



Revealing a Novel Landscape of the Association Between Blood Lipid Levels and Alzheimer's Disease: A Meta-Analysis of a Case-Control Study

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Tang Q, Wang F, Yang J, Peng H, Li Y, Li B and Wang S (2020) Revealing a Novel Landscape of the Association Between Blood Lipid Levels and Alzheimer's Disease: A Meta-Analysis of a Case-Control Study. Front. Aging Neurosci. 11:370. doi: 10.3389/fnagi.2019.00370 **Objectives:** Blood lipid profiles have been ambiguously reported as biomarkers of AD in recent years. This study was conducted to evaluate the correlation between blood lipid levels and AD in later-life and to explore the effectiveness and reliability of blood lipid profiles as biomarkers of AD.

Methods: Database searching was conducted using PubMed, the Cochrane Library, EMBASE, and Medline. This study was designed following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria. Review Manager 5.3 (RevMan 5.3) software was adopted to perform meta-analysis evaluating the standard mean difference (SMD) with its 95% confidence intervals (CI).

Results: A total of 5,286 participants were enrolled from 27 case–control studies in this meta-analysis. The pooled results demonstrated that total cholesterol (TC) level was significantly associated with AD in late-life (SMD = 0.17, 95% CI: [0.01, 0.32], P = 0.03), especially in the subgroup under 70 years old (SMD: 0.45, 95% CI: [0.11, 0.79], P = 0.01) and the subgroup of Western population (SMD: 0.29, 95% CI: [0.04, 0.53], P = 0.02). In the subgroup under 70 years old, the high-density lipoprotein cholesterol (HDL-C) level (SMD = -0.50, 95% CI: [-0.76, -0.25], P = 0.0001) and the low-density lipoprotein cholesterol (LDL-C) level (SMD = 0.59, 95% CI: [0.02, 1.16], P = 0.04) in the AD group were significantly lower and higher than in the control group, respectively. In the subgroup with a sample size larger than 100 subjects, the LDL-C level was significantly higher in AD patients than in the control elderly group (SMD = 0.31, 95% CI: [0.05, 0.56], P = 0.02). There was no significant association between triglyceride (TG) levels and AD in late-life (SMD = -0.00, 95% CI: [-0.12, 0.12], P = 1.00).

Conclusion: TC can be a new predictive biomarker of AD or cognitive decline in later-life. Increased TC levels are found to be associated with an elevated risk of AD. Decreased HDL-C levels and increased LDL-C levels may relate to an elevated risk of AD in subjects aged 60–70. Further comprehensive researches will be necessary in the future.

Keywords: Alzheimer's disease, blood lipid levels, total cholesterols, high-density lipoprotein cholesterol, lowdensity lipoprotein cholesterol, triglyceride, biomarker, meta-analysis

INTRODUCTION

Alzheimer's Disease (AD) is the most common type of all neurodegenerative diseases and is marked with three continuous stages, which includes preclinical stage, mild cognitive impairment (MCI) stage, and dementia stage (Zarrouk et al., 2018). Around 50 million people are suffering from dementia worldwide, two-thirds of whom are diagnosed with AD. The brain of an AD patient is identified as synaptic dysfunction, tau phosphorylation and accumulation of the amyloid- β peptide (A β) in brain tissues (Querfurth and LaFerla, 2010); the 42-residue form of A β (A β 42) is the main segment of the deposits (Sittiwet et al., 2018). AD kills more people in the U.S. than breast cancer and prostate cancer combined. It has developed into a major public health problem and there will be a new case somewhere in the world every 3 s (Patterson, 2018).

In the past, behavioral testing and neuroimaging were commonly used to diagnose AD. The concentration of Aβ42 and the phosphorylation of total-tau (t-tau) and phospho-tau (ptau) (Hampel et al., 2011; Dubois et al., 2014) are accepted as biomarkers of AD (Zarrouk et al., 2018). However, these methods may not only be invasive but also unaffordable to some patients. Blood lipid profiles as biomarkers may be more accessible, affordable, and less invasive modalities to detect and diagnose AD (Zarrouk et al., 2018; Liu et al., 2019). Some lipids extracted from peripheral blood have been validated to predict development to either amnestic mild cognitive impairment (aMCI) or AD with over 90% accuracy (Mapstone et al., 2014). The blood-based lipid profiles were an appropriate source for AD biomarker screening (Zarrouk et al., 2018).

Alois Alzheimer noted that there are cholesterol and triglycerides inside lipid droplets, the accumulation of which was related to cellular stress and resulting in AD (Alzheimer, 1907). Blood lipid profiles have potentially modifiable influencing factors, including age, sex, diet, exercise, medications, educational levels, and/or lifestyle, such as smoking, eating habits, and various other personal choices. Measures can be applied earlier to prevent worsening cognitive decline potentially when blood lipid levels are abnormal. Studies on the risk factors of AD are critical to the prevention and treatment of AD and cognitive impairment. Nevertheless, there is still no coherent conclusion in this field. The parameters of blood lipid profiles have been recognized as potential biomarkers and have been reported to be associated with the risk of AD, which include total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) (Wu et al., 2019). Lipids including TC and HDL-C are currently used as tools to assess the risk of AD and dementia in midlife (Anstey et al., 2017). It has been proven that middle-aged high cholesterol levels are related to cognitive impairment or AD in old age (Rantanen et al., 2017), and midlife cholesterol has been shown to predict AD (Kivipelto et al., 2001; Strand et al., 2013). However, the relationship between AD and cholesterol or lipid levels in the elderly has not been determined yet.

The opinion that blood lipid profiles can be biomarkers of AD is still ambiguous, which is limited by a lack of compatible data for pooling on the association between lipid and cognitive outcomes (Pappolla et al., 2003; Popp et al., 2012). The present study aims to evaluate the link between blood lipid levels and AD and whether they are reliable biomarkers of AD in the later-life of patients.

METHODS

Search Strategy

This study was designed following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria (Stroup et al., 2000; Moher et al., 2009). Databases including PubMed, Embase, the Cochrane Library and Medline were retrieved for qualified literature that was published before March 2019. Only English-language literatures were reviewed in this study. The search strategy followed the PICOS principles. Mesh terms and topic terms were used as the searching term, including "Cholesterol," and "Alzheimer's disease," "AD," "Alzheimer*," "Senile Dementia," "Alzheimer Type Dementia," "Alzheimer Type Dementia," and "ATD." Additional published literature identified in the selection of the reference of the initially retrieved articles was also investigated in our meta-analysis.

Inclusion Criteria

Studies were identified eligible if they met the criteria as defined below:

- (1) Patients who were diagnosed with AD and at least 60 years old were defined as participants of the case group. The diagnosis criteria were based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984).
- (2) Participants did not use lipid-lowering drugs during the study.
- (3) The mean age of the population was older than 60 years old.
- (4) The control group was composed of the counterpart of the case group who were not diagnosed with AD and had normal cognition.

References	Nation	Region	Study type	Data source	San	nple size	Mean ag	e (range)	Gendar r	atio (M/F)	Outcome	NOS scores
					AD	Control	AD	Control	AD	Control		
Chen et al. (2019)	China	Asia	Case-control	Single-centered	117	117	67.64 ± 6.65	66.06 ± 6.00	56/61	44/73	TC, TG HDL-C, LDL-C	7
Kouzuki et al. (2018)	Japan	Asia	Case-control	Single-centered	42	18	80.5 ± 5.7	75.6 ± 5.5	16/26	5/13	TC, TG HDL-C, LDL-C	5
Li et al. (2017)	China	Asia	Case-control	Single-centered	118	120	71.81 ± 9.66	70.45 ± 9.52	75/43	68/52	TC, TG HDL-C, LDL-C	6
Zheng et al. (2016)	China	Asia	Case-control	Multi-centered	207	256	80.67 ± 8.19	81.66 ± 6.38	68/139	89/167	TC, TG HDL-C, LDL-C	5
Yassine et al. (2016)	America	North America	Case-control	Single-centered	26	47	77 ± 10	78 ± 7	9/17	20/27	TC	7
Alam et al. (2014)	India	Asia	Case-control	Single-centered	75	120	66.2 ± 9.2	63.8 ± 8.2	na	na	TC, TG HDL-C, LDL-C	8
Chang et al. (2014)	China	Asia	Case-control	Multi-centered	44	62	80 ±8.92	79.63 ± 7.85	na	na	TC, TG, HDL-C	6
Li et al. (2015a)	China	Asia	Case-control	Single-centered	201	257	76.79 ± 5.65	75.88 ± 6.50	90/111	121/136	TC, TG HDL-C, LDL-C	6
Zhao et al. (2014)	China	Asia	Case-control	Single-centered	48	37	69.32 ± 5.53	71.06 ± 5.87	23/25	19/18	TC, TG HDL-C, LDL-C	5
Popp et al. (2013)	Switzerland	Europe	Case-control	Single-centered	106	87	71.1 ± 7.87	67.7 ± 9.13	36/68	44/43	TC	8
Xiao et al. (2012)	China	Asia	Case-control	Single-centered	104	104	77.8 ± 6.74	76.5 ± 6.14	57/47	56/48	TC, TG HDL-C, LDL-C	5
Popp et al. (2012)	Switzerland	Europe	Case-control	Single-centered	53	43	71.23 ± 8.29	67.33 ± 9.04	20/33	21/22	TC	8
Zengi et al. (2011)	Turkey	Asia	Case-control	Single-centered	21	20	76 ± 7.8	81 ± 7.2	10/11	11/9	TC, TG HDL-C, LDL-C	7
Singh et al. (2012)	India	Asia	Case-control	Single-centered	70	75	50-85	50-85	na	na	TC, TG HDL-C, LDL-C	6
Kolsch et al. (2010)	Germany	Europe	Case-control	Multi-centered	411	201	71.9 ± 8.5	69.5 ± 6.9	162/249	106/95	TC	5
Cascalheira et al. (2009)	Portugal	Europe	Case-control	Single-centered	19	36	75.6 ± 2.11	70.7 ± 1.73	10/9	18/18	TC	8
Ban et al. (2009)	Japan	Asia	Case-control	Single-centered	197	47	80 ± 14.04	75 ± 6.86	79/118	29/18	TG, HDL-C, LDL-C	5
Raygani et al. (2006)	Iran	Asia	Case-control	Multi-centered	94	111	74.2 ± 10	72 ± 11.4	41/53	41/70	TC, TG HDL-C, LDL-C	7
Cankurtaran et al. (2005)	Turkey	Asia	Case-control	Single-centered	120	803	74 ± 7.6	71.4 ± 5.9	41/79	297/504	TC, TG HDL-C, LDL-C	7
Yamamoto et al. (2005)	Japan	Asia	Case-control	Single-centered	61	32	80 ± 6	77 ± 5	24/37	17/15	TC, TG HDL-C, LDL-C	6
Watanabe et al. (2004)	Japan	Asia	Case-control	Single-centered	34	63	76 ± 9	72 ± 11	34 man only	63 man only	TC, TG HDL-C, LDL-C	6
Borroni et al. (2003)	Italy	Europe	Case-control	Single-centered	60	45	71.4 ± 9.7	71.2 ± 8.7	22/38	16/29	TC	7
Teunissen et al. (2003)	The Netherlands	Europe	Case-control	Single-centered	34	61	73.22 ± 10.04	68.39 ± 6.68	14/20	35/26	TC	6
Schonknecht et al. (2002)	Germany	Europe	Case-control	Single-centered	14	10	75.4 ± 10.3	69.0 ± 5.8	8/6	6/4	TC	7
Hoshino et al. (2002)	Japan	Asia	Case-control	Single-centered	82	40	77 ± 6.8	84.2 ± 3.1	23/59	13/27	HDL-C, LDL-C	5
Wada (2000)	Japan	Asia	Case-control	Single-centered	36	15	77.3 ± 4.9	71.8 ± 6.1	17/19	2/13	TC, TG HDL-C, LDL-C	6
de Bustos et al. (2000)	Spain	Europe	Case-control	Multi-centered	44	21	73.8 ± 8.3	69.3 ± 5.6	18/26	8/13	TC	7

AD, Alzheimer's Disease; TC, Total Cholesterol; TG, Triglyceride; HDL-C, High-density Lipoprotein Cholesterol; LDL-C, Low-density Lipoprotein Cholesterol; M, male; F, female; MMSE, Mini-Mental State Examination; NOS, Newcastle-Ottawa Scale; na, not available.

- (5) The study reported its original data in the mean, standard deviation (SD), or standard errors (SE) of blood lipid profiles (TC, HDL-C, LDL-C, and TG).
- (6) Case-control studies of human beings are eligible for this review.
- (7) Studies were published in English between January 2000 and March 2019.

Exclusion Criteria

- (1) Twin studies and studies with duplicate data, incomplete or erroneous reporting of data.
- (2) Case-control studies reporting other types of dementia such as vascular dementia, dementia with Lewy bodies, frontotemporal dementia, mixed dementia and other secondary or post-traumatic dementia, not AD.
- (3) The participants of the control group were diagnosed with other types of dementia such as vascular dementia, dementia with Lewy bodies, frontotemporal dementia, mixed dementia, and other secondary or post-traumatic dementia.
- (4) Participants who were suffering from severe physical or mental disease.

- (5) The quality of literature judged by the Newcastle-Ottawa Scale was low (scores < 5).
- (6) Studies reporting inadequate information, for example, data only contained mean without SD/SE.

Data Extraction

The following data have been extracted independently and cross-checked by two authors (Qianyun Tang and Fengling Wang): first authors, titles of references, time of publication, nations, and regions, study designs, sample sizes, data sources, mean ages, outcomes, quality scores, and diagnostic criteria of AD. The extracted data were noted in an Excel file, which was checked by the third author (Shuhong Wang). Any disagreements were resolved after discussion.

Quality Evaluation

Studies were assessed for bias using the Newcastle–Ottawa Scale (NOS) by two reviewers (Qianyun Tang and Fengling Wang) (Stang, 2010). There will be a third reviewer (Shuhong Wang) to discuss the results if any disagreement exists. Each case-control study was evaluated according to eight points



covering three parts as follows: selection, comparability, and exposure. We use stars to symbolize scores of each item in the scale, with one star representing one point and nine stars as the highest quality. Studies with scores <5 were regarded as low quality.

Statistical Analysis

Review Manager 5.3 (RevMan 5.3) software was applied to conduct the present meta-analysis. Dichotomous data were reported in terms of the odds ratio (OR), with 95% CI, and continuous data were reported in terms of the standard mean difference (SMD), with 95% CI. An α value equal to 0.1 and a *P*-value of < 0.05 were considered statistically significant. The heterogeneity of each study was analyzed using the I^2 statistic and the Cochrane-Q test. Studies with an I^2 statistic between 25 and 50% were considered to be low-heterogeneous, those between 50 and 75% to be moderate-heterogeneous, and those greater than 75% to be high-heterogeneous. In a study with a P > 0.1, or $I^2 \leq 50\%$, signifying little heterogeneity between studies, a fixed-effect model was employed, or a random effect model was adopted.

RESULTS

Search Results

The literature search yielded a total of 2,617 articles, with 2,593 articles collected through database searching and 24 additional articles identified through other searching methods. A total of 1,183 articles remained after duplicate articles were removed. After reviewing the titles and abstracts, 799 articles were found to be unrelated and then excluded, while 384 studies were identified as potentially eligible for inclusion. After reviewing the full article, 357 articles were excluded, since 232 were reviews, 35 were cross-sectional studies, 22 were reporting incomplete data, 18 were cohort studies, 15 involved subjects whose mean age was under 60, 15 were animal trials, 10 were inaccessible, 8 were twin studies, and 2 had participants using statins. After excluding the above papers, 27 articles (Table 1) were eligible for inclusion in this meta-analysis (de Bustos et al., 2000; Wada, 2000; Hoshino et al., 2002; Schonknecht et al., 2002; Borroni et al., 2003; Teunissen et al., 2003; Watanabe et al., 2004; Cankurtaran et al., 2005; Yamamoto et al., 2005; Ravgani et al., 2006; Ban et al., 2009; Cascalheira et al., 2009; Kolsch et al., 2010; Zengi

TABLE 2 | Newcastle-Ottawa quality assessment scale for case control studies.

References		Selectio	on		Comparability	/	Exposure		Quality Scores‡
	Definition of cases	Representativeness of cases	Selection of Controls	Definition of Controls	Basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	_
Chen et al. (2019)	*	*	*	*	**	-	*	-	7
Kouzuki et al. (2018)	*	-	*	*	*	-	*	-	5
Li et al. (2017)	*	*	-	*	**	-	*	-	6
Zheng et al. (2016)	*	*	-	*	*	-	*	-	5
Yassine et al. (2016)	*	*	*	*	*	*	*	-	7
Alam et al. (2014)	*	*	*	*	**	*	*	-	8
Chang et al. (2014)	*	*	-	*	*	*	*	-	6
Li et al. (2015a)	*	-	*	*	*	*	*	-	6
Zhao et al. (2014)	*	-	-	*	*	*	*	-	5
Popp et al. (2013)	*	*	*	*	**	*	*	-	8
Xiao et al. (2012)	*	-	-	*	*	*	*	-	5
Popp et al. (2012)	*	*	*	*	**	*	*	-	8
Zengi et al. (2011)	*	*	*	*	*	*	*	-	7
Singh et al. (2012)	*	*	*	*	*	-	*	-	6
Kolsch et al. (2010)	*	-	-	*	*	*	*	-	5
Cascalheira et al. (2009)	*	*	*	*	**	*	*	-	8
Ban et al. (2009)	*	-	*	*	*	-	*	-	5
Raygani et al. (2006)	*	-	*	*	**	*	*	-	7
Cankurtaran et al. (2005)	*	*	-	*	**	*	*	-	7
Yamamoto et al. (2005)	*	-	*	*	*	*	*	-	6
Watanabe et al. (2004)	*	*	*	*	*	-	*	-	6
Borroni et al. (2003)	*	*	*	*	**	-	*	-	7
Teunissen et al. (2003)	*	-	*	*	**	-	*	-	6
Schonknecht et al. (2002)	*	-	*	*	**	*	*	-	7
Hoshino et al. (2002)	*	-	*	*	*	-	*	-	5
Wada (2000)	*	-	*	*	**	-	*	-	6
de Bustos et al. (2000)	*	*	*	*	**	-	*	-	7

Stars are awarded such that the highest-quality studies are awarded up to nine stars. A maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability categories. \ddagger One star \bigstar for one score.

TABLE 3 | Results of meta-analysis.

Outcomes of interest	Studies, no.	AD, no.	Control, no.	SMD (95%CI)	P-value*	Effect model		Hete	erogeneit	У
							χ ²	df	I ² , %	P-value
TC	25	2159	2761	0.17 [0.01, 0.32]	0.03	RE	131.02	24	82	<0.00001
HDL-C	18	1671	2297	-0.15 [-0.34, 0.05]	0.15	RE	127.09	17	87	< 0.00001
LDL-C	17	1627	2235	0.18 [-0.02, 0.38]	0.08	RE	118.96	16	87	<0.00001
TG	17	1589	2257	-0.00 [-0.12, 0.12]	1.00	RE	42.09	16	62	0.0004

AD, Alzheimer's Disease; TC, Total Cholesterol; TG, Triglyceride; HDL-C, High-density Lipoprotein Cholesterol; LDL-C, Low-density Lipoprotein Cholesterol; SMD, standardized mean difference; 95%Cl, 95% confidence interval; RE, random effects model.

