the dichotomous variable as far as we know. However, a more detailed relations might be obscured due to an artificially inappropriate definition of alcohol drinking. Heterogeneity of alcohol exposure definition in primary studies made it more difficult to explore the relation of alcohol and risk of MCI or PDM. Based on the above considerations, and to meet the applicable scope of the dose effect meta-analysis model, we only included the primary studies with at least three levels of alcohol exposure.

Primary studies eligible to Part 1 of this study seemed few apparently. We found no significant relation between any alcohol intake categories and risk of MCI in categorical meta-analysis. To our knowledge, none of exiting study had reported the dose–response relation between alcohol intake and risk of MCI clearly. However, a potential weak relation could be found when pooled in drinks/week, but it disappeared when pooled in grams/day. We could not exclude the potential bias of defining the transfer criteria artificially, although researchers always did so based on previous study [7, 18–20]. As there was significant clinical uncertainty of the same drinking frequency, and heterogeneous amounts of alcohol was contained in one drink in different areas, the finding should be interpreted with a high degree of caution. All in all, the circumstantial results seemed far from robust and needs to be further verified by future research.

We found a potential nonlinear relation between alcohol intake and risk of PDM in this meta-analysis for the first time. Of the included five studies, only one study reported a significant relation in a certain dose (< 1 drinks/day, HR = 0.15; 95% CI 0.03- 0.78) [9]. Only heavy alcohol intake was found significant associated with risk of PDM in categorical meta-analysis. The results in dose–response meta-analysis corroborated. We revealed a risky alcohol intake dose (> 16 drinks/week, or 27.5 g/day) for PDM. Sensitivity analysis when adding another prospective study using "RR" as statistic index showed higher thresholds for safe alcohol intake. However, this relation was influenced by Xu [11] and Koch [12]. The relation seemed to be not robust enough. It might be due to some eligible studies were not high-quality [10, 11] and the larger effect size contributed by Xu [11] and Koch [12]. Thus, it should be confirmed by more study in the future. And relation between risk of PDM

and alcohol intake that was less than the threshold or severe high intake need to be more clarified.

Many studies explored the association between alcohol intake and risk of dementia. One meta-analysis found a significant dose–response relation between alcohol intake and risk of dementia [7]. It revealed that modest alcohol intake (≥ 12.5 g/day) was associated with a reduced risk of dementia with 6 g/day of alcohol conferring a lowest risk, while heavy drinking (≥ 23 drinks/week or ≥ 38 g/day) would significantly elevate the risk. Our results provided a smaller threshold (16 drinks/week or 27.5 g/day) for safe alcohol intake dose for preventing dementia. Alcohol drinking might be more dangerous to cognitive function when taking MCI into consideration. Ding found that increased alcohol intake was associated with brain atrophy [44]. In the contrast, Gu found light to moderate alcohol intake was associated with larger total brain volume and was potentially beneficial for brain aging [45]. Furthermore, Chen highlighted the dose-dependent effects of vascular risk factors (VRF) on bilateral dorsolateral prefrontal cortex (DLPFC) in MCI individuals, and the dynamic compensatory neural processes that fluctuated along with variations of VRF loading could be key role in the progression of MCI [46]. These findings indicated complex neurophysiological mechanism explaining such clinical feature.

As noticed, though no significant statistical heterogeneity was found between included studies, heterogeneous diagnostic criteria and procedures for MCI in primary studies might lead to potential bias. It may be because that the concept of MCI continued to evolve and improve during the past decades even based on observation on different populations [38]. Additionally, the fact that studies originated from different countries or continents might bring about potential clinical heterogeneity too. To be specific, different regions often signified heterogeneous ethnicity, alcohol measurement, drinking preferences and so on which might contribute to different results finally [47]. However, we couldn't conduct further exploration based on above considerations due to data limitation, which could rely on more detailed reported data for resolution in the future.

The primary strength of our study was that it was the first dose–response meta-analysis to assess the relation between alcohol intake and MCI as well as PDM. And the dose–response design which could better assess the strength of causal relation [48]. Another significant strength of our study was the prospective design of included studies. Furthermore, we had used "hazard ratio" as an index to explain our results. There were also some limitations to this study. Firstly, the included study and pooled sample size were limited. It explained the instability of our results to some extent. Secondly, we could not conduct more subgroup exploration due to the restriction of data about the influence of type of alcohol [45, 49], gender [50], apolipoprotein E4 status [51] etc. Thirdly, we couldn't avoid possible misclassification of alcohol intake when considering that alcohol dose consumed was always self-reported in primary studies. Fourthly, we cannot exclude the potentially spurious association caused by some confounders as adjusted confounders were inconsistent in different studies. Lastly, we could not explore more about the influence of different originated regions of included studies as well as heterogeneous diagnostic criteria and procedures for MCI on pooled results due to data limitation.

Conclusion

There was a nonlinear dose–response relation between alcohol intake and risk of PDM. Excessive alcohol intake (> 16 drinks/week, or 27.5 g/day) was associated with higher risk of PDM. And there was a potential unstable linear dose–response relation between alcohol intake and risk of MCI. High quality studies should be conducted to exam our preliminary results.

Author contributions KY, PY were responsible for the conception and design of the study. YL and LH were in charge literature search data acquisition. YL, LH, JL and XH selected eligible studies, and extracted the data. YL and PY analyzed and interpreted the data. YL wrote the first draft of the manuscript. Other co-authors had given critical advice to the manuscript. All authors read and approved the final manuscript. We sincerely thanked XZ, YG, JF and XH for important help in getting the full articles though they could not be identified as co-authors. And we would like to thank the authors of the article "Risk Factors for Mild Cognitive Impairment, Dementia and Mortality: The Sydney Memory and Ageing Study" [10] for providing us with the extra data we requested.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Human and animal rights As this study was a meta-analysis based on published studies, as such, did not involve human or animal participants. And there is no need for an ethical approval or informed consent requested by animal and human experiments.

Informed consent For this type of study: a systematic review based on published studies, informed consent is not required.

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