~		AD			Control			Std. Mean Difference	Std. Mean Difference	в		AD		C	ontrol			Std. Mean Difference	Std. Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	1 SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI	Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV, Random, 95% CI
lam 2014	170.7	31.7	75	167.6	5 22.8	120	4.5%	0.12 [-0.17, 0.40]		Alam 2014	40.5	95	75	42.4	83	120	6.0%	-0.221-0.50.0.071	
orroni 2003	225.7	40.1	60	200.	5 48.9	45	4.0%	0.57 [0.17, 0.96]		Res 2000	40.0	4	107	50	0.0	47	E 79/	1 20 10 02 1 001	
ankurtaran2005	213.9	44.6	120	213	2 46.5	803	5.0%	0.04 [-0.15, 0.23]	+	Dan 2009	30		197	30	3	41	3.176	1.20 [0.92, 1.59]	
Cascalheira 2009	189.98	10.02	19	186.8	3.55	36	3.1%	0.47 [-0.10, 1.03]		Cankurtaran2005	57.1	22.8	120	55.8	14.9	803	6.4%	0.08 [-0.11, 0.27]	
Chang2014	4.43	1.04	44	4.2	5 1.24	62	4.0%	0.15 [-0.23, 0.54]		Chang2014	1.06	0.2	44	1.03	0.3	62	5.4%	0.11 [-0.27, 0.50]	
chen 2018	214.01	43,18	117	191.9	5 37.62	117	4.7%	0.54 [0.28, 0.80]		Chen 2018	54.2	15.12	117	60.04	9.56	117	6.1%	-0.46 [-0.72, -0.20]	
Koutuki 2017	100 3	45.1	42	211	300	18	3.3%	-0.04 [-0.36, 0.46]		Hoshino2002	52.3	14.1	82	53.4	12.4	40	5.5%	-0.081-0.46.0.301	
Kölsch 2010	234.13	47.84	411	241.1	3 50.05	201	5.1%	-0.14 [-0.31, 0.02]		Kouzuki 2017	64.5	21.6	42	63.7	21.4	18	4.5%	0.041.0.52 0.591	
Li H 2017	4.24	1.13	118	4.65	5 0.75	120	4.7%	-0.43 [-0.68, -0.17]		NULL CONT	4.0	21.0	44	00.1	0.04	10	4.070	0.04 [-0.02, 0.00]	
Popp 2012	235.76	46.61	53	225.3	3 39.67	43	3.9%	0.24 [-0.17, 0.64]		LI H 2017	1.25	0.36	118	1,41	0.34	120	6.1%	-0.46 [-0.71, -0.20]	
Popp 2013	238	47.77	106	21	5 46.17	87	4.5%	0.49 [0.20, 0.77]		Raygani 2006	35	6.6	94	40.2	7.4	111	6.0%	-0.74 [-1.02, -0.45]	
Raygani 2006	185	29	94	175	5 24.5	111	4.6%	0.37 [0.10, 0.65]		Singh2012	41.54	8.4	70	46.29	9.09	75	5.7%	-0.54 [-0.87, -0.21]	
Schonknecht 2002	193.4	21.5	14	182.	22.6	10	2.1%	0.47 [-0.35, 1.29]		Wada2000	69	21	36	64	19	15	4.2%	0.24 [-0.36, 0.85]	
Singh2012 Toupisson 2003	258 78	14 34	34	248.2	3 30.37	61	4.179	1.37 [1.01, 1.73]		Watanabe2004	50	14	34	50	15	63	5.2%	0.00 [-0.42, 0.42]	
Naria2000	194	33	36	20	7 40	15	2.9%	-0.361-0.97 0.241		Vice 2012	1 22	0.21	104	1.44	0.21	104	6.0%	0.251.0.62 .0.091	
Watanabe2004	167	29	34	176	5 36	63	3.8%	-0.26 [-0.68, 0.15]		Vamamata 2005	1.00	45	64		40	22	E 201	0.00[-0.03, -0.00]	
Gao 2012	4.48	0.89	104	4.	1 1.04	104	4.6%	0.39 [0.12, 0.67]		ramamoto2005	02	15	01	01	18	32	5.2%	0.06 [-0.37, 0.49]	1
ramamoto2005	187	38	61	190	0 44	32	3.8%	-0.07 [-0.50, 0.35]		Yu2014	1.32	0.36	201	1.33	0.77	257	6.4%	-0.02 [-0.20, 0.17]	T
Yassine 2016	185	33	26	18	31	47	3.5%	0.12 [-0.35, 0.60]		Zengi2012	1.24	0.078	21	1.26	0.073	20	4.1%	-0.26 [-0.87, 0.36]	
Yu2014	5.12	0.98	201	4.8	0.69	257	5.0%	0.30 [0.12, 0.49]		Zhao2014	45.9	10.3	48	57.8	14.6	37	5.0%	-0.95 [-1.41, -0.50]	
2bao2014	9.73	20.21	21	4.9	48.0	20	3.8%	-0.85 [-1.49, -0.21]		Zheng2016	1.3	0.34	207	1.38	0.41	256	6.4%	-0.21 [-0.39, -0.03]	-
Zheng2016	4.76	1.07	207	4.5	7 1.24	256	5.0%	0.16[-0.02, 0.35]					241			- 30		terest event	
										Total (95% CI)			1671			2207	100.0%	0 15 1.0 24 0.051	•
Total (95% CI)			2159			2761	100.0%	0.17 [0.01, 0.32]	•	Total (55% Ci)			10/1			2231	100.076	-0.10[-0.34, 0.00]	
Heterogeneity: Tau ^a =	0.11; Chi	*= 131.	02, df =	24 (P	< 0.0000	11); l ² = 8	82%	-	1 05 0 05 1	Heterogeneity: Tau ² :	= 0.15; Ch	$h^2 = 12$	7.09, df	= 17 (P	< 0.000	(01); I ² =	87%		-2 -1 0 1 3
lest for overall effect:	Z = 2.14 ((P = 0.0)	3)						Control AD	Test for overall effect	: Z = 1.44	+ (P = 0.	.15)						Control AD
C										D									Collect AD
0		AD			Control		-	Std. Mean Difference	Std. Mean Difference	U		AD		C	ontrol			Std. Mean Difference	Std. Mean Difference
Indu as Cubaraun		00	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random. 95% Cl
study of Subgroup	Mean	50	10181	THIS OFF															
Nam 2014	Mean 104.4	28.8	75	100.6	21.8	120	6.3%	0.15 [-0.14, 0.44]		Alam 2014	170.7	31.7	75	167.6	22.8	120	4.5%	0.12 [-0.17, 0.40]	
Alam 2014 Bao 2009	Mean 104.4 123	28.8	75 107	100.6	21.8	120	6.3%	0.15 [-0.14, 0.44]		Alam 2014 Borroni 2003	170.7 225.7	31.7 40.1	75 60	167.6 200.5	22.8 48.9	120 45	4.5%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96]	<u> </u>
Alam 2014 Ban 2009	Mean 104.4 123	28.8	75 197	100.6	21.8	120 47	6.3% 6.1%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12]		Alam 2014 Borroni 2003 Cankurtaran2005	170.7 225.7 213.9	31.7 40.1 44.6	75 60 120	167.6 200.5 212	22.8 48.9 46.5	120 45 803	4.5% 4.0% 5.0%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23]	
Alam 2014 Ban 2009 Dankurtaran2005	Mean 104.4 123 129	28.8 2 44.2	75 197 120	100.6 121 130.3	21.8 4 60.9	120 47 803	6.3% 6.1% 6.8%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17]	+	Alam 2014 Borroni 2003 Cankurtaran2005 Cascalheira 2009 Chano2014	170.7 225.7 213.9 189.98 4.43	31.7 40.1 44.6 10.02	75 60 120 19 44	167.6 200.5 212 186.89 4.25	22.8 48.9 46.5 3.55 1.24	120 45 803 36 62	4.5% 4.0% 5.0% 3.1% 4.0%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54]	
Alam 2014 Ban 2009 Cankurtaran2005 Chen 2018	Mean 104.4 123 129 130.67	28.8 2 44.2 34.73	75 197 120 117	100.6 121 130.3 95.25	21.8 4 60.9 23.46	120 47 803 117	6.3% 6.1% 6.8% 6.4%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47]		Alam 2014 Borroni 2003 Cankurtaran2005 Cascalheira 2009 Chang2014 Chen 2018	170.7 225.7 213.9 189.98 4.43 214.01	31.7 40.1 44.6 10.02 1.04 43.18	75 60 120 19 44 117	167.6 200.5 212 186.89 4.25 191.96	22.8 48.9 46.5 3.55 1.24 37.62	120 45 803 36 62 117	4.5% 4.0% 5.0% 3.1% 4.0% 4.7%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54] 0.54 [0.28, 0.80]	
Alam 2014 San 2009 Cankurtaran2005 Chen 2018 Hoshino2002	Mean 104.4 123 129 130.67 119.1	28.8 2 44.2 34.73 27.7	75 197 120 117 82	100.6 121 130.3 95.25 110	21.8 4 60.9 23.46 24.4	120 47 803 117 40	6.3% 6.1% 6.8% 6.4% 5.8%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72]	+	Alam 2014 Borroni 2003 Cankurtaran2005 Cascalheira 2009 Chang2014 Chen 2018 de Bustos 2000	170.7 225.7 213.9 189.98 4.43 214.01 5.48	31.7 40.1 44.6 10.02 1.04 43.18 1.89	75 60 120 19 44 117 44	167.6 200.5 212 186.89 4.25 191.96 5.54	22.8 48.9 46.5 3.55 1.24 37.62 1	120 45 803 36 62 117 21	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54] 0.54 [-0.26, 0.40] -0.04 [-0.56, 0.48]	
Nam 2014 San 2009 Cankurtaran2005 Chen 2018 Hoshino2002 Kouzuki 2017	Mean 104.4 123 129 130.67 119.1 110.8	28.8 2 44.2 34.73 27.7 39.4	75 197 120 117 82 42	100.6 121 130.3 95.25 110 119.2	21.8 4 60.9 23.46 24.4 35.7	120 47 803 117 40 18	6.3% 6.1% 6.8% 6.4% 5.8% 4.7%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72] -0.22 [-0.77, 0.34]		Alam 2014 Borroni 2003 Cankurtaran2005 Cascalheira 2009 Chang2014 Chen 2018 de Bustos 2000 Kouzuki 2017	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1	75 60 120 19 44 117 44 42	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9	120 45 803 36 62 117 21 18	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 3.2%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54] 0.54 [0.28, 0.80] -0.04 [-0.56, 0.48] -0.27 [-0.82, 0.29]	
Nam 2014 San 2009 Cankurtaran2005 Chen 2018 Hoshino2002 Couzuki 2017 i H 2017	Mean 104.4 123 129 130.67 119.1 110.8 2.38	28.8 2 44.2 34.73 27.7 39.4 0.9	75 197 120 117 82 42 118	100.6 121 130.3 95.25 110 119.2 2.66	21.8 4 60.9 23.46 24.4 35.7 0.46	120 47 803 117 40 18 120	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72] -0.22 [-0.77, 0.34] -0.36 [-0.65, 0.13]		Alam 2014 Borroni 2003 Cankurtaran2005 Cascalheira 2009 Chang2014 Chen 2018 de Bustos 2000 Kouzuki 2017 Kölsch 2010	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84	75 60 120 19 44 117 44 42 411	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05	120 45 803 36 62 117 21 18 201	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 3.2% 5.1%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54] 0.54 [0.28, 0.80] -0.04 [-0.56, 0.48] -0.27 [-0.82, 0.29] -0.14 [-0.31, 0.02]	
Alam 2014 Ban 2009 Cankurtaran2005 Chen 2018 Hoshino2002 Kouzuki 2017 Li H 2017 Demoni 2005	Mean 104.4 123 129 130.67 119.1 110.8 2.38	28.8 2 44.2 34.73 27.7 39.4 0.9	75 197 120 117 82 42 118	100.6 121 130.3 95.25 110 119.2 2.66	21.8 4 60.9 23.46 24.4 35.7 0.46	120 47 803 117 40 18 120	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72] -0.22 [-0.77, 0.34] -0.39 [-0.65, -0.13] 0.137 [-0.14, 0.44]		Alam 2014 Borroni 2003 Cankuttana2005 Chang2014 Chen 2018 de Bustos 2000 Kouzuki 2017 Kölsch 2010 Li H 2017	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13	75 60 120 19 44 117 44 411 118	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75	120 45 803 36 62 117 21 18 201 120	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 5.1% 4.7%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54] 0.54 [0.28, 0.80] -0.04 [-0.56, 0.48] -0.27 [-0.82, 0.29] -0.14 [-0.31, 0.02] -0.43 [-0.68, -0.17]	
Ilam 2014 San 2009 Sankuttaran2005 Chen 2018 Hoshino2002 Kouzuki 2017 Ji H 2017 Raygani 2006	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5	75 197 120 117 82 42 118 94	100.6 121 130.3 95.25 110 119.2 2.66 158.5	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8	120 47 803 117 40 18 120 111	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72] -0.22 [-0.77, 0.34] -0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44]		Alam 2014 Borroni 2003. Cankurtaran2005 Cascalheira 2009 Chang2014 Chen 2018 de Bustos 2000 Kozuzki 2017 Kölsch 2010 Li H 2017 Popp 2012 Dop 2012	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61	75 60 120 19 44 117 44 42 411 118 53	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17	120 45 803 36 62 117 21 18 201 120 43	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 5.1% 4.7% 3.9%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54] 0.54 [-0.28, 0.80] -0.04 [-0.56, 0.48] -0.27 [-0.82, 0.29] -0.14 [-0.31, 0.02] -0.43 [-0.68, -0.17] 0.24 [-0.17, 0.64] -0.00 0, 0.77]	
Alam 2014 San 2009 Cankurtaran2005 Shen 2018 Hoshino2002 Kouzuki 2017 Ji H 2017 Raygani 2006 Singh2012	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63	75 197 120 117 82 42 118 94 70	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61	120 47 803 117 40 18 120 111 75	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4% 6.0%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.24 [-0.04, 0.77, 0.34] -0.22 [-0.77, 0.34] 0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44] 0.95 [0.61, 1.29]		Alam 2014 Borroni 2003 Cankurtaran2005 Cascalheira 2009 Chang2014 Chen 2018 de Bustos 2000 Koluzuki 2017 Kölsch 2010 Li H 2017 Popp 2012 Popp 2013 Barunari 2006	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 20	75 60 120 19 44 117 44 42 411 118 53 106 94	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 17 ⁴	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5	120 45 803 36 62 117 21 18 201 120 43 87	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 5.1% 4.7% 3.9% 4.5%	0.12 [-0.17, 0.40] 0.57 [0.17, 0.96] 0.04 [-0.15, 0.23] 0.47 [-0.10, 1.03] 0.15 [-0.23, 0.54] 0.54 [0.28, 0.80] -0.04 [-0.56, 0.46] -0.27 [-0.82, 0.29] -0.14 [-0.31, 0.02] -0.43 [-0.68, -0.17] 0.24 [-0.17, 0.64] 0.49 [0.20, 0.77] 0.37 [0.10, 0.65]	
Jam 2014 ana 2009 Cankurtaran2005 Chen 2018 Ioshino2002 Iouzuki 2017 i H 2017 Iaygani 2006 ingh2012 Vada2000	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26	75 197 120 117 82 42 118 94 70 36	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36	120 47 803 117 40 18 120 111 75 15	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4% 6.0% 4.4%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72] -0.22 [-0.77, 0.34] -0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44] 0.95 [0.61, 1.29] -0.13 [-0.74, 0.47]		Aim 2014 Bornoni 2003 Cankutrana12005 Casacihiera 2009 Chang2014 Chen 2018 de Bustos 2000 Kouzuki 2017 Kölsch 2010 Li H 2017 Popp 2012 Popp 2013 Raygari 2006 Schonknecht 2003	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 29 21.5	75 60 120 19 44 117 44 42 411 118 53 106 94 14	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6	120 45 803 36 62 117 21 18 201 120 43 87 111 10	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 5.1% 4.7% 3.9% 4.5% 4.6% 2.1%	$\begin{array}{c} 0.12 \left[-0.17, \ 0.40 \right] \\ 0.57 \left[0.17, \ 0.40 \right] \\ 0.57 \left[0.17, \ 0.40 \right] \\ 0.47 \left[-0.10, \ 1.03 \right] \\ 0.47 \left[-0.23, \ 0.54 \right] \\ 0.54 \left[0.23, \ 0.54 \right] \\ 0.56 \left[0.28, \ 0.80 \right] \\ -0.24 \left[-0.56, \ 0.48 \right] \\ -0.27 \left[-0.82, \ 0.29 \right] \\ -0.14 \left[-0.66, \ 0.17 \right] \\ 0.24 \left[-0.57, \ 0.64 \right] \\ 0.42 \left[-0.20, \ 0.77 \right] \\ 0.37 \left[0.10, \ 0.55 \right] \\ 5.15 \left[-0.25, \ 1.29 \right] \\ -0.47 \left[-0.25, \ 1.29 \right] \\ -0.45 \left[-0$	
Nam 2014 Jam 2014 Jan 2009 Cankurtaran2005 Chen 2018 Hoshino2002 (ouzuki 2017 J H 2017 Raygani 2006 Jingh 2012 Vada2000 Vatanabe2004	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25	75 197 120 117 82 42 118 94 70 36 34	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36	120 47 803 117 40 18 120 111 75 15 63	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4% 6.0% 4.4% 5.5%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72] -0.22 [-0.77, 0.34] -0.39 [-0.65, -0.13] 0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44] 0.95 [0.61, 1.29] -0.13 [-0.74, 0.47] -0.33 [-0.30, 0.45]		Alam 2014 Borroni 2003 Canahurtanan2005 Cascahera 2009 Chang2014 Chen 2018 de Bustos 2000 Kouzuki 2017 Kölsch 2010 Li H 2017 Popp 2012 Popp 2012 Popp 2012 Raygani 2006 Schonknecht 2002 Singh2012	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 29 21.5 38.84	75 60 120 19 44 117 44 42 411 118 53 106 94 14 70	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7 122.03	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6 30.37	120 45 803 36 62 117 21 18 201 120 43 87 111 10 75	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 5.1% 4.7% 3.9% 4.5% 4.6% 2.1% 2.1%	$\begin{array}{c} 0.12 \left[-0.17, \ 0.40 \right] \\ 0.57 \left[0.17, \ 0.40 \right] \\ 0.67 \left[0.17, \ 0.40 \right] \\ 0.47 \left[-0.10, \ 1.03 \right] \\ 0.47 \left[-0.10, \ 1.03 \right] \\ 0.54 \left[-0.28, \ 0.47 \right] \\ 0.41 \left[-0.33, \ 0.02 \right] \\ 0.41 \left[-0.33, \ 0.02 \right] \\ 0.43 \left[-0.33, \ 0.02 \right] \\ 0.44 \left[-0.23, \ 0.47 \right] \\ 0.48 \left[0.20, \ 0.77 \right] \\ 0.47 \left[-0.35, \ 1.29 \right] \\ 0.47 \left[-0.11, \ 1.73 \right] \\ 0.47 \left[-0.11, \ $	
tony of subgroup lam 2014 an 2009 ankurtaran2005 chen 2018 losshino2002 louzuki 2017 H 2017 laygani 2006 ingh2012 laygani 2006 kanabe2004 iao 2012	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66	75 197 120 117 82 42 118 94 70 36 34 104	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.4	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82	120 47 803 117 40 18 120 111 75 15 63 104	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4% 5.5% 6.4%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] -0.22 [-0.77, 0.34] -0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44] 0.95 [0.61, 1.29] -0.13 [-0.74, 0.47] 0.03 [-0.39, 0.45] 0.08 [-0.10, 0.35]		Alam 2014 Borroni 2003 Canchurdarand/005 Cascathera 2009 Chang2014 Chen 2016 de Bustos 2000 Kouzuki 2017 Kölsch 2010 Li H 2017 Popp 2012 Popp 2013 Raygari 2008 Schonknecht 2002 Singh2012 Teuruissen 2003	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 29 21.5 38.84 14.34	75 60 120 19 44 117 44 42 411 118 53 106 94 14 70 34	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.3 215 175 182.7 122.03 248.23	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6 30.37 19.19	120 45 803 36 62 117 21 18 201 120 43 87 111 10 75 61	4.5% 4.0% 5.0% 3.1% 4.0% 4.7% 3.3% 5.1% 4.7% 3.9% 4.6% 2.1% 4.8% 3.8%	$\begin{array}{c} 0.12 \ -0.17, \ 0.40] \\ 0.57 \ (0.17, \ 0.40] \\ 0.47 \ (-0.17, \ 0.50] \\ 0.47 \ -0.17, \ 0.53] \\ 0.47 \ -0.17, \ 0.54] \\ 0.54 \ -0.28, \ 0.56] \\ 0.54 \ -0.28, \ 0.52] \\ -0.44 \ -0.68, \ 0.48] \\ -0.44 \ -0.68, \ 0.47] \\ -0.45 \ -0.68, \ 0.47] \\ -0.45 \ -0.68, \ 0.47] \\ -0.45 \ -0.68, \ 0.47] \\ -0.45 \ -0.58, \ 1.29] \\ -0.45 \ -0.68, \ 0.47] \\ -0.45 \ -0.58, \ 1.29] \\ -0.45 \ -0.68, \ 0.47] \\ -0.45 \ -0.58, \ 1.29] \\ -0.45 \ -0.58 \ -0.58] \\ -0.45 \ -0.58 \ -0.58] \\ -0.45 \ -0.58 \ -0.58] \\ -0.45 \ -0.58 \ -0.58] \\ -0.45 \ -0.58 \ -0.58] \\ -0.45 \ -0.58 \ -0.58 \ -0.58] \\ -0.45 \ -0.58 \ $	
http://disautropy.com/ Jam 2014 Jan 2009 Jankurtaran2005 Chen 2018 Jostimo2002 Josczuki 2017 J H 2017 J H 2017 J H 2017 J H 2017 J J 2006 Jingh2012 Vada2000 Vatanabe2004 Gao 2012 (Janasobe2004	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 109	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 25	75 197 120 117 82 42 118 94 70 36 34 104	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.4	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82 28	120 47 803 117 40 18 120 111 75 15 63 104 22	6.3% 6.1% 6.8% 6.4% 5.8% 6.5% 6.4% 5.5% 6.4% 5.5% 6.4%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] -0.02 [-0.21, 0.17] 1.19 [0.91, 1.47] 0.34 [-0.04, 0.72] -0.22 [-0.77, 0.34] 0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44] 0.55 [0.61, 1.29] -0.13 [-0.74, 0.47] 0.03 [-0.39, 0.45] 0.08 [-0.19, 0.35] 0.08 [-0.19, 0.35]		Aam 2014 Boroni 2003 Canchurdaran2005 Cascahear 2009 Chang2014 Chan 2018 de Bustos 2000 Kouzuki 2017 Kolisch 2010 Li H 2017 Popp 2012 Popp 2012 Popp 2013 Raygar 2006 Schonknecht 2002 Sing/2012 Teunissen 2003 Wada2000	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78 194	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 29 21.5 38.84 14.34 33	75 60 120 19 44 117 44 42 411 118 503 106 503 106 94 14 70 34 36	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7 122.03 248.23 207	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6 30.37 19.19 40	120 45 803 36 62 117 21 120 43 87 111 10 75 61 15	4.5% 4.0% 5.0% 3.1% 4.7% 3.3% 5.1% 4.7% 3.9% 4.5% 4.6% 4.6% 4.6% 4.1% 5.8% 4.8% 2.9%	$\begin{array}{c} 0.12 \left[-0.17, \ 0.40 \right] \\ 0.57 \left[0.17, \ 0.69 \right] \\ 0.67 \left[0.17, \ 0.69 \right] \\ 0.47 \left[-0.10, \ 0.33 \right] \\ 0.15 \left[-0.23, \ 0.54 \right] \\ 0.54 \left[-0.23, \ 0.54 \right] \\ 0.54 \left[-0.25, \ 0.56 \right] \\ 0.41 \left[-0.31, \ 0.62 \right] \\ 0.27 \left[-0.82, \ 0.37 \right] \\ 0.14 \left[-0.31, \ 0.64 \right] \\ 0.48 \left[0.20, \ 0.77 \right] \\ 0.48 \left[0.20, \ 0.77 \right] \\ 0.48 \left[0.20, \ 0.77 \right] \\ 0.47 \left[-0.35, \ 1.29 \right] \\ 0.58 \left[0.17, \ 0.68 \right] \\ 0.47 \left[-0.36, \ 0.27 \right] \\ 0.58 \left[0.77, \ 0.24 \right] $	
httery of subgroup Jamkurtaran2005 Zhen 2018 Soshinc2002 Gouzuki 2017 LH 2017 Raygani 2006 jingh2012 Vatanabe2004 Gao 2012 'amamoto2005	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36	75 197 120 117 82 42 118 94 70 36 34 104 61	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.4 105	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82 38	120 47 803 117 40 18 120 111 75 15 63 104 32	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4% 5.5% 6.4% 5.5%	$\begin{array}{c} 0.15 \left[0.14 , 0.44 \right] \\ 0.80 \left[0.47 , 1.12 \right] \\ -0.02 \left[-0.21 , 0.17 \right] \\ 1.19 \left[0.91 , 1.47 \right] \\ 0.34 \left[-0.04 , 0.72 \right] \\ -0.22 \left[-0.77 , 0.34 \right] \\ -0.39 \left[-0.55 , -0.13 \right] \\ 0.17 \left[-0.11 , 0.44 \right] \\ 0.95 \left[0.61 , 1.29 \right] \\ -0.13 \left[-0.74 , 0.47 \right] \\ 0.03 \left[-0.35 , 0.51 \right] \\ 0.08 \left[-0.19 , 0.35 \right] \\ 0.08 \left[-0.35 , 0.51 \right] \\ \end{array}$		Aam 2014 Boroni 2003 Cascahera 2009 Chang2014 Chen 2016 de Bustos 2000 Kouzuk 2017 Kölsch 2010 Li H 2017 Popp 2012 Popp 2013 Raygara 2006 Sichonknecht 2002 Singh2012 Teunissen 2009 Watanabe/2004	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78 194 167	31.7 40.1 44.6 10.02 1.04 43.189 45.1 47.84 1.13 46.61 47.77 29 21.5 38.84 14.34 14.34 14.34 29	75 60 120 19 44 117 44 411 118 505 106 94 14 70 34 36 34	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7 122.03 248.23 207 176	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6 30.37 19.19 40 36	120 45 803 36 62 117 21 18 201 120 43 87 111 10 75 61 15 63	4.5% 4.0% 5.0% 3.1% 4.7% 3.3% 5.1% 4.7% 3.9% 4.5% 4.6% 2.1% 4.8% 2.9% 3.8%	$\begin{array}{c} 0.12 \ -0.17, \ 0.40] \\ 0.57 \ 0.17, \ 0.40] \\ 0.47 \ -0.17, \ 0.58] \\ 0.47 \ -0.17, \ 0.58] \\ 0.47 \ -0.17, \ 0.58] \\ 0.56 \ -0.28, \ 0.58] \\ 0.56 \ -0.28 \ -0.28, \ 0.58] \\ -0.47 \ -0.58 \ -0.28 \ -$	
tany of subatrola an 2019 ankurtaran2005 hen 2018 ossino2002 ouzuki 2017 H 2017 iaygani 2006 ingh2012 /ada2000 /atanabe2004 /atanabe2004 /atanabe2004 juanamoto2005 u2014	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36 1.09	75 197 120 117 82 42 118 94 70 36 34 104 61 201	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.4 105 2.46	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82 38 1.13	120 47 803 117 40 18 120 111 75 15 63 104 32 257	6.3% 6.1% 6.8% 6.4% 5.8% 6.5% 6.4% 5.5% 6.4% 5.5% 6.4% 5.5% 6.8%	$\begin{array}{c} 0.15 \left[-0.14, 0.44 \right] \\ 0.80 \left[0.47, 1.12 \right] \\ -0.02 \left[-0.21, 0.77 \right] \\ 1.19 \left[0.51, 1.47 \right] \\ 0.34 \left[-0.40, 0.72 \right] \\ -0.22 \left[-0.77, 0.34 \right] \\ 0.39 \left[-0.65, -0.13 \right] \\ 0.17 \left[-0.11, 0.44 \right] \\ 0.95 \left[0.61, 1.29 \right] \\ -0.13 \left[-0.74, 0.47 \right] \\ 0.03 \left[-0.39, 0.45 \right] \\ 0.08 \left[-0.35, 0.51 \right] \\ 0.08 \left[-0.35, 0.51 \right] \\ 0.13 \left[-0.06, 0.31 \right] \end{array}$		Alam 2014 Boroni 2003 Canacheria 2009 Chang2014 Chen 2016 de Bustos 2000 Kouzuki 2017 Royga 2012 Pope 2012 Pope 2012 Pope 2012 Raygan 2006 Schonknecht 2002 Singh2012 Teunissen 2009 Watanabe2004 Watanabe2004	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78 194.4 169.89 258.78 194.4 167 4.48	31.7 40.1 44.6 10.02 1.04 43.18 45.1 47.84 1.13 46.61 47.77 29 21.5 38.84 14.34 14.34 14.34 33 29 0.89	75 60 120 19 44 117 44 42 411 118 53 106 94 106 94 106 34 36 34	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7 122.03 248.23 207 176 4.1	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6 30.37 19.19 40 36 1.04	120 45 803 36 62 117 21 18 201 120 43 87 111 10 75 61 15 63 104	4.5% 4.0% 5.0% 3.1% 4.7% 3.3% 5.1% 4.7% 3.9% 4.5% 4.6% 2.1% 3.8% 4.6% 3.8% 4.6%	$\begin{array}{c} 0.12 \ [-0.17, \ 0.40] \\ 0.57 \ [0.17, \ 0.40] \\ 0.67 \ [0.17, \ 0.40] \\ 0.41 \ [-0.17, \ 0.50] \\ 0.47 \ [-0.10, \ 1.03] \\ 0.47 \ [-0.10, \ 1.03] \\ 0.45 \ [-0.23, \ 0.54] \\ -0.44 \ [-0.23, \ 0.$	
tiony of subapticute lam 2014 lam 2019 ankutrana2005 then 2018 lostinic2002 lostinic2002 lostinic2002 laggani 2006 ingh2012 vada2000 Vatanabe2004 lao 2012 amamoto2005 u2014 eng/2012	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6 2.79	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36 1.09 0.22	75 197 120 117 82 42 118 94 70 36 34 104 61 201 21	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.4 105 2.46 2.88	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82 38 1.13 0.021	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20	6.3% 6.1% 6.8% 6.4% 5.8% 6.5% 6.4% 6.0% 4.4% 5.5% 6.4% 5.5% 6.8% 4.3%	$\begin{array}{c} 0.15 \ [-0.14, 0.44] \\ 0.86 \ [0.47, 1.12] \\ -0.02 \ [-0.21, 0.147] \\ 1.19 \ [0.91, 1.47] \\ 0.34 \ [-0.40, 0.72] \\ -0.22 \ [-0.77, 0.34] \\ -0.39 \ [-0.65, -0.13] \\ 0.07 \ [-0.13, [-0.74, 0.47] \\ 0.95 \ [0.61, 1.29] \\ -0.13 \ [-0.74, 0.47] \\ 0.03 \ [-0.39, 0.45] \\ 0.06 \ [-0.19, 0.35] \\ 0.06$		Alam 2014 Borroni 2003 Canachimetara0005 Casachimeta 2009 Chang2014 de Bustos de Bustos de Bustos 2000 Kouzuki 2017 Kölsch 2010 Li H 2017 Popp 2013 Popp 2013 Raygan 2012 Raygan 2012 Teurissen 2003 Watana62004 Xiao 2012 Yanamolo2005	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78 194 167 4.48 187	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 29 21.5 38.84 14.34 33 29 0.89 38.89 38 38 38 38 30 39 30 39 30 39 30 30 30 30 30 30 30 30 30 30 30 30 30	75 60 120 19 44 117 44 42 411 118 53 106 94 106 94 70 34 36 34 104 61	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.63 225.33 215 175 182.7 122.03 248.23 207 176 4.1 190	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6 30.37 19.19 40 36 1.04 40 36	120 45 803 62 117 21 18 201 120 43 87 111 10 75 61 15 63 104 32	4.5% 4.0% 5.0% 4.7% 3.3% 5.1% 4.7% 3.2% 4.6% 4.6% 2.1% 3.8% 4.6% 3.8% 4.6% 3.8% 4.6% 3.8% 4.6% 3.8%	$\begin{array}{c} 0.12 \left[0.17 \\ 0.40 \right] \\ 0.57 \left[0.17 \\ 0.47 \right] \\ 0.047 \left[1-0.10 \\ 0.057 \\ 0.17 \\ 0.10 \\ 0.05 \\ 0.0$	
http://or.subigitation Jamkuttaran2005 Jamkuttaran2005 Jamkuttaran2005 John 2018 doshino2002 (ouzuki 2017) J H 2017 Jaygani 2006 ingfi2012 Vatanabe2004 iao 2012 iamamoto2005 u2014 engi2012 hao2014	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6 2.79 138.2	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36 1.09 0.22 34.7	75 197 120 117 82 42 118 94 70 36 34 104 61 201 21 48	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.4 105 2.46 2.88 136.8	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82 38 1.13 0.021 16.4	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20 37	6.3% 6.1% 6.8% 6.4% 6.5% 6.4% 6.0% 4.4% 5.5% 6.4% 5.5% 6.8% 4.3% 5.5%	$\begin{array}{c} 0.15 \left[-0.14, 0.44 \right] \\ 0.80 \left[0.47, 1.12 \right] \\ -0.02 \left[-0.21, 0.01, 0.01, 0.01 \right] \\ 0.02 \left[-0.21, 0.01, 0.01, 0.01 \right] \\ 0.03 \left[-0.04, 0.72 \right] \\ 0.02 \left[-0.77, 0.34 \right] \\ -0.21 \left[-0.77, 0.34 \right] \\ 0.05 \left[-0.61, 1.29 \right] \\ -0.13 \left[-0.30, 0.45 \right] \\ 0.03 \left[-0.30, 0.45 \right] \\ 0.08 \left[-0.30$		Alam 2014 Bennesi 2003 Cascubrers 2009 Charag2014 Chen 2010 Rouzuk 2017 March 2017 Popp 2013 Revgan 2000 Bichonknecht 2002 Singkhörlz Fersp 2012 Revgan 2000 Bichonknecht 2002 Singkhörlz Fersp 2012 Revgan 2000 Walaszool Walaszool Yamamob2005 Yamamob2005	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78 194 167 4.48 187 185 5 12	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 29 21.5 38.84 14.34 33 29 0.89 38 33 0.98	75 60 120 19 44 117 44 42 411 118 53 106 94 14 70 34 36 34 104 61 201	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7 122.03 248.23 207 176 4.1 190 181 4.81	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 22.6 30.37 19.19 40 36 1.04 44 31 0.69	120 45 803 62 117 21 18 201 120 43 87 111 10 75 61 53 104 32 47 257	4.5% 4.0% 5.0% 3.1% 4.7% 3.3% 4.7% 3.2% 4.7% 3.9% 4.5% 4.6% 3.8% 3.8% 3.8% 3.8% 5.5%	$\begin{array}{c} 0.12 \left[0.17 \\ 0.40 \right] \\ 0.57 \left[0.17 \\ 0.47 \right] \\ 0.47 \left[0.10 \\ 0.47 \right] \\ 0.47 \left[0.20 \\$	
tang of subgroup ankurtaran2005 hen 2018 loshina2018 loshina2002 locuziki 2017 i H 2017 vads2000 vatanabe2004 iao 2012 amamoto2005 u2014 hang2012 hang2014 hang2014	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6 2.79 138.2 2.78	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36 1.09 0.22 34.7 0.89	75 197 120 117 82 42 118 94 42 118 94 70 36 34 104 61 201 21 48 207	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.46 2.46 2.48 136.8 2.7	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82 38 1.13 0.021 16.4 1	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20 37 256	6.3% 6.1% 6.8% 6.4% 5.8% 6.4% 6.5% 6.4% 5.5% 6.4% 5.5% 6.4% 5.5% 6.8% 5.5% 6.8% 5.5% 6.8% 5.5% 6.8% 5.5% 6.8% 5.5% 6.8% 5.5% 6.8% 5.5%	$\begin{array}{c} 0.15 [= 14, 0.44] \\ 0.80 [0.47, 1.12] \\ 0.02 [= 0.21, 0.77] \\ 1.19 [0.91, 1.47] \\ 0.34 [= 0.04, 0.72] \\ 0.23 [= 0.65, -0.13] \\ 0.39 [= 0.65, -0.13] \\ 0.39 [= 0.65, -0.13] \\ 0.17 [= 0.71, 0.44] \\ 0.95 [0.61, 1.23] \\ 0.13 [= 0.74, 0.47] \\ 0.03 [= 0.38, 0.45] \\ 0.08 [= 0.35, 0.51] \\ 0.08 [= 0.35, 0.51] \\ 0.36 [= 0.38, 0.45] \\ 0.08 [= 0.35, 0.51] \\ 0.36 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.38, 0.45] \\ 0.08 [= 0.10, 0.27] \\ 0.05 [= 0.38, 0.46] \\ 0.08 [= 0.10, 0.27] \\ 0.05 [= 0.38, 0.46] \\ 0.08 [= 0.10, 0.27] \\ 0.05 [= 0.38, 0.46] \\ 0.08 [= 0.10, 0.27] \\ 0.05 [= 0.38, 0.46] $		Alam 2014 Bornesi 2003 Casautherea 2005 Casautherea 2005 Casautherea 2005 Casautherea 2005 de Buates 2000 Koucuka 2017 Kolacha 2010 Li H 2017 Popo 2012 Birgh0112 Sirgh0112 Sirgh0112 Teuristean 2003 Webateb2004 Webateb2004 Xiao 2012 Yamamodoz005 Yamamodoz05 Yamamo	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78 194 167 4.43 185 5.12 4.73	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 1.13 46.61 47.77 215 38.84 14.34 33 29 0.89 38 33 0.98 0.21	75 60 120 144 117 44 411 118 53 106 94 14 16 34 36 34 36 34 104 61 26 201	167.6 200.5 212 186.89 4.25 191.96 5.191.96 5.191.96 5.25 191.94 225.3 225 182.7 122.03 248.23 207 176 4.1 190 181 4.87 4.93	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 24.5 22.6 30.37 19.19 40 36 1.04 44 31 0.69 0.25	120 45 803 62 117 21 120 43 87 111 10 75 61 15 61 15 61 15 3104 32 47 250	4.5% 4.0% 5.0% 3.1% 4.7% 3.32% 4.7% 3.32% 4.6% 4.6% 2.9% 4.8% 3.8% 4.8% 3.8% 5.0% 5.0%	$\begin{array}{c} 0.12 \left[+ 0.17 \right] , 0.40 \\ 0.57 \left[+ 0.17 \right] , 0.49 \\ 0.047 \left[+ 0.15 \right] , 0.30 \\ 0.47 \left[+ 0.31 \right] , 0.30 \\ 0.47 \left[+ 0.31 \right] , 0.30 \\ 0.47 \left[+ 0.31 \right] , 0.30 \\ 0.47 \left[+ 0.35 \right] , 0.47 \\ 0.48 \left[+ 0.32 \right] , 0.47 \\ 0.48 \left[+ 0.32 \right] , 0.47 \\ 0.48 \left[+ 0.48 \right] , 0.47 \\ 0.48 \\ 0.$	
tinny of subapticular lam 2014 ankutaran2005 ankutaran2005 toba 2018 loschino2002 ouzuki 2017 i H 2017 laygani 2006 iingh2012 vada2000 Vatanaba2004 anamoto2005 vu2014 anag0121 hao2014 heng2016	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6 2.79 138.2 2.78	28.8 2 44.2 34.73 27.7 39.4 45.63 26 25 0.66 36 1.09 0.22 34.7 0.89	75 197 120 117 82 42 42 118 94 70 36 34 104 61 201 21 48 207	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.46 2.46 2.46 2.48 136.8 2.7	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 0.82 38 1.13 0.021 16.4 1	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20 37 256	6.3% 6.1% 6.8% 6.4% 5.8% 6.5% 6.4% 5.5% 6.4% 5.5% 6.8% 4.3% 5.5% 6.8%	$\begin{array}{c} 0.15 \left[\begin{array}{c} 0.14 \\ 0.46 \end{array} \right] (0.47 \\ 0.12 \end{array} \left[\begin{array}{c} 0.27 \\ 0.02 \end{array} \right] (0.27 \\ 0.12 \end{array} \left[\begin{array}{c} 0.27 \\ 0.02 \end{array} \right] (0.27 \\ 0.02 \end{array} \left[\begin{array}{c} 0.27 \\ 0.04 \end{array} \right] (0.04 \\ 0.07 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \\ 0.05 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \\ 0.05 \\ 0.05 \end{array} \left[\begin{array}{c} 0.27 \\ 0.05 \end{array} \right] (0.05 \\ 0.05 \\ 0.05 \\ 0.05 \\ 0.05 \end{array} \right] (0.05 \\ 0$		Alam 2014 Bennesi 2003 Cascubrers 2009 Charg2014 Chen 2010 Rouzuk 2017 Mount 2017 Popp 2013 Revgan 2006 Bichonknecht 2002 Singk7012 Teurissen 2000 Walas2009 Walasz000 Walasz000 Walasz000	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 24 24 235.76 238 185 193.4 169.89 258.78 194 167 4.48 187 185 5.12 4.73 204.5	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 1.13 46.61 1.13 46.61 47.77 29 9 21.5 38.84 43.3 38.84 14.34 33 20.89 38 33 30.988 33 30.989 20.3	75 60 120 19 44 41 117 44 42 411 118 53 50 53 40 104 53 34 34 36 34 104 61 26 201 21 1 48	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7 122.03 248.23 207 176 4.1 1900 181 4.87 4.93 213.6	22.8 48.9 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 745.17 22.6 30.37 19.19 40 36 1.04 40 36 0.25 48.9	120 455 803 62 117 21 120 43 87 111 120 43 87 61 15 61 15 61 15 63 104 43 227 200 237	4.5% 4.0% 5.0% 3.1% 4.7% 3.2% 5.1% 4.7% 3.2% 4.6% 4.8% 3.8% 4.6% 3.8% 5.0% 5.0% 5.0% 5.2.8%	$\begin{array}{c} 0.12 \left[+ 0.17 \\ 0.60 \\ 0.57 \left[+ 0.17 \\ 0.67 \\ 0.57 \left[+ 0.17 \\ 0.58 \\ 0.67 \\ 0.57 \\ $	
tany of subgroup amkurtaran2005 hen 2018 loshina2002 loszuki 2017 i H 2017 aygani 2006 ingh2012 Vada2000 vada2000 i amamot2005 u2014 heng2012 hao2014 heng2016 columna 2006 columna 2006 loss 2017 amamot2016 columna 2006 columna 2006 columna 2006 columna 2006 columna 2006 columna 2006 columna 2006 columna 2006 columna 2007 columna 2007 c	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6 2.79 138.2 2.78	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36 1.09 0.22 34.7 0.89	75 197 120 117 82 42 42 118 94 70 36 34 104 61 201 21 48 207	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.46 2.88 136.8 2.7	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 36 0.82 38 1.13 0.021 16.4 1	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20 37 256	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4% 5.5% 6.4% 5.5% 6.4% 5.5% 6.8% 4.3% 5.5% 6.8% 4.3% 5.5% 6.8%	$\begin{array}{c} 0.15 [= 14, 0.44] \\ 0.80 [0.47, 1.12] \\ 0.02 [= 0.21, 0.77] \\ 1.19 [0.91, 1.47] \\ 0.34 [= 0.04, 0.72] \\ 0.23 [= 0.65, -0.13] \\ 0.39 [= 0.65, -0.13] \\ 0.39 [= 0.65, -0.13] \\ 0.17 [= 0.71, 0.44] \\ 0.95 [0.61, 1.29] \\ 0.13 [= 0.74, 0.47] \\ 0.03 [= 0.38, 0.45] \\ 0.08 [= 0.35, 0.51] \\ 0.08 [= 0.35, 0.51] \\ 0.36 [= 0.35, 0.51] \\ 0.36 [= 0.38, 0.48] \\ 0.08 [= 0.10, 0.27] \end{array}$		Alam 2014 Bernesi 2003 Casautheres 2003 Casautheres 2005 Casautheres 2005 Casautheres 2005 Casautheres 2005 del Buatos 2000 Koucuka 2017 Kolacha 2010 Li H 2017 Popo 2012 Revplana 2006 Stepp0112 Teuristean 2003 Webatos2004 Webatos2004 Webatos2004 Webatos2004 Zanagrof12 Zheng2015	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238.185 193.4 169.89 258.78 194 167.7 4.48 185 5.12 4.73 204.5 4.76	31.7 40.1 44.6 10.02 1.04 43.18 1.89 45.1 47.84 47.84 47.77 29 20.5 5 38.84 40.45 1 14.46 47.77 29 20.5 5 38.84 40.45 1 14.46 43.88 33 30.98 80.98 80.98 10.94 10.02 10.	75 600 120 19 44 411 118 53 106 53 106 94 414 14 14 700 34 36 34 36 34 104 61 201 211 21 201	167.6 200.5 212 186.89 4.25 191.96 5.54 211.1 241.13 4.65 225.33 215 175 182.7 122.03 248.23 207 176 4.1 190 181 1 4.87 4.93 213.6 4.57	22.8.9 46.5 3.55 1.24 46.5 3.55 1.24 1 39.9 50.05 0.75 39.67 24.5 22.6 30.37 19.19 40 36 1.04 44 431 0.69 0.25 48.9 1.24	120 45 803 36 62 117 21 18 201 120 43 87 111 10 75 63 104 43 77 257 200 7 37 256	4.5% 4.0% 5.1% 4.0% 4.7% 3.2% 4.7% 3.3% 4.5% 4.5% 2.1% 5.1% 5.4% 2.8% 3.8% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0	$\begin{array}{c} 0.12 \left[0.17, 0.69 \right] \\ 0.07 \left[0.17, 0.69 \right] \\ 0.047 \left[0.31, 1.03 \right] \\ 0.47 \left[0.31, 0.31 \right] \\ 0.47 \left[0.43, 0.32 \right] \\ 0.47 \left[0.43, 0.32 \right] \\ 0.47 \left[0.43, 0.32 \right] \\ 0.47 \left[0.13, 0.49 \right] \\ 0.47 \left[0.14, 0.47 \right] \\ 0.48 \left[1.44, 0.27 \right] $	
http://diam.2014 Jam 2014 Jam 2009 Jamkuttarat2005 Chen 2018 Joszuka 2017 Ji H 2017 Raygani 2006 Singh2012 Vadaz000 Watanaba2004 Gao 2012 Yamamoto2005 fuz014 Zheng2016 Fotal (95% CI)	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6 2.79 138.2 2.78	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36 1.09 0.22 34.7 0.89	75 197 120 117 82 42 118 94 70 36 34 104 61 201 21 48 207 1627	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.4 105 2.46 2.88 136.8 2.7	21.8 4 23.46 23.46 24.4 35.7 0.46 22.8 24.61 36 0.82 38 1.13 0.021 16.4 1	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20 37 256 2235	6.3% 6.1% 6.8% 6.4% 6.5% 6.4% 6.5% 6.4% 6.4% 6.4% 6.4% 6.4% 6.8% 5.5% 6.8% 6.8% 100.0%	0.15 [-0.14, 0.44] 0.80 [0.47, 1.12] 0.02 [-0.21, 0.01] 0.34 [-0.04, 0.72] 0.34 [-0.04, 0.72] 0.22 [-0.77, 0.34] 0.39 [-0.64, 1.29] 0.17 [-0.11, 0.44] 0.95 [0.61, 1.29] 0.13 [-0.66, 0.31] 0.36 [-0.38, 0.45] 0.06 [-0.3, 0.51] 0.13 [-0.06, 0.31] 0.36 [-0.80, 0.04] 0.05 [-0.38, 0.04]\\ 0.05 [-0.38, 0.04]\\ 0.05 [-0.		Alam 2014 Bennesi 2003 Casculterar 2005 Casculterar 2005 Chargo14 Chen 2016 Alben 2016 Alben 2017 Hosp 2012 Popp 2013 Raygar 2006 Bichonkneht 2002 Singh2012 Teurissen 2003 Wideal2000 Wideal2002 Wideal2005 Wideal2005 Wideal2005 Zhargo112 Zhargo112 Zhargo114 Zhargo116	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 169.89 258.78 194 167 4.48 187 185 5.12 4.73 204.5 4.76	31.7 40.1 10.02 1.04 43.18 45.1 1.13 47.84 45.1 1.13 46.61 47.77 29 9.21.5 38.84 14.34 33.88 44.14 33 3.88 44 14.34 33 3.98 8.021 20.3 3.098 0.21 20.3 1.07	75 60 120 19 44 117 44 42 411 118 53 30 6 34 104 61 26 201 21 48 8207	167.6 200.5 212 212 186.89 4.25 5.54 211.1 241.13 241.13 241.2 25.53 215 775 225.33 215 782.7 122.03 248.23 207 7176 4.1 1990 4.57 4.93 213.6 4.57	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 0.75 39.67 46.17 22.6 30.37 19.19 19.19 40 36 1.04 4 431 0.69 0.25 48.9 1.24	120 453 366 622 117 121 120 120 120 120 120 120 120 120 120	4.5% 4.0% 5.1% 4.0% 4.7% 3.3% 5.1% 4.7% 5.1% 4.7% 5.1% 4.5% 4.6% 3.8% 4.6% 3.8% 4.6% 3.8% 5.0% 5.0%	$\begin{array}{c} 0.12 \left[+ 0.17 \\ 0.60 \\ 0.57 \\ 0.17 \\ 0.17 \\ 0.17 \\ 0.57 \\ 0.17 \\ 0.57 \\ 0.17 \\ 0.57 \\$	
Jano 2014 Jana 2014 Jana 2009 Jankutaran2005 Chen 2018 Hoshino2002 Gozuki 2017 H 2017 Agygani 2006 Singh2012 Watanabe2004 Gao 2012 Amamoto2005 Yu2014 Zhao2014 Zhao2014 Zhao2015 Fotal (95% Cf)	Mean 104.4 123 129 130.67 119.1 110.8 2.38 162.5 106.13 110 95 2.46 108 2.6 2.79 138.2 2.78 0.15; Chii	28.8 2 44.2 34.73 27.7 39.4 45.63 26 25 0.66 36 1.09 0.22 34.7 0.89	75 197 120 117 82 42 42 42 42 42 118 94 70 36 34 104 61 201 21 48 207 1627 96, df =	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 94 2.46 158.5 71.47 114 94 2.48 136.8 2.7 147 105 2.466 2.88 136.8 2.7	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 0.82 38 1.13 0.021 16.4 1 < 0.0000	120 47 803 117 40 18 120 111 15 63 104 32 257 20 37 256 2235 11); F =	6.3% 6.1% 6.8% 6.4% 5.8% 6.5% 6.4% 5.5% 6.4% 5.5% 6.4% 5.5% 6.8% 4.3% 5.5% 6.8% 100.0% 87%	0.15 [0.14, 0.44] 0.85 [0.17, 1.12] 0.02 [-021, 0.17] 1.19 [0.91, 1.47] 0.24 [-0.04, 0.472] 0.24 [-0.04, 0.472] 0.25 [-0.7, 0.34] 0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44] 0.05 [0.61, 1.247] 0.03 [-0.30, 0.45] 0.08 [-0.30, 0.45] 0.08 [-0.30, 0.45] 0.08 [-0.30, 0.45] 0.08 [-0.30, 0.45] 0.08 [-0.30, 0.45] 0.08 [-0.10, 0.27] 0.18 [-0.02, 0.38]		Aan 2014 Bornes 2003 Casabines 2003 Casabines 2003 Casabines 2005 Casabines 2005 Chango 2014 Kolach 2010 Li H 2017 Popo 2012 Popo 2012 Revpen 2002 Sandrokes 2000 Velasized 2012 Yamanoba2000 Velasized 2012 Yamanoba2004 Xalao 2012 Yamanoba2004 Y	170.7 225.7 213.9 189.98 4.43 214.01 5.48 199.3 234.13 4.24 235.76 238 185 193.4 185 193.4 169.89 258.78 194 167 4.48 187 185 5.12 4.73 204.5 4.76	31.7 40.1 10.02 1.04 43.18 45.1 1.89 45.1 1.89 45.1 47.84 47.84 47.84 47.84 47.77 29 21.5 38.84 14.34 33 38.84 14.34 33 39 0.89 38.83 30.89 38.83 30.89 30.80 30.8	75 60 120 19 44 411 118 53 53 53 106 53 106 53 106 53 106 53 106 53 106 53 106 53 106 53 106 53 100 120 19 94 42 411 19 94 4 42 411 19 94 4 42 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 4 20 19 94 4 20 10 19 94 4 20 10 10 10 10 10 10 10 10 10 10 10 10 10	167.6 200.5 212 186.89 4.25 5.54 211.13 4.65 225.33 215 182.7 175 182.7 175 182.7 176 4.1 120.33 207 176 4.1 181 4.87 4.93 213.6 4.57	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 39.67 39.67 39.67 724.5 22.6 30.37 19.19 40 0.69 0.69 0.69 1.24	120 453 366 62 117 121 188 201 120 120 120 120 43 87 111 120 43 87 111 155 61 155 61 155 47 7256 2761	4.5% 4.0% 5.1% 4.0% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1% 5.1	$\begin{array}{c} 0.12 \left[+ 0.17 \right] , 0.40 \\ 0.57 \left[+ 0.17 \right] , 0.49 \\ 0.047 \left[+ 0.15 \right] , 0.03 \\ 0.47 \left[+ 0.15 \right] , 0.03 \\ 0.47 \left[+ 0.15 \right] , 0.03 \\ 0.47 \left[+ 0.05 \right] , 0.04 \\ 0.47 \left[+ 0.05 \right] , 0.38 \\ 0.47 \left[+ 0.05 \right] , 0.48 \\ 0.47 \\ 0.48 \\ $	 + 1 + 1
stanty or subgitude Jam 2014 Ban 2009 Cankutaran2005 Chen 2018 Hostinic2002 Kouzuki 2017 Li H 2017 Raygani 2006 Singh2012 Watanabe2004 Kiao 2012 Yamamoto2005 Yamamoto2005 Yamamoto2005 Yamamoto2005 Tu2014 Zheng2016 Total (95% CI) Hoterogeneity, Tau ² = Test for overall effect:	Mean 104.4 123 129 130.67 119.1 110.8 2.38 106.13 106.2 106.13 110 95 2.46 108 2.66 2.79 138.2 2.78 0.15; Chii Z	28.8 2 44.2 34.73 27.7 39.4 0.9 24.5 45.63 26 25 0.66 36 1.09 0.22 34.7 0.89 2.2 34.7 0.89	75 197 120 117 82 42 118 94 70 36 34 104 61 201 21 48 207 1627 96, df = 8)	100.6 121 130.3 95.25 110 119.2 2.66 158.5 71.47 114 4 2.46 2.88 136.8 2.7 = 16 (P	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 0.82 38 1.13 0.021 16.4 1 \$ \$	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20 37 256 2235 2235	6.3% 6.1% 6.8% 6.4% 5.5% 6.4% 6.0% 6.4% 5.5% 6.4% 5.5% 6.8% 4.3% 5.5% 6.8%	0.15 [-0.14, 0.44] 0.85 [0.47, 1.12] -0.02 [-0.21, 0.01] 0.34 [-0.04, 0.72] 0.24 [-0.04, 0.72] 0.24 [-0.77, 0.34] 0.39 [-0.46, -0.13] 0.17 [-0.11, 0.46, -0.13] -0.13 [-0.74, 0.47] 0.03 [-0.38, 0.45] 0.03 [-0.38, 0.45] 0.08 [-0.19, 0.35] 0.08 [-0.19, 0.31] -0.56 [-0.38, 0.07] 0.05 [-0.38, 0.07] 0.05 [-0.38, 0.07] 0.05 [-0.38, 0.07] 0.05 [-0.38, 0.07] 0.05 [-0.38, 0.07] 0.18 [-0.02, 0.38]		Alan 2014 Bennes 203 Casculteres 203 Casculteres 205 Casculteres 205 Charago 14 Chen 2010 de Buttos 2000 Charago 14 Chen 2010 de Buttos 2000 Lui 2017 Popo 2013 Revgare 2006 Schonknecht 2002 Schonknecht 2002 Wata2000 Wata2000 Wata2000 Yudgi 2005 Yudgi 20	170.7 225.7 213.9 189.93 214.01 5.48 199.3 234.13 4.24 235.76 238.7 185 193.4 169.89 258.78 194 167 4.48 185 5.12 4.73 204.56 4.73 204.56 0.111: Chi	31.7 40.1 40.1 1.002 1.04 43.18 1.89 45.1 1.13 46.61 1.13 46.61 1.13 29 21.5 38.84 47.77 29 21.5 38.84 43.3 29 21.5 38.84 43.3 29 20.3 38 33 0.98 8 33 0.21 0.21 .07 4 .01 20.3 20.3 20.3 20.3 20.3 20.3 20.3 20.3	75 60 120 19 44 411 14 42 411 118 53 53 106 94 411 118 53 50 94 411 153 53 106 34 34 61 201 21 21 207 21 59 90 2.07 20 90 94 94 94 94 94 94 94 94 94 94 94 94 94	167.6 200.5 212 212 186.89 211.1 191.96 5.54 221.1 4.65 225.33 207 122.03 248.23 207 176 4.1 1900 181 4.87 4.93 213.2 215.2 21	22.8 48.9 46.5 3.55 1.24 37.62 1 39.9 50.05 7.26 46.17 24.5 22.6 30.37 19.19 40 36 1.04 44 31 0.69 2.48.9 1.24	1200 45 60 45 36 62 117 18 201 117 18 201 120 43 87 111 10 75 61 15 63 104 47 257 256 2761 11); P =	4.5% 4.0% 5.1% 4.0% 5.1% 4.7% 3.3% 4.7% 3.3% 4.7% 3.8% 4.6% 5.1% 4.1% 3.8% 5.8% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0	0.11210.17.040 0.2710.17.049 0.0410.15.0230 0.0410.15.0230 0.0410.22.049 0.0410.22.049 0.0410.22.049 0.0410.22.049 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.20.0410 0.0410.10.0410 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.0400 0.0410.04000 0.0410.04000 0.0410.04000 0.0410.040000000000	
http://disabult/table/ Jam 2014 Jam 2019 Jam 2019 Jam 2019 Jam 2019 Jam 2019 Jam 2019 Jam 2019 Jam 2019 Jam 2017 Jam 2017 Jam 2017 Jam 2012 Vatanabe2004 Jam 2012 Jam 2014 Jam 2014 Jam 2014 Jam 2014 Jam 2014 Jam 2014 Jam 2014 Jam 2016 Jam 2017 Jam	Mean 104.4 123 129 130.67 119.1 110.8 2.36 162.5 106.13 110 95 2.46 108 2.6 2.79 138.2 2.78 0.15; Chir Z = 1.78 (28.8 244.2 34.73 27.7 39.4 45.63 26 25 0.66 36 1.09 0.22 34.7 0.89	75 197 120 117 82 42 118 94 70 36 34 104 61 201 21 48 207 1627 96, df = 8)	100.6 121 130.3 95255 110 119.2 2.66 158.5 71.47 114 94 2.46 2.88 136.8 2.7 = 16 (P	21.8 4 60.9 23.46 24.4 35.7 0.46 22.8 24.61 36 0.82 38 1.13 0.021 16.4 1 <<0.0000	120 47 803 117 40 18 120 111 75 15 63 104 32 257 20 37 256 2235 11); I ² =	6.3% 6.1% 6.8% 6.4% 5.8% 4.7% 6.5% 6.4% 5.5% 6.4% 5.5% 6.8% 6.8% 6.8% 6.8%	0.15 [0.14, 0.44] 0.85 [0.17, 1.12] 0.02 [-021, 0.17] 1.19 [0.91, 1.47] 0.24 [-0.04, 0.472] 0.24 [-0.04, 0.472] 0.25 [-0.7, 0.34] 0.39 [-0.65, -0.13] 0.17 [-0.11, 0.44] 0.05 [0.61, 1.247] 0.13 [-0.74, 0.045] 0.08 [-0.35, 0.51] 0.13 [-0.06, 0.31] 0.65 [-0.38, 0.48] 0.08 [-0.10, 0.27] 0.18 [-0.02, 0.38]	-1 -0.5 0 0.5 1	Alam 2014 Bernesi 2003 Casabahera 2003 Casabahera 2005 Casabahera 2005 Casabahera 2005 Casabahera 2005 Casabahera 2005 Kolacha 2010 Li H 2017 Popo 2012 Popo 2012 Raygea 2005 Sandrahova 2005 Sandrahova 2005 Sandrahova 2005 Velasi 2016 Yamamoba 2016 Yamamoba 2016 Yamamoba 2016 Zheng 2016 Text (af 551; C) Heterogenetity: Taria	$\begin{array}{c} 170.7\\ 225.7\\ 213.9\\ 189.84\\ 34\\ 214.01\\ 5.84\\ 199.3\\ 234.13\\ 4.24\\ 235.76\\ 238\\ 185\\ 238\\ 185\\ 194.1\\ 169.99\\ 258.78\\ 193.4\\ 169.99\\ 193.4\\ 167\\ 165\\ 5.2\\ 24.5\\ 4.73\\ 204.5\\ 4.76\\ 0.11; Chi\\ 2 = 2.14\\ \end{array}$	31.7 40.1 10.02 1.04 43.18 45.1 1.89 45.1 1.13 46.61 1.13 46.61 1.13 46.61 1.13 29 21.5 58.84 47.77 29 21.5 58.84 47.77 29 21.5 58.84 47.84 33 30.98 9.889 38 33 0.98 9.021 1.07 20.3 1.07 20.3 21.07	75 600 120 19 44 4117 44 42 4111 118 53 106 94 4 14 70 34 106 94 4 104 61 201 21 21 9 201 2159 2159 20.02, df - 33)	167.6 200.5 212 186.89 4.25 5.54 221.11 241.13 4.65 225.33 215. 122.03 248.23 207 176 6 4.1 192.03 248.23 207 176.6 4.1 19.06 4.5 122.05 248.23 207 176.6 4.5 122.05 248.23 207 248.23 207 248.23 207 248.25 247.25	22.8 48.9 46.5 3.55 1.24 37.62 1 39.95 50.05 39.67 24.6.17 24.6.17 24.6.17 24.6.17 24.6.17 30.37 19.19 40 36 1.04 431 0.69 0.25 48.9 1.24	120 45 85 86 82 117 21 18 201 120 120 43 87 111 10 43 87 111 10 75 61 104 32 257 200 37 256 2761 11; P = 1	4.5% 4.0% 5.1% 4.0% 5.1% 4.7% 3.3% 4.7% 3.3% 4.7% 4.7% 4.7% 4.7% 3.3% 4.6% 3.8% 3.8% 3.8% 3.8% 3.8% 5.0% 2.8% 3.8% 5.0% 2.8% 3.8% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0% 5.0	$\begin{array}{c} 0.12 \left[0.17 \\ 0.47 \right] \left[0.17 \\ 0.57 \\ 0.17$	

FIGURE 2 | Forest plots of the overall meta-analysis for the effects of the four parameters of blood lipid levels on AD risk with a random-effects model. (A) TC levels, (B) HDL-C levels, (C) LDL-C levels, (D) TG levels. SMD, standardized mean difference; Cl, confidence interval.

et al., 2011; Popp et al., 2012, 2013; Singh et al., 2012; Xiao et al., 2012; Alam et al., 2014; Chang et al., 2014; Zhao et al., 2014; Li et al., 2015b, 2017; Yassine et al., 2016; Zheng et al., 2016; Kouzuki et al., 2018; Chen et al., 2019). One Flow diagram of the literature selection is provided in **Figure 1**. The results of the quality assessment are displayed in **Table 2**.

Characteristics of the Included Studies

The characteristics of the 27 included studies are summarized in **Table 1**. The study designs were all case-control. A total of 5,286 subjects were eligible for the present meta-analysis. All of the studies were published between January 2000 and March 2019. The sample sizes of all studies ranged from 24 to 923. The mean age of the participants of each study ranged from 66 to 80.67 and from 63.8 to 84.2, respectively. The qualities of the collected studies were moderate to good. The NOS scores range 5–8, with an average score of 6.33 (the details are shown in **Table 2**). Most of the collected studies were singlecenter trials. In total, 16 studies came from Asia and 9 came from Europe and the Americas (8 came from Europe and 1 came from North America). Diagnostic, inclusion and exclusion criteria for participants were all clearly reported in all the investigated literature. The case groups of those studies were mainly moderate AD according to MMSE scores that have been reported (Folstein et al., 1975). This study mainly evaluated four outcomes: TC, HDL-C, LDL-C, and TG. For further analysis of extreme heterogeneity, we stratified the collected studies into several subgroups.

Subgroup	References	SMD	95% CI	P-value	Effect model	Hetero	ogeneity
						12 (%)	P-value
тс	Cankurtaran et al., 2005	0.17	[0.01, 0.32]	0.03	RE	82	<0.00001
Asia	Popp et al., 2012	0.1	[-0.10, 0.30]	0.33	RE	85	< 0.00001
Europe and America	Alzheimer, 1907	0.29	[0.04, 0.53]	0.02	RE	71	0.0005
Mean age ≤ 70	Liu et al., 2019	0.45	[0.11, 0.79]	0.01	RE	86	<0.00001
Mean age > 70	Moher et al., 2009	0.05	[-0.09, 0.20]	0.47	RE	72	< 0.00001
Sample size < 100	Anstey et al., 2017	-0.01	[-0.25, 0.24]	0.96	RE	60	0.006
Sample size ≥ 100	Strand et al., 2013	0.26	[0.07, 0.46]	0.007	RE	87	< 0.00001
Before 2010	Wu et al., 2019	0.18	[-0.03, 0.38]	0.09	RE	59	0.009
2010 and beyond	Pappolla et al., 2003	0.16	[-0.05, 0.37]	0.14	RE	87	< 0.00001
HDL-C	Moher et al., 2009	-0.15	[-0.34, 0.05]	0.15	RE	87	<0.00001
Mean age ≤ 70	Patterson, 2018	-0.50	[-0.76, -0.25]	0.0001	RE	60	<0.06
Mean age > 70	Strand et al., 2013	-0.03	[-0.26, 0.19]	0.78	RE	87	<0.00001
Sample size < 100	Dubois et al., 2014	-0.16	[-0.52, 0.21]	0.4	RE	68	0.008
Sample size ≥ 100	Rantanen et al., 2017	-0.12	[-0.34, 0.10]	0.25	RE	90	< 0.00001
Before 2010	Liu et al., 2019	0.11	[-0.35, 0.58]	0.63	RE	92	<0.00001
2010 and beyond	Anstey et al., 2017	-0.3	[-0.45, -0.14]	0.0001	RE	65	0.002
LDL-C	Stroup et al., 2000	0.18	[-0.02, 0.38]	0.08	RE	87	< 0.00001
Mean age ≤ 70	Patterson, 2018	0.59	[0.02, 1.16]	0.04	RE	92	< 0.00001
Mean age > 70	Kivipelto et al., 2001	0.06	[-0.09, 0.22]	0.44	RE	70	< 0.00001
Sample size < 100	Dubois et al., 2014	-0.06	[-0.26, 0.13]	0.53	RE	0	0.6
Sample size ≥ 100	Anstey et al., 2017	0.31	[0.05, 0.56]	0.02	RE	91	< 0.00001
Before 2010	Liu et al., 2019	0.2	[-0.04, 0.43]	0.11	RE	70	0.002
2010 and beyond	Wu et al., 2019	0.17	[-0.13, 0.47]	0.27	RE	91	< 0.00001
TG	Stroup et al., 2000	0	[-0.12, 0.12]	1	RE	62	0.0004
Mean age ≤ 70	Patterson, 2018	0.17	[-0.22, 0.55]	0.4	RE	83	0.0006
Mean age > 70	Kivipelto et al., 2001	-0.03	[-0.15, 0.09]	0.64	RE	51	0.02
Sample size < 100	Dubois et al., 2014	-0.13	[-0.56, 0.29]	0.54	RE	77	0.0006
Sample size ≥ 100	Anstey et al., 2017	0.04	[-0.07, 0.14]	0.51	RE	47	0.04
Before 2010	Dubois et al., 2014	-0.08	[-0.26, 0.10]	0.37	RE	39	0.14
2010 and beyond	Anstey et al., 2017	0.05	[-0.11, 0.21]	0.55	RE	69	0.0004

SMD, mean difference; 95%Cl, 95% confidence interval; RE, random effects model; TC, Total Cholesterol; TG, Triglyceride; HDL-C, High-density Lipoprotein Cholesterol; LDL-C = Low-density Lipoprotein Cholesterol.

Meta-Analysis Results TC and AD

Out of the 27 studies, 25 investigated literature, with a total of 4,920 participants measuring the TC. The results of our study are presented in **Table 3**. The pooled effects suggested that TC levels in the AD group were significantly higher than in the control group (SMD = 0.17, 95% CI: [0.01, 0.32], P = 0.03). Concerning high heterogeneity (P < 0.00001; $I^2 = 82\%$), the random-effects model was applied. The forest plot of the pooled analysis is presented in **Figure 2A**.

Given the effects of the mean age of participants, regions of studies, publication time of papers, and sample sizes of studies, we performed a stratified analysis according to these characteristics (the results are presented in **Table 4**). TC levels were discovered significantly associated with AD in the subgroup of "*mean age* \leq 70 years old" (SMD: 0.45, 95% CI: [0.11, 0.79], P = 0.01), while no significant difference was found in the subgroup

of "mean age > 70 years old" (SMD: 0.05, 95% CI: [-0.09, 0.20], P = 0.47; the forest plot is reported in **Figure 3**). It is inconsistent with the result of a previous study that reported that TC levels had a negative relationship with AD in the population aged 70 years and above (Folstein et al., 1975). No racial or regional differences were found in TC levels between the AD group and the control group in Asia (SMD: 0.10, 95% CI: [-0.10, 0.30], P = 0.33), whereas the TC levels of the AD group were significantly higher than that of the control group in Europe and the Americas (SMD: 0.29, 95% CI: [0.04, 0.53], P = 0.02) (the forest plot is reported in Figure 4). A significant association between the TC levels and AD also existed, but only when sample size was larger than 100 (SMD = 0.26, 95% CI: [0.07, 0.46], P = 0.007). When sample size was small (sample size < 100), there was no significant difference (SMD = -0.01, 95% CI: [-0.25, 0.24], P = 0.96; the forest plot is reported in Figure 5). It is reasonable to believe that data with a larger sample size are more trustworthy since a larger sample

		AD		с	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	lotal	Weight	IV. Random, 95% CI	IV, Random, 95% Cl
8.1.1 age ≤ 70									
Alam 2014	170.7	31.7	75	167.6	22.8	120	4.5%	0.12 [-0.17, 0.40]	
Chen 2018	214.01	43.18	117	191.96	37.62	117	4.7%	0.54 [0.28, 0.80]	
Popp 2012	235.76	46.61	53	225.33	39.67	43	3.9%	0.24 [-0.17, 0.64]	
Popp 2013	238	47.77	106	215	46.17	87	4.5%	0.49 [0.20, 0.77]	
Singh2012	169.89	38.84	70	122.03	30.37	75	4.1%	1.37 [1.01, 1.73]	
Teunissen 2003	258.78	14.34	34	248.23	19.19	61	3.8%	0.59 [0.17, 1.02]	
Zhao2014	204.5	20.3	48	213.6	48.9	37	3.8%	-0.25 [-0.68, 0.18]	
Subtotal (95% CI)			503			540	29.4%	0.45 [0.11, 0.79]	
Heterogeneity: Tau ² =	0.18; Chi	² = 42.1	7, df =	6 (P < 0.	00001);	$I^2 = 86$	6%		
Test for overall effects	Z = 2.58	(P = 0.0	1)						
8.1.2 age > 70									
Borroni 2003	225.7	40.1	60	200.5	48.9	45	4.0%	0.57 [0.17, 0.96]	
Cankurtaran2005	213.9	44.6	120	212	46.5	803	5.0%	0.04 [-0.15, 0.23]	
Cascalheira 2009	189.98	10.02	19	186.89	3.55	36	3.1%	0.47 [-0.10, 1.03]	
Chang2014	4.43	1.04	44	4.25	1.24	62	4.0%	0.15 [-0.23, 0.54]	
de Bustos 2000	5.48	1.89	44	5.54	1	21	3.3%	-0.04 [-0.56, 0.48]	
Kouzuki 2017	199.3	45.1	42	211.1	39.9	18	3.2%	-0.27 [-0.82, 0.29]	
Kölsch 2010	234.13	47.84	411	241.13	50.05	201	5.1%	-0.14 [-0.31, 0.02]	
Li H 2017	4.24	1.13	118	4.65	0.75	120	4.7%	-0.43 [-0.68, -0.17]	
Raygani 2006	185	29	94	175	24.5	111	4.6%	0.37 [0.10, 0.65]	
Schonknecht 2002	193.4	21.5	14	182.7	22.6	10	2.1%	0.47 [-0.35, 1.29]	
Wada2000	194	33	36	207	40	15	2.9%	-0.36 [-0.97, 0.24]	
Watanabe2004	167	29	34	176	36	63	3.8%	-0.26 [-0.68, 0.15]	
Xiao 2012	4.48	0.89	104	4.1	1.04	104	4.6%	0.39 [0.12, 0.67]	
Yamamoto2005	187	38	61	190	44	32	3.8%	-0.07 [-0.50, 0.35]	
Yassine 2016	185	33	26	181	31	47	3.5%	0.12 [-0.35, 0.60]	
Yu2014	5.12	0.98	201	4.87	0.69	257	5.0%	0.30 [0.12, 0.49]	
Zengi2012	4.73	0.21	21	4.93	0.25	20	2.8%	-0.85 [-1.49, -0.21]	
Zheng2016	4.76	1.07	207	4.57	1.24	256	5.0%	0.16 [-0.02, 0.35]	
Subtotal (95% CI)			1656			2221	70.6%	0.05 [-0.09, 0.20]	•
Heterogeneity: Tau ² =	0.06; Chi	² = 60.9	1, df =	17 (P < 0	0.00001); l ² = 7	2%		
Test for overall effect:	Z = 0.73	(P = 0.4	7)						
Total (95% CI)			2159			2761	100.0%	0 17 [0 01 0 32]	•
Hotorogonoity: Tau ² -	0 11. Chi	2 - 131	02 df -	- 24 (D -	0.0000	1). 12 -	920/		
Test for overall offect	7 = 2 14	(P = 0.0)	3)	24 (F	0.0000	1), 1 -	02 /0		-1 -0.5 0 0.5 1
Test for overall effect	2 - 2.14	(I - 0.0	21 46-	4 (D - 0	04) 12	70.00			Control AD

FIGURE 3 | Forest plot of stratified analysis for the effects of TC levels on AD risk in different age groups with a random-effects model. SMD, standardized mean difference; CI, confidence interval.

size in a clinical experiment is of great consequence. Finally, there was no strong correlation between TC levels and AD in both groups (SMD = 0.18, 95% CI: [-0.03, 0.38], P = 0.09 in "before 2010"; SMD = 0.16, 95% CI: [-0.05, 0.37], P = 0.14 in "2010 and beyond," the forest plot is reported in **Figure 6**). Even with societal development and the changes in diet structure and living habits in the past decade, no significant changes appeared in the relationship between TC levels and AD.

HDL-C and AD

Eighteen studies with 3,968 participants measured HDL-C levels; the meta-analysis results are presented in **Table 3**. These eighteen studies were all conducted in Asia. The pool effects indicated that HDL-C levels was not associated with AD (SMD = -0.15, 95% CI: [-0.34, 0.05], P = 0.15). With the high heterogeneity (P < 0.00001; $I^2 = 87\%$), the random-effects model was adopted. **Figure 2B** exhibits the forest plot of the pooled analysis.

Similarly, after the stratified analysis, HDL-C levels were presented a negative association with AD in the "mean age \leq 70 years old" subgroup (SMD = -0.50, 95% CI: [-0.76, -0.25], P =0.0001). However, no obvious association was found between HDL-C levels and AD in the "mean age > 70 years old" subgroup (SMD = -0.03, 95% CI: [-0.26, 0.19], P = 0.78; the forest plot

is reported in **Figure 7**). There was no significant association in either the "sample size < 100" (SMD = -0.16, 95% CI: [-0.52, 0.21], P = 0.40) or the "Sample size ≥ 100 " group (SMD = -0.14, 95% CI: [-0.38, 0.10], P = 0.25; the forest plot is reported in **Figure 8**). In the "2010 and beyond" subgroup, the AD group was significantly linked with decreased HDL-C levels (SMD = 0.11, 95% CI: [-0.35, 0.58], P = 0.0001), which was inconsistent with the result of the "before 2010" group (SMD = -0.30, 95% CI: [-0.45, -0.14], P = 0.63, the forest plot is reported in **Figure 9**). The results of the stratified analysis are shown in **Table 4**. HDL-C levels had a positive correlation with cognitive functioning in people under 70 years old. In addition, in line with TC levels, HDL-C levels had no strong relation with AD in the past decade.

LDL-C and AD

A total of 17 studies with 3,862 participants measured LDL-C levels and the results of the meta-analysis are listed in **Table 3**. These studies were all conducted in Asia. After pooling data, the results revealed that LDL-C levels had no significant relation with AD (SMD = 0.18, 95% CI: [-0.02, 0.38], P = 0.08). Figure 2C exhibits the forest plot of the pooled analysis.

According to the results of the stratified analyses, in the group of "sample size \geq 100," the AD group indicated significant



difference; CI, confidence interval.

correlation with increased LDL-C levels (SMD = 0.31, 95% CI: [0.05, 0.56], P = 0.02), whereas there was no strong association between LDL-C levels with AD in the "sample size < 100" group (SMD = -0.06, 95% CI: [-0.26, 0.13], P = 0.53; the forest plot is reported in Figure 10). There was also no significant difference in the groups of "mean age \leq 70 years old" (SMD = 0.59, 95% CI: [0.02, 1.16], P = 0.04) and of "mean age > 70 years old" (SMD = 0.06, 95% CI: [-0.09, 0.22], P = 0.44;the forest plot is reported in Figure 11). When studies were stratified according to the time of publication, no significant difference was found between the two subgroups of "before 2010" (SMD = 0.20, 95% CI: [-0.04, 0.43], P = 0.11) and "2010 and beyond" (SMD = 0.17, 95% CI: [-0.13, 0.47], P = 0.27; the forest plot is reported in Figure 12). As mentioned before, studies involving a larger sample size are more persuasive. In patients who were under 70 years old, there was a negative association between LDL-C levels and cognitive functioning. Therefore, we may find a new method to affect cognition in its early stages at the LDL-C level. Timing is important; after age 70, it may make no sense to slow the progression of AD through this method.

TG and AD

There were 17 studies covering 3746 participants that measured TG levels. The result of meta-analysis is exhibited in **Table 3**. These studies were all conducted in Asia. The results of the pooled effects showed no significant association between TG levels and AD (SMD = -0.00, 95% CI: [-0.12, 0.12], P = 1.00). **Figure 2D** indicates the forest plot of the pooled analysis.

The results of the pooled effects of all subgroups demonstrated no associations between TG and AD. The results were listed below: "mean age \leq 70 years old" (SMD = 0.17, 95% CI: [-0.22, 0.55], P = 0.40), "mean age > 70 years old" (SMD = -0.03, 95% CI: [-0.15, 0.09], P = 0.64; the forest plot is reported in **Figure 13**), "sample size < 100" (SMD = 0.13, 95% CI: [-0.56, 0.29], P = 0.54), "Sample size \geq 100" (SMD = 0.04, 95% CI: [-0.07, 0.14], P = 0.51; the forest plot reported in **Figure 14**). We have found no obvious association between the TG levels and AD in either the subgroups of "before 2010" (SMD = -0.08, 95% CI: [-0.26, 0.10], P = 0.37) or of "2010 and beyond" (SMD = 0.05, 95% CI: [-0.11, 0.21], P = 0.55; the forest plot is reported in **Figure 15**).

Chudu or Cubaroup	Meen	AD	Total	Maan	ontroi	Total	Maight	N Bandom 05% C	Std. Mean Difference
A 44 4 Semale size		50	Total	Mean	50	Total	weight	IV, Kandom, 95% C	I IV, Random, 95% CI
1.14.1 Sample size	100	40.00	10	400.00	0.55	20	0.40/	0 47 1 0 40 4 001	
Cascalheira 2009	189.98	10.02	19	186.89	3.55	36	3.1%	0.47 [-0.10, 1.03]	
de Bustos 2000	5.48	1.89	44	5.54	1	21	3.3%	-0.04 [-0.56, 0.48]	
Kouzuki 2017	199.3	45.1	42	211.1	39.9	18	3.2%	-0.27 [-0.82, 0.29]	
Popp 2012	235.76	46.61	53	225.33	39.67	43	3.9%	0.24 [-0.17, 0.64]	
Schonknecht 2002	193.4	21.5	14	182.7	22.6	10	2.1%	0.47 [-0.35, 1.29]	
Teunissen 2003	258.78	14.34	34	248.23	19.19	61	3.8%	0.59 [0.17, 1.02]	
Wada2000	194	33	36	207	40	15	2.9%	-0.36 [-0.97, 0.24]	
Watanabe2004	167	29	34	176	36	63	3.8%	-0.26 [-0.68, 0.15]	
Yassine 2016	185	33	26	181	31	47	3.5%	0.12 [-0.35, 0.60]	
Zengi2012	4.73	0.21	21	4.93	0.25	20	2.8%	-0.85 [-1.49, -0.21]	
Zhao2014	204.5	20.3	48	213.6	48.9	37	3.8%	-0.25 [-0.68, 0.18]	
Subtotal (95% CI)			371			371	36.2%	-0.01 [-0.25, 0.24]	—
Heterogeneity: Tau ²	= 0.10; Chi	² = 24.7	5, df =	10 (P = 0	0.006); I	$^{2} = 60\%$	6		
Test for overall effect	: Z = 0.06	(P = 0.9	6)						
1.14.2 Sample size	≥ 100								
Alam 2014	170.7	31.7	75	167.6	22.8	120	4.5%	0.12 [-0.17, 0.40]	
Borroni 2003	225.7	40.1	60	200.5	48.9	45	4.0%	0.57 [0.17, 0.96]	
Cankurtaran2005	213.9	44.6	120	212	46.5	803	5.0%	0.04 [-0.15, 0.23]	+-
Chang2014	4.43	1.04	44	4.25	1.24	62	4.0%	0.15 [-0.23, 0.54]	
Chen 2018	214.01	43.18	117	191.96	37.62	117	4.7%	0.54 [0.28, 0.80]	
Kölsch 2010	234.13	47.84	411	241.13	50.05	201	5.1%	-0.14 [-0.31, 0.02]	
Li H 2017	4.24	1.13	118	4.65	0.75	120	4.7%	-0.43 [-0.68, -0.17]	
Popp 2013	238	47.77	106	215	46.17	87	4.5%	0.49 [0.20, 0.77]	
Raygani 2006	185	29	94	175	24.5	111	4.6%	0.37 [0.10, 0.65]	_
Singh2012	169.89	38.84	70	122.03	30.37	75	4.1%	1.37 [1.01, 1.73]	
Xiao 2012	4.48	0.89	104	4.1	1.04	104	4.6%	0.39 [0.12, 0.67]	
Yamamoto2005	187	38	61	190	44	32	3.8%	-0.07 [-0.50, 0.35]	
Yu2014	5.12	0.98	201	4.87	0.69	257	5.0%	0.30 [0.12, 0.49]	
Zheng2016	4.76	1.07	207	4.57	1.24	256	5.0%	0.16 [-0.02, 0.35]	
Subtotal (95% CI)			1788			2390	63.8%	0.26 [0.07, 0.46]	◆
Heterogeneity: Tau ²	= 0.11; Chi	² = 101.	75, df =	= 13 (P <	0.0000	1); I ² =	87%		
Test for overall effect	: Z = 2.71	(P = 0.0	07)						
Total (95% CI)			2159			2761	100.0%	0.17 [0.01, 0.32]	◆
Heterogeneity: Tau ²	= 0.11: Chi	² = 131	02. df =	= 24 (P <	0.0000	1): $ ^2 =$	82%		L I I I I
Test for overall effect	Z = 2.14	(P = 0.0)	(3)	2. (2.0000	.,,.	0270		-2 -1 0 1 2
Test for subgroup diff	erences: ($hi^2 = 2$	96 df =	= 1 (P = 0	0 0 9 1 ²	= 66 29	2/0		Control AD

FIGURE 5 | Forest plot of stratified analysis for the effects of IC levels on AD risk in groups with different sample sizes with a random-effects mo standardized mean difference; CI, confidence interval.

DISCUSSION

The aims of this study were to validate the association between AD and blood lipid levels, and whether blood lipid profiles could be used as biomarkers for AD diagnosis. In summary, our meta-analysis demonstrated five points: (a) elevated TC levels were associated with a higher risk of AD in later life, especially in Occidentals and subjects aged 60-70, which may be due to different eating habits in different regions, resulting in different cholesterol intakes (Menotti and Puddu, 2015). TC levels may be effective biomarkers for diagnosing AD. (b) In the subgroup of subjects aged 60-70, LDL-C levels were proven to have a positive correlation with AD, while HDL-C levels had a negative correlation with AD. (c) In the subgroup of studies containing a sample size over 100, LDL-C levels were found to have a positive correlation with AD in later-life. (d) The subgroup of studies published between 2010 and 2019 revealed that HDL-C levels had a negative correlation with AD in later-life. (e) TG levels had no significant association with AD in later-life.

Cholesterol is identified as the most plentiful type of lipid in the central nervous system, and \sim 25% of total amount of cholesterol is contained in human brain (Bjorkhem and

Meaney, 2004; Cermenati et al., 2015), which is not only the primary component of lipid in nerve cell and glial cell membrane but also the key component of myelin sheath (Hussain et al., 2019). A recent study has found that microglia and the activation of NLRP3 inflammasome are vital for the pathogenesis of AD in tau, which supports the amyloid-cascade hypothesis of AD (Ising et al., 2019). Besides, cholesterol exerts an essential influence in plasma membrane regionalization, signal transduction, myelin sheath formation, and synaptic formation and maintenance (Chernick et al., 2019). Peripheral blood cholesterols can affect the human brain and AD through the blood-brain barrier (BBB) (Gamba et al., 2019). Our results showed that elevated TC levels were significantly associated with AD patients in later life. It can be inferred that elevated TC levels can be applied to diagnose AD and relative cognitive impairment in later-life patients. The result of a longitudinal study was consistent with our result that high TC levels were related to an increased risk of AD incidence (Ma et al., 2017). Additionally, some studies reported that hypercholesterolemia was identified as a risk factor for neurodegenerative disease, which resulted from the increase of the permeability of the BBB, inducing synaptic dysfunction and impairing neuron morphology (Merino-Serrais et al., 2019). Other studies have

		AD		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI
1.13.1 before 2010									
Borroni 2003	225.7	40.1	60	200.5	48.9	45	4.0%	0.57 [0.17, 0.96]	
Cankurtaran2005	213.9	44.6	120	212	46.5	803	5.0%	0.04 [-0.15, 0.23]	
Cascalheira 2009	189.98	10.02	19	186.89	3.55	36	3.1%	0.47 [-0.10, 1.03]	+
de Bustos 2000	5.48	1.89	44	5.54	1	21	3.3%	-0.04 [-0.56, 0.48]	
Raygani 2006	185	29	94	175	24.5	111	4.6%	0.37 [0.10, 0.65]	
Schonknecht 2002	193.4	21.5	14	182.7	22.6	10	2.1%	0.47 [-0.35, 1.29]	
Teunissen 2003	258.78	14.34	34	248.23	19.19	61	3.8%	0.59 [0.17, 1.02]	· · · · ·
Wada2000	194	33	36	207	40	15	2.9%	-0.36 [-0.97, 0.24]	
Watanabe2004	167	29	34	176	36	63	3.8%	-0.26 [-0.68, 0.15]	
Yamamoto2005	187	38	61	190	44	32	3.8%	-0.07 [-0.50, 0.35]	
Subtotal (95% CI)			516			1197	36.4%	0.18 [-0.03, 0.38]	◆
Heterogeneity: Tau ² =	0.06; Chi	² = 22.0	1, df =	9 (P = 0.	009); l²	= 59%			
Test for overall effect:	Z = 1.70	(P = 0.0)	9)						
1.13.2 2010 and beyo	ond								
Alam 2014	170.7	31.7	75	167.6	22.8	120	4.5%	0.12 [-0.17, 0.40]	
Chang2014	4.43	1.04	44	4.25	1.24	62	4.0%	0.15 [-0.23, 0.54]	
Chen 2018	214.01	43.18	117	191.96	37.62	117	4.7%	0.54 [0.28, 0.80]	
Kouzuki 2017	199.3	45.1	42	211.1	39.9	18	3.2%	-0.27 [-0.82, 0.29]	
Kölsch 2010	234.13	47.84	411	241.13	50.05	201	5.1%	-0.14 [-0.31, 0.02]	
Li H 2017	4.24	1.13	118	4.65	0.75	120	4.7%	-0.43 [-0.68, -0.17]	
Popp 2012	235.76	46.61	53	225.33	39.67	43	3.9%	0.24 [-0.17, 0.64]	
Popp 2013	238	47.77	106	215	46.17	87	4.5%	0.49 [0.20, 0.77]	
Singh2012	169.89	38.84	70	122.03	30.37	75	4.1%	1.37 [1.01, 1.73]	
Xiao 2012	4.48	0.89	104	4.1	1.04	104	4.6%	0.39 [0.12, 0.67]	
Yassine 2016	185	33	26	181	31	47	3.5%	0.12 [-0.35, 0.60]	
Yu2014	5.12	0.98	201	4.87	0.69	257	5.0%	0.30 [0.12, 0.49]	
Zengi2012	4.73	0.21	21	4.93	0.25	20	2.8%	-0.85 [-1.49, -0.21]	
Zhao2014	204.5	20.3	48	213.6	48.9	37	3.8%	-0.25 [-0.68, 0.18]	
Zheng2016	4.76	1.07	207	4.57	1.24	256	5.0%	0.16 [-0.02, 0.35]	
Subtotal (95% CI)			1643			1564	63.6%	0.16 [-0.05, 0.37]	-
Heterogeneity: Tau ² =	0.14; Chi	² = 109.	01, df =	= 14 (P <	0.0000	1); I ² =	87%		
Test for overall effect:	Z = 1.46	(P = 0.1	4)						
Total (95% CI)			2159			2761	100.0%	0.17 [0.01, 0.32]	◆
Heterogeneity: Tau ² =	0 11 Chi	² = 131	02 df :	= 24 (P <	0 0000	1): ² =	82%	the fact of the second	
Test for overall effect:	7 = 2.14	(P = 0.0)	3)	24 (1 4	0.0000	.,,	02/0		-1 -0.5 0 0.5 1
root for overall effect.	6 - 2.14	0.0	<i>o</i> ,						Control AD

FIGURE 6 | Forest plot of stratified analysis for the effects of TC levels on AD risk in studies published before and after 2010 with a random-effects model. SMD, standardized mean difference; CI, confidence interval.

8.2.1 age ≤ 70 Alam 2014 Chen 2018 Singh2012 Zhao2014 Subtotal (95% CI)	40.5 54.2	9.5	76						
Alam 2014 Chen 2018 Singh2012 Zhao2014 Subtotal (95% CI)	40.5 54.2	9.5	75						
Chen 2018 Singh2012 Zhao2014 Subtotal (95% CI)	54.2		15	42.4	8.3	120	6.0%	-0.22 [-0.50, 0.07]	
Singh2012 Zhao2014 Subtotal (95% CI)	41 54	15.12	117	60.04	9.56	117	6.1%	-0.46 [-0.72, -0.20]	
Zhao2014 Subtotal (95% CI)	41.04	8.4	70	46.29	9.09	75	5.7%	-0.54 [-0.87, -0.21]	
Subtotal (95% CI)	45.9	10.3	48	57.8	14.6	37	5.0%	-0.95 [-1.41, -0.50]	
oubtotal (55% Ol)			310			349	22.8%	-0.50 [-0.76, -0.25]	•
Heterogeneity: Tau ² =	= 0.04; Cł	ni² = 7.5	3, df =	3 (P = 0	0.06); l²	= 60%			
Test for overall effect	: Z = 3.84	(P = 0.	0001)						
8.2.2 age > 70									
Ban 2009	58	1	197	56	3	47	5.7%	1.26 [0.92, 1.59]	
Cankurtaran2005	57.1	22.8	120	55.8	14.9	803	6.4%	0.08 [-0.11, 0.27]	
Chang2014	1.06	0.2	44	1.03	0.3	62	5.4%	0.11 [-0.27, 0.50]	- <u>-</u>
Hoshino2002	52.3	14.1	82	53.4	12.4	40	5.5%	-0.08 [-0.46, 0.30]	
Kouzuki 2017	64.5	21.6	42	63.7	21.4	18	4.5%	0.04 [-0.52, 0.59]	
i H 2017	1.25	0.36	118	1.41	0.34	120	6.1%	-0.46 [-0.71, -0.20]	
Raygani 2006	35	6.6	94	40.2	7.4	111	6.0%	-0.74 [-1.02, -0.45]	
Wada2000	69	21	36	64	19	15	4.2%	0.24 [-0.36, 0.85]	
Watanabe2004	50	14	34	50	15	63	5.2%	0.00 [-0.42, 0.42]	
Xiao 2012	1.33	0.31	104	1.44	0.31	104	6.0%	-0.35 [-0.63, -0.08]	
Yamamoto2005	62	15	61	61	18	32	5.2%	0.06 [-0.37, 0.49]	
Yu2014	1.32	0.36	201	1.33	0.77	257	6.4%	-0.02 [-0.20, 0.17]	
Zengi2012	1.24	0.078	21	1.26	0.073	20	4.1%	-0.26 [-0.87, 0.36]	
Zheng2016	1.3	0.34	207	1.38	0.41	256	6.4%	-0.21 [-0.39, -0.03]	
Subtotal (95% CI)	0.45.01	12 - 400	1301	- 40 /5	- 0.00	1940	- 070/	-0.03 [-0.20, 0.19]	
Test for overall offect	- 0.15; Cr	P = 100	78)	- 13 (P	< 0.00	001); I*	- 01%		
rest for overall effect	. 2 - 0.20	(F = 0.	10)						
Total (95% CI)			1671			2297	100.0%	-0.15 [-0.34, 0.05]	•
Heterogeneity: Tau ² =	= 0.15; Cł	ni² = 127	7.09, df	= 17 (F	< 0.00	001); l²	= 87%	-	1 05 0 05 1
Test for overall effect	: Z = 1.44	(P = 0.	15)						-1 -0.5 0 0.5 1

FIGURE 7 | Forest plot of stratified analysis for the effects of HDL-C levels on AD risk in different age groups with a random-effects model. SMD, standardized mean difference; CI, confidence interval.



revealed that hypercholesterolemia predicted a progression to AD in patients with aMCI and that patients taking lipidlowering drugs are less likely to develop AD (Li et al., 2011; Romero-Sevilla et al., 2018). Moreover, when cholesterol was lowered, the Precursor Protein of AB (APP) was swallowed into cells to decompose, which could reduce the extracellular presence of A β and the risk of AD (Martins et al., 2009). Furthermore, oxysterols (oxidative metabolites of cholesterols) may participate in AD progression via Liver X Receptors (LXR), which are key components in cholesterol homeostasis (Gamba et al., 2019; Merino-Serrais et al., 2019; Mouzat et al., 2019). For example, 24-hydroxycholesterol (24-OHC) can impede hyperphosphorylation of tau induced by deposition of AB in SK-N-BE cells by regulating the deacetylase sirtuin 1. As a neuroprotective oxysterol, 24-OHC was also validated to modulate synaptic function in hippocampal neurons of rats through LXR (Testa et al., 2018). Furthermore, genomewide association studies (GWAS) verified that some genes like ABCA7, TREM2, DAPK1, and ADAMTS1 were associated with AD. The proteins expressed by these genes participated in tau binding proteins, endocytosis, innate immunity, APP, cholesterol metabolism, etc. (Kim et al., 2016; Efthymiou and Goate, 2017; Kunkle et al., 2019).

HDL-Cs are the most critical subtype of lipoprotein granules. Small HDL-C particles are able to enter into the brain, and they also circulate in the peripheral blood. As the only lipoprotein in CSF, HDL has been found to regulate intracellular

cholesterol homeostasis and amyloid protein metabolism in the brain (Bahrami et al., 2019). In this study, we identified that HDL-C levels were negatively associated with AD, which is consistent with the previous finding that higher levels of HDL may reduce the risk of the late-onset AD (Reitz et al., 2010). This association may be due to the neuroprotective effect of small-sized HDL (Ohtani et al., 2018). HDL-C has also been verified to functionally prevent aggregation and polymerization of AB in the human brain and prevent the inflammation caused in neurodegenerative processes (Koudinov et al., 1998; Olesen and Dago, 2000; Cockerill et al., 2001). Moreover, HDL-C was able to change the APP degradation by interrupting the clearance of $A\beta$ and promoting the amyloid fibrillary formation (Koch and Jensen, 2016). On the other hand, decreased HDL-C levels may reduce the risk of cardiovascular and cerebrovascular diseases (CVD) as well as the development of AD or vascular dementia. Meanwhile, HDL-C deficiency had been identified to contribute to cognitive impairment by affecting the risk of atherosclerosis (Bahrami et al., 2019).

LDL-C levels were presented significantly higher in AD patients than in elderly people with normal cognition in studies with a large sample size (over 100 participants). A possible explanation for the implications of our results is that LDL-C levels might promote the metabolism of $A\beta$ in the human brain, the formation of cortical plaques and tangles, as well as the creation of neurotoxicity fibrils and neuritis,

Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95% CI	IV. Random, 95% Cl
4.5.1 before 2010									
Ban 2009	58	1	197	56	3	47	5.7%	1.26 [0.92, 1.59]	
Cankurtaran2005	57.1	22.8	120	55.8	14.9	803	6.4%	0.08 [-0.11, 0.27]	+
Hoshino2002	52.3	14.1	82	53.4	12.4	40	5.5%	-0.08 [-0.46, 0.30]	
Ravgani 2006	35	6.6	94	40.2	7.4	111	6.0%	-0.74 [-1.02, -0.45]	
Wada2000	69	21	36	64	19	15	4.2%	0.24 [-0.36, 0.85]	
Watanabe2004	50	14	34	50	15	63	5.2%	0.00 [-0.42, 0.42]	
Yamamoto2005	62	15	61	61	18	32	5.2%	0.06 [-0.37, 0.49]	
Subtotal (95% CI)			624			1111	38.1%	0.11 [-0.35, 0.58]	
Heterogeneity: Tau ² =	= 0.36; Ch	i² = 79.	38, df =	6 (P <	0.0000	1); ² =	92%		
Test for overall effect	Z = 0.48	(P = 0.	63)						
4.5.2 2010 and bevo	nd								
Alam 2014	40.5	95	75	424	83	120	6.0%	-0 22 [-0 50 0 07]	
Chang2014	1.06	0.2	44	1.03	0.3	62	5.4%	0.11 [-0.27, 0.50]	
Chen 2018	54.2	15.12	117	60.04	9.56	117	6.1%	-0.46 [-0.72, -0.20]	
Kouzuki 2017	64.5	21.6	42	63.7	21.4	18	4.5%	0.04 [-0.52, 0.59]	
Li H 2017	1.25	0.36	118	1.41	0.34	120	6.1%	-0.46 [-0.71, -0.20]	
Singh2012	41.54	8.4	70	46.29	9.09	75	5.7%	-0.54 [-0.87, -0.21]	
Xiao 2012	1.33	0.31	104	1.44	0.31	104	6.0%	-0.35 [-0.63, -0.08]	
Yu2014	1.32	0.36	201	1.33	0.77	257	6.4%	-0.02 [-0.20, 0.17]	
Zengi2012	1.24	0.078	21	1.26	0.073	20	4.1%	-0.26 [-0.87, 0.36]	
Zhao2014	45.9	10.3	48	57.8	14.6	37	5.0%	-0.95 [-1.41, -0.50]	
Zheng2016	1.3	0.34	207	1.38	0.41	256	6.4%	-0.21 [-0.39, -0.03]	
Subtotal (95% CI)			1047			1186	61.9%	-0.30 [-0.45, -0.14]	◆
Heterogeneity: Tau ² =	= 0.04; Ch	i² = 28.	47, df =	10 (P =	= 0.002); I ² = 6	5%		
Test for overall effect	z = 3.80	(P = 0.	0001)						
Total (95% CI)			1671			2297	100.0%	-0.15 [-0.34, 0.05]	•
Heterogeneity: Tau ² =	= 0.15: Ch	i ² = 127	.09. df	= 17 (P	< 0.00	001); l ²	= 87%		
Test for overall effect	7 - 1 //	(P = 0)	15)	(.		.,, .			-1 -0.5 0 0.5 1

FIGURE 9 | Forest plot of stratified analysis for the effects of HDL-C levels on AD risk in studies published before and after 2010 with a random analysis model. SMD, standardized mean difference; CI, confidence interval.

Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% Cl
4.2.1 Sample size -	< 100								
Kouzuki 2017	110.8	39.4	42	119.2	35.7	18	4.7%	-0.22 [-0.77, 0.34]	
Wada2000	110	26	36	114	36	15	4.4%	-0.13 [-0.74, 0.47]	
Watanabe2004	95	25	34	94	36	63	5.5%	0.03 [-0.39, 0.45]	
Yamamoto2005	108	36	61	105	38	32	5.5%	0.08 [-0.35, 0.51]	
Zengi2012	2.79	0.22	21	2.88	0.021	20	4.3%	-0.56 [-1.18, 0.07]	
Zhao2014	138.2	34.7	48	136.8	16.4	37	5.5%	0.05 [-0.38, 0.48]	
Subtotal (95% CI)			242			185	29.8%	-0.06 [-0.26, 0.13]	•
Heterogeneity: Tau ²	= 0.00; Chi	² = 3.64	, df = 5	(P = 0.0)	60); I ² =	0%			
Test for overall effect	et: Z = 0.63	(P = 0.5	3)						
4.2.2 Sample size	≥ 100								
Alam 2014	104.4	28.8	75	100.6	21.8	120	6.3%	0 15 [-0 14 0 44]	
Ban 2009	123	2	197	121	4	47	6.1%	0.80 [0.47, 1.12]	
Cankurtaran2005	129	44.2	120	130.3	60.9	803	6.8%	-0.02 [-0.21, 0.17]	
Chen 2018	130.67	34.73	117	95.25	23 46	117	6.4%	1, 19 [0, 91, 1, 47]	
Hoshino2002	119.1	27.7	82	110	24.4	40	5.8%	0.34 [-0.04, 0.72]	
Li H 2017	2.38	0.9	118	2.66	0.46	120	6.5%	-0.39 [-0.65, -0.13]	
Ravgani 2006	162.5	24.5	94	158.5	22.8	111	6.4%	0.17 [-0.11, 0.44]	+
Singh2012	106.13	45.63	70	71.47	24.61	75	6.0%	0.95 [0.61, 1.29]	
Xiao 2012	2.46	0.66	104	2.4	0.82	104	6.4%	0.08 [-0.19, 0.35]	
Yu2014	2.6	1.09	201	2.46	1.13	257	6.8%	0.13 [-0.06, 0.31]	
Zheng2016	2.78	0.89	207	2.7	1	256	6.8%	0.08 [-0.10, 0.27]	
Subtotal (95% CI)			1385			2050	70.2%	0.31 [0.05, 0.56]	-
Heterogeneity: Tau ²	= 0.16; Chi	² = 108.	76, df =	= 10 (P ·	< 0.000	01); l ² =	= 91%		
Test for overall effect	et: Z = 2.37	(P = 0.0	2)						
Total (95% CI)			1627			2235	100.0%	0.18 [-0.02, 0.38]	◆
Heterogeneity: Tau ²	= 0.15; Chi	² = 118.	96, df =	= 16 (P ·	< 0.000	01); l ² =	= 87%	_	
Test for overall effect	$t \cdot 7 = 1.78$	(P = 0.0)	8)						-1 -0.5 0 0.5 1

FIGURE 10 | Forest plot of stratified analysis for the effect of LDL-C levels on AD risks in groups with different sample sizes with a random-effects model. SMD, standardized mean difference; CI, confidence interval.

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
8.3.1 age ≤ 70									
Alam 2014	104.4	28.8	75	100.6	21.8	120	6.3%	0.15 [-0.14, 0.44]	
Chen 2018	130.67	34.73	117	95.25	23.46	117	6.4%	1.19 [0.91, 1.47]	
Singh2012	106.13	45.63	70	71.47	24.61	75	6.0%	0.95 [0.61, 1.29]	
Zhao2014	138.2	34.7	48	136.8	16.4	37	5.5%	0.05 [-0.38, 0.48]	
Subtotal (95% CI)			310			349	24.1%	0.59 [0.02, 1.16]	
Heterogeneity: Tau ² =	= 0.31: Chi	² = 36.3	3. df =	3 (P < 0	.00001); $ ^2 = 9$	2%		
Test for overall effect	: Z = 2.04	(P = 0.0)	4)	- (-					
8.3.2 age > 70									
Ban 2009	123	2	197	121	4	47	6.1%	0.80 [0.47, 1.12]	
Cankurtaran2005	129	44.2	120	130.3	60.9	803	6.8%	-0.02 [-0.21, 0.17]	
Hoshino2002	119.1	27.7	82	110	24.4	40	5.8%	0.34 [-0.04, 0.72]	
Kouzuki 2017	110.8	39.4	42	119.2	35.7	18	4.7%	-0.22 [-0.77, 0.34]	
Li H 2017	2.38	0.9	118	2.66	0.46	120	6.5%	-0.39 [-0.65, -0.13]	
Raygani 2006	162.5	24.5	94	158.5	22.8	111	6.4%	0.17 [-0.11, 0.44]	+
Wada2000	110	26	36	114	36	15	4.4%	-0.13 [-0.74, 0.47]	
Watanabe2004	95	25	34	94	36	63	5.5%	0.03 [-0.39, 0.45]	
Xiao 2012	2.46	0.66	104	2.4	0.82	104	6.4%	0.08 [-0.19, 0.35]	
Yamamoto2005	108	36	61	105	38	32	5.5%	0.08 [-0.35, 0.51]	
Yu2014	2.6	1.09	201	2.46	1.13	257	6.8%	0.13 [-0.06, 0.31]	+
Zengi2012	2.79	0.22	21	2.88	0.021	20	4.3%	-0.56 [-1.18, 0.07]	
Zheng2016	2.78	0.89	207	2.7	1	256	6.8%	0.08 [-0.10, 0.27]	<u> </u>
Subtotal (95% CI)			1317			1886	75.9%	0.06 [-0.09, 0.22]	•
Heterogeneity: Tau ² =	= 0.05; Chi	² = 40.5	0, df =	12 (P <	0.0001); l ² = 7	0%		
Test for overall effect	: Z = 0.77	(P = 0.4	4)						
Total (95% CI)			1627			2235	100.0%	0.18 [-0.02, 0.38]	
Heterogeneity: Tau ²	= 0 15 [.] Chi	² = 119	96 df -	= 16 (P	< 0.000	01) 12 =	= 87%		-+-+-+-+-++
Test for overall offect	-7 = 1.79	P = 0.0	8) 8)	- 10 (P	- 0.000	01), I -	01 /0		-1 -0.5 0 0.5 1
Test for subgroup diff	oroncos: ($hi^2 = 2$	12 df -	- 1 (P -	0.08)	2 - 68 0	10/_		Control AD

FIGURE 11 | Forest plot of stratified analysis for the effects of LDL-C levels on AD risk in different age groups with a random-effects model. SMD, standardized mean difference; CI, confidence interval.

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.6.1 before 2010							-		
Ban 2009	123	2	197	121	4	47	6.1%	0.80 [0.47, 1.12]	
Cankurtaran2005	129	44.2	120	130.3	60.9	803	6.8%	-0.02 [-0.21, 0.17]	-
Hoshino2002	119.1	27.7	82	110	24.4	40	5.8%	0.34 [-0.04, 0.72]	
Raygani 2006	162.5	24.5	94	158.5	22.8	111	6.4%	0.17 [-0.11, 0.44]	+
Wada2000	110	26	36	114	36	15	4.4%	-0.13 [-0.74, 0.47]	
Watanabe2004	95	25	34	94	36	63	5.5%	0.03 [-0.39, 0.45]	
Yamamoto2005	108	36	61	105	38	32	5.5%	0.08 [-0.35, 0.51]	
Subtotal (95% CI)			624			1111	40.4%	0.20 [-0.04, 0.43]	◆
Heterogeneity: Tau ² =	0.07; Chi	² = 20.3	2, df =	6 (P = 0).002); I	² = 70%	5		
Test for overall effect:	Z = 1.62 ((P = 0.1	1)						
4.6.2 2010 and bevor	nd								
Alam 2014	104.4	28.8	75	100.6	21.8	120	6.3%	0.15[-0.14, 0.44]	
Chen 2018	130.67	34.73	117	95.25	23.46	117	6.4%	1.19 [0.91, 1.47]	
Kouzuki 2017	110.8	39.4	42	119.2	35.7	18	4.7%	-0.22 [-0.77, 0.34]	
Li H 2017	2.38	0.9	118	2.66	0.46	120	6.5%	-0.39 [-0.65, -0.13]	
Singh2012	106.13	45.63	70	71.47	24.61	75	6.0%	0.95 [0.61, 1.29]	
Xiao 2012	2.46	0.66	104	2.4	0.82	104	6.4%	0.08 [-0.19, 0.35]	
Yu2014	2.6	1.09	201	2.46	1.13	257	6.8%	0.13 [-0.06, 0.31]	+
Zengi2012	2.79	0.22	21	2.88	0.021	20	4.3%	-0.56 [-1.18, 0.07]	
Zhao2014	138.2	34.7	48	136.8	16.4	37	5.5%	0.05 [-0.38, 0.48]	
Zheng2016	2.78	0.89	207	2.7	1	256	6.8%	0.08 [-0.10, 0.27]	
Subtotal (95% CI)			1003			1124	59.6%	0.17 [-0.13, 0.47]	-
Heterogeneity: Tau ² =	0.21; Chi	² = 98.5	6, df =	9 (P < 0	0.00001); l² = 9	1%		
Test for overall effect:	Z = 1.10 ((P = 0.2	7)						
Total (95% CI)			1627			2235	100.0%	0.18 [-0.02, 0.38]	◆
Heterogeneity: Tau ² =	0.15; Chi	² = 118.	96. df =	= 16 (P	< 0.000	01); l ² =	87%		
Test for overall effect:	Z = 1.78	(P = 0.0)	8)	1			-		-1 -0.5 0 0.5 1
Test for subaroup diffe	erences: C	$chi^2 = 0.$	02. df =	= 1 (P =	0.90). I	$^{2} = 0\%$			Control AD

standardized mean difference; CI, confidence interval.

Sludy of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% Cl	IV. Random, 95% CI
8.4.1 age ≤ 70							-		
Alam 2014	129	43.7	75	122.6	31.3	120	6.6%	0.17 [-0.11, 0.46]	
Chen 2018	109.63	49.18	117	121.34	53.17	117	7.2%	-0.23 [-0.49, 0.03]	
Singh2012	157.96	76.81	70	158.19	53.02	75	6.0%	-0.00 [-0.33, 0.32]	
Zhao2014	125.2	45.8	48	89.4	36.8	37	4.3%	0.84 [0.39, 1.29]	
Subtotal (95% CI)			310			349	24.1%	0.17 [-0.22, 0.55]	
Heterogeneity: Tau ² =	= 0.12: Chi	$^{2} = 17.2$	6. df =	3(P = 0)	0006): 1	² = 83%	6		
Test for overall effect	: Z = 0.85	(P = 0.4)	0)	. (,, .		•		
			-,						
8.4.2 age > 70									
Ban 2009	82	42.11	197	86	27.42	47	6.1%	-0.10 [-0.42, 0.22]	
Cankurtaran2005	147.1	86.5	120	144.7	76	803	8.4%	0.03 [-0.16, 0.22]	
Chang2014	1.34	0.77	44	1.41	0.97	62	5.1%	-0.08 [-0.46, 0.31]	
Kouzuki 2017	119.1	68.4	42	140.7	66.3	18	3.3%	-0.31 [-0.87, 0.24]	
Li H 2017	1.2	0.57	118	1.19	0.43	120	7.2%	0.02 [-0.23, 0.27]	
Raygani 2006	162.5	24.5	94	158.5	22.8	111	6.9%	0.17 [-0.11, 0.44]	
Wada2000	103	52	36	142	96	15	2.9%	-0.57 [-1.18, 0.04]	
Watanabe2004	82	58	34	103	65	63	4.7%	-0.33 [-0.75, 0.09]	
Xiao 2012	1.36	0.62	104	1.32	0.71	104	6.9%	0.06 [-0.21, 0.33]	
Yamamoto2005	80	42	61	89	41	32	4.6%	-0.21 [-0.64, 0.21]	
Yu2014	1.85	1.12	201	1.98	1.4	257	8.5%	-0.10 [-0.29, 0.08]	
Zengi2012	1.53	0.55	21	1.73	0.67	20	2.8%	-0.32 [-0.94, 0.30]	
Zheng2016	1.54	1.06	207	1.26	0.62	256	8.5%	0.33 [0.15, 0.52]	
Subtotal (95% CI)			1279			1908	75.9%	-0.03 [-0.15, 0.09]	•
Heterogeneity: Tau ² =	= 0.02; Chi	² = 24.5	2, df =	12 (P = 0	0.02); l²	= 51%			
Test for overall effect	: Z = 0.46	(P = 0.6	4)						
Total (95% CI)			1589			2257	100.0%	-0.00 [-0.12, 0.12]	
Heterogeneity: Tau ²	= 0.04 · Chi	² = 42 0	9 df =	16 (P = 0	0004	$l^2 = 62$	%		
Test for overall effect	7 = 0.01	P = 1.0	0)	10 (1 (,	1 02	/0		-1 -0.5 0 0.5 1

FIGURE 13 | Forest plot of stratified analysis for the effects of TG levels on AD risk in different age groups with a random-effects model. SMD, standardized mean difference; CI, confidence interval.

Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% CI
4.3.1 Sample size <	100								
Kouzuki 2017	119.1	68.4	42	140.7	66.3	18	3.3%	-0.31 [-0.87, 0.24]	
Wada2000	103	52	36	142	96	15	2.9%	-0.57 [-1.18, 0.04]	
Watanabe2004	82	58	34	103	65	63	4.7%	-0.33 [-0.75, 0.09]	
Yamamoto2005	80	42	61	89	41	32	4.6%	-0.21 [-0.64, 0.21]	
Zengi2012	1.53	0.55	21	1.73	0.67	20	2.8%	-0.32 [-0.94, 0.30]	
Zhao2014	125.2	45.8	48	89.4	36.8	37	4.3%	0.84 [0.39, 1.29]	
Subtotal (95% CI)			242			185	22.6%	-0.13 [-0.56, 0.29]	
Heterogeneity: Tau ² =	0.22; Chi	² = 21.7	4, df =	5 (P = 0.	0006); I	² = 77%	6		
Test for overall effect:	Z = 0.62	(P = 0.5	4)						
4.3.2 Sample size \geq	100								
Alam 2014	129	43.7	75	122.6	31.3	120	6.6%	0.17 [-0.11, 0.46]	
Ban 2009	82	42.11	197	86	27.42	47	6.1%	-0.10 [-0.42, 0.22]	
Cankurtaran2005	147.1	86.5	120	144.7	76	803	8.4%	0.03 [-0.16, 0.22]	
Chang2014	1.34	0.77	44	1.41	0.97	62	5.1%	-0.08 [-0.46, 0.31]	
Chen 2018	109.63	49.18	117	121.34	53.17	117	7.2%	-0.23 [-0.49, 0.03]	
Li H 2017	1.2	0.57	118	1.19	0.43	120	7.2%	0.02 [-0.23, 0.27]	
Raygani 2006	162.5	24.5	94	158.5	22.8	111	6.9%	0.17 [-0.11, 0.44]	+
Singh2012	157.96	76.81	70	158.19	53.02	75	6.0%	-0.00 [-0.33, 0.32]	
Xiao 2012	1.36	0.62	104	1.32	0.71	104	6.9%	0.06 [-0.21, 0.33]	
Yu2014	1.85	1.12	201	1.98	1.4	257	8.5%	-0.10 [-0.29, 0.08]	+
Zheng2016	1.54	1.06	207	1.26	0.62	256	8.5%	0.33 [0.15, 0.52]	
Subtotal (95% CI)			1347			2072	77.4%	0.04 [-0.07, 0.14]	•
Heterogeneity: Tau ² =	0.01; Chi	² = 18.8	4, df =	10 (P = 0	0.04); l²	= 47%			
Test for overall effect:	Z = 0.66	(P = 0.5	1)						
Total (95% CI)			1589			2257	100.0%	-0.00 [-0.12, 0.12]	+
Heterogeneity: Tau ² =	0.04; Chi	² = 42.0	9, df =	16 (P = 0	0.0004);	; I ² = 62	%	-	
Test for overall effect:	Z = 0.01	(P = 1.0	0)						Control AD
Test for subaroup diffe	rences: 0	Chi ² = 0.	57. df =	= 1 (P = 0).45). I ²	= 0%			Control AD

standardized mean difference; CI, confidence interval.



to speed up the progression of cognitive impairment related to dementia (Galasko et al., 1997; Gandy, 2005; Lv et al., 2016). In accordance with the results of the present study, a longitudinal study of elderly Chinese people has revealed that higher TC levels and LDL-C levels were associated with faster cognitive decline (Ma et al., 2017). Notably, as a key factor in cholesterol homeostasis, ApoE4 could decrease LDL receptor and LDL clearance, and increase cholesterol level by binding with TG-rich very-low-density lipoprotein. In addition, ApoE4 has been verified to contribute to the susceptibility for AD by disordering the lipids and cholesterol levels (Henry et al., 2018). Furthermore, LDL-C had been found positively associated with the densities of neuron plaques, which hints at the onset of the neurodegenerative disease (Lesser et al., 2011). However, higher LDL-C levels have also been reported to be positively associated with better memory function. It may be due to the fact that LDL-C may negatively be associated with AD only when the increase lasts for a long enough duration (Leritz et al., 2016). Therefore, follow-up cohort studies with a large sample size are needed to strengthen our results in this study.

We were not able to prove that TG levels had any association with AD in our study. However, previous studies reported a negative relationship between TG and memory performance (de Frias et al., 2007; Morley and Banks, 2010; van den Kommer et al., 2012; Leritz et al., 2016). It may be due to the fact that higher levels of TG contribute to reduced cognitive performance via CVD risk factors (Iturria-Medina et al., 2016). This inconsistency may be due to the age differences of participants in various studies and the differing methods of measurement.

Two specific biomarkers $A\beta$ and Tau have been used to diagnose AD via amyloid imaging and monitoring their levels in CSF. However, only when cognitive symptoms developed apparently can they be applied clinically (Efthymiou and Goate, 2017). The present study investigated the possibility and feasibility of TCs as novel biomarkers of AD. Concerning the large number of studies and large sample sizes investigated in this study, the results could be promising. TC levels can be altered by several factors; in the future, lowering TC levels are expected to be an important factor in retarding or reversing the condition of cognitive decline in AD, and more RCT or cohort researches are necessarily needed to conduct. The highlights of this study are as follows: (a) a meta-analysis was conducted to assess the associations between blood lipid levels and AD and they were indeed linked. (b) Our results may be more representative and reliable since the population of our study was not limited to one nation or one continent. (c) The meta-analysis followed the MOOSE guidelines. Nevertheless, there are still several limitations we have to point out: (a) this study is a meta-analysis for casecontrol studies. The results will be more reliable if blood lipid levels are monitored over a long-term period in longitudinal researches. (b) The heterogeneity of our study appeared high even though we conducted stratified analyses. The source of high heterogeneity may result from varying stages of disease progression, multiple methods of blood lipid measurement, and other differences among demographic characteristics. (c) We may not control the confounding factors since some articles did not provide sufficient raw data about educational levels, the results of cognitive tests such as Mini-Mental State Examination (MMSE), methods of measurements, status of patients such as comorbidities, etc.

CONCLUSION

In the present study, TC levels were strongly associated with AD in later-life. TC could be a new diagnostic biomarker of AD in later life. The significant associations between HDL-C/LDL-C and AD have not been discovered though, we may use them as references in a specific population. For example, lower HDL-C levels and higher LDL-C levels may relate to a higher risk of AD in populations aged 60–70. Remarkably, this kind of relationship should be explained carefully. TG levels are found to have no association with AD. Further comprehensive researches will be necessary in the future. As a biomarker, we are looking forward to prevent AD by monitoring the concentrations of TC. We also hope that it can be applied for early diagnosis of AD before the onset of symptoms and more AD patients benefit from it.

REFERENCES

- Alam, R., Tripathi, M., Mansoori, N., Parveen, S., Luthra, K., Lakshmy, R., et al. (2014). Synergistic epistasis of paraoxonase 1 (rs662 and rs85460) and apolipoprotein E4 genes in pathogenesis of Alzheimer's disease and vascular dementia. Am. J. Alzheimer's Dis. Other Dement. 29, 769–776. doi: 10.1177/1533317514539541
- Alzheimer A. (1907). Uber eine eigenartige Erkrankung der Hirnrinde. *Allgemeine Zeitschrift Für Psychiatrie* 64, 146–8.
- Anstey, K. J., Ashby-Mitchell, K., and Peters, R. (2017). Updating the Evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. J. Alzheimer's Dis. 56, 215–228. doi: 10.3233/JAD-160826
- Bahrami, A., Barreto, G. E., Lombardi, G., Pirro, M., and Sahebkar, A. (2019). Emerging roles for high-density lipoproteins in neurodegenerative disorders. *BioFactors* 45, 725–739. doi: 10.1002/biof.1541
- Ban, Y., Watanabe, T., Suguro, T., Matsuyama, T. A., Iso, Y., Sakai, T., et al. (2009). Increased plasma urotensin-II and carotid atherosclerosis are associated with vascular dementia. *J. Atherosclerosis Thrombosis* 16, 179–187. doi: 10.5551/jat.E608
- Bjorkhem, I., and Meaney, S. (2004). Brain cholesterol: long secret life behind a barrier. Arteriosclerosis Thrombosis Vasc. Biol. 24, 806–815. doi: 10.1161/01.ATV.0000120374.59826.1b
- Borroni, B., Colciaghi, F., Lenzi, G. L., Caimi, L., Cattabeni, F., Di Luca, M., et al. (2003). High cholesterol affects platelet APP processing in controls and in AD patients. *Neurobiol. Aging* 24, 631–636. doi: 10.1016/S0197-4580(02)00190-2
- Cankurtaran, M., Yavuz, B. B., Halil, M., Dagli, N., Cankurtaran, E. S., and Ariogul, S. (2005). Are serum lipid and lipoprotein levels related to dementia? *Arch. Gerontol. Geriatr.* 41, 31–39. doi: 10.1016/j.archger.2004.10.008
- Cascalheira, J. F., Joao, S. S., Pinhancos, S. S., Castro, R., Palmeira, M., Almeida, S., et al. (2009). Serum homocysteine: interplay with other circulating and genetic factors in association to Alzheimer's type dementia. *Clin. Biochem.* 42, 783–790. doi: 10.1016/j.clinbiochem.2009.02.006
- Cermenati, G., Mitro, N., Audano, M., Melcangi, R. C., Crestani, M., De Fabiani, E., et al. (2015). Lipids in the nervous system: from biochemistry and molecular biology to patho-physiology. *Biochim. Biophys. Acta* 1851, 51–60. doi: 10.1016/j.bbalip.2014.08.011

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

QT, FW, JY, BL, and SW chose the topic. QT, JY, HP, and YL searched the literature. QT was responsible for literature searching, data analyzing, and writing of the first draft. QT, FW, and SW extracted and reviewed the data. SW and BL performed data management and figure modification. QT and BL modified the paper.

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- Chang, L., Wang, Y., Ji, H., Dai, D., Xu, X., Jiang, D., et al. (2014). Elevation of peripheral BDNF promoter methylation links to the risk of Alzheimer's disease. *PLoS ONE* 9:e110773. doi: 10.1371/journal.pone.0110773
- Chen, H., Du, Y., Liu, S., Ge, B., Ji, Y., and Huang, G. (2019). Association between serum cholesterol levels and Alzheimer's disease in China: a case-control study. *Int. J. Food Sci. Nutr.* 70, 405–411. doi: 10.1080/09637486.2018.1508426
- Chernick, D., Ortiz-Valle, S., Jeong, A., Qu, W., and Li, L. (2019). Peripheral versus central nervous system APOE in Alzheimer's disease: interplay across the blood-brain barrier. *Neurosci. Lett.* 708:134306. doi: 10.1016/j.neulet.2019.134306
- Cockerill, G. W., Huehns, T. Y., Weerasinghe, A., Stocker, C., Lerch, P. G., Miller, N. E., et al. (2001). Elevation of plasma high-density lipoprotein concentration reduces interleukin-1-induced expression of E-selectin in an *in vivo* model of acute inflammation. *Circulation* 103, 108–112. doi: 10.1161/01.CIR.103.1.108
- de Bustos, F., Molina, J. A., Jimenez-Jimenez, F. J., Garcia-Redondo, A., Gomez-Escalonilla, C., Porta-Etessam, J., et al. (2000). Serum levels of coenzyme Q10 in patients with Alzheimer's disease. J. Neural Transmission. 107, 233–239. doi: 10.1007/s007020050019
- de Frias, C. M., Bunce, D., Wahlin, A., Adolfsson, R., Sleegers, K., Cruts, M., et al. (2007). Cholesterol and triglycerides moderate the effect of apolipoprotein E on memory functioning in older adults. J. Gerontol. Series B Psychol. Sci. Soc. Sci. 62, P112–P118. doi: 10.1093/geronb/62.2.P112
- Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K., et al. (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol.* 13, 614–629. doi: 10.1016/S1474-4422(14)70090-0
- Efthymiou, A. G., and Goate, A. M. (2017). Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. *Mol. Neurodegenerat.* 12:43. doi: 10.1186/s13024-017-0184-x
- Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198. doi: 10.1016/0022-3956(75)90026-6
- Galasko, D., Clark, C., Chang, L., Miller, B., Green, R. C., Motter, R., et al. (1997). Assessment of CSF levels of tau protein in mildly demented patients with Alzheimer's disease. *Neurology* 48, 632–635. doi: 10.1212/WNL.4 8.3.632

- Gamba, P., Staurenghi, E., Testa, G., Giannelli, S., Sottero, B., and Leonarduzzi, G. (2019). A crosstalk between brain cholesterol oxidation and glucose metabolism in Alzheimer's Disease. *Front. Neurosci.* 13:556. doi: 10.3389/fnins.2019. 00556
- Gandy, S. (2005). The role of cerebral amyloid beta accumulation in common forms of Alzheimer disease. *J. Clin. Investig.* 115, 1121–1129. doi: 10.1172/JCI200525100
- Hampel, H., Wilcock, G., Andrieu, S., Aisen, P., Blennow, K., Broich, K., et al. (2011). Biomarkers for Alzheimer's disease therapeutic trials. *Prog. Neurobiol.* 95, 579–593. doi: 10.1016/j.pneurobio.2010.11.005
- Henry, N., Krammer, E. M., Stengel, F., Adams, Q., Van Liefferinge, F., Hubin, E., et al. (2018). Lipidated apolipoprotein E4 structure and its receptor binding mechanism determined by a combined cross-linking coupled to mass spectrometry and molecular dynamics approach. *PLoS Comput. Biol.* 14:e1006165. doi: 10.1371/journal.pcbi.1006165
- Hoshino, T., Kamino, K., and Matsumoto, M. (2002). Gene dose effect of the APOE-epsilon4 allele on plasma HDL cholesterol level in patients with Alzheimer's disease. *Neurobiol. Aging* 23, 41–45. doi: 10.1016/S0197-4580(01)00252-4
- Hussain, G., Wang, J., Rasul, A., Anwar, H., Imran, A., Qasim, M., et al. (2019). Role of cholesterol and sphingolipids in brain development and neurological diseases. *Lipids Health Dis.* 18:26. doi: 10.1186/s12944-019-0965-z
- Ising, C., Venegas, C., Zhang, S., Scheiblich, H., Schmidt, S. V., Vieira-Saecker, A., et al. (2019). NLRP3 inflammasome activation drives tau pathology. *Nature*. 575:669–673. doi: 10.1038/s41586-019-1769-z
- Iturria-Medina, Y., Sotero, R. C., Toussaint, P. J., Mateos-Perez, J. M., and Evans, A. C. (2016). Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat. Commun.* 7:11934. doi: 10.1038/ncomms11934
- Kim, B. M., You, M. H., Chen, C. H., Suh, J., Tanzi, R. E., and Ho Lee, T. (2016). Inhibition of death-associated protein kinase 1 attenuates the phosphorylation and amyloidogenic processing of amyloid precursor protein. *Hum. Mol. Genet.* 25, 2498–2513. doi: 10.1093/hmg/ddw114
- Kivipelto, M., Helkala, E. L., Laakso, M. P., Hanninen, T., Hallikainen, M., Alhainen, K., et al. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 322, 1447–1451. doi: 10.1136/bmj.322.7300.1447
- Koch, M., and Jensen, M. K. (2016). HDL-cholesterol and apolipoproteins in relation to dementia. *Curr. Opin. Lipidol.* 27, 76–87. doi: 10.1097/MOL.0000000000257
- Kolsch, H., Heun, R., Jessen, F., Popp, J., Hentschel, F., Maier, W., et al. (2010). Alterations of cholesterol precursor levels in Alzheimer's disease. *Biochim. Biophys. Acta* 1801, 945–950. doi: 10.1016/j.bbalip.2010.03.001
- Koudinov, A. R., Berezov, T. T., Kumar, A., and Koudinova, N. V. (1998). Alzheimer's amyloid beta interaction with normal human plasma high density lipoprotein: association with apolipoprotein and lipids. *Clin. Chim. Acta* 270, 75–84. doi: 10.1016/S0009-8981(97)00207-6
- Kouzuki, M., Nagano, M., Suzuki, T., Katsumata, Y., Nakamura, S., Takamura, A., et al. (2018). Cerebrospinal fluid biomarkers of Alzheimer's disease are associated with carotid plaque score and hemodynamics in intraand extra-cranial arteries on ultrasonography. J. Clin. Neurosci. 49, 32–36. doi: 10.1016/j.jocn.2017.12.006
- Kunkle, B. W., Grenier-Boley, B., Sims, R., Bis, J. C., Damotte, V., Naj, A. C., et al. (2019). Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. *Nat. Genet.* 51, 414–430. doi: 10.1038/s41588-019-0358-2
- Leritz, E. C., McGlinchey, R. E., Salat, D. H., and Milberg, W. P. (2016). Elevated levels of serum cholesterol are associated with better performance on tasks of episodic memory. *Metab. Brain Dis.* 31, 465–473. doi: 10.1007/s11011-016-9797-y
- Lesser, G. T., Beeri, M. S., Schmeidler, J., Purohit, D. P., and Haroutunian, V. (2011). Cholesterol and LDL relate to neuritic plaques and to APOE4 presence but not to neurofibrillary tangles. *Curr. Alzheimer Res.* 8, 303–312. doi: 10.2174/156720511795563755
- Li, H., Zhou, J., Yue, Z., Feng, L., Luo, Z., Chen, S., et al. (2017). A complex association between ABCA7 genotypes and blood lipid levels in Southern Chinese Han patients of sporadic Alzheimer's disease. J. Neurol. Sci. 382, 13–17. doi: 10.1016/j.jns.2017.09.016

- Li, J., Wang, Y. J., Zhang, M., Xu, Z. Q., Gao, C. Y., Fang, C. Q., et al. (2011). Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology* 76, 1485–1491. doi: 10.1212/WNL.0b013e318217e7a4
- Li, W., Yu, Z., Hou, D., Zhou, L., Deng, Y., Tian, M., et al. (2015a). Relationship between adiponectin gene polymorphisms and late-onset Alzheimer's disease. *PLoS ONE* 10:e0125186. doi: 10.1371/journal.pone.0125186
- Li, W., Yu, Z., Hou, D., Zhou, L., Deng, Y., Tian, M., et al. (2015b). Correction: relationship between adiponectin gene polymorphisms and late-onset Alzheimer's Disease. *PLoS ONE*. 10:e0130521. doi: 10.1371/journal.pone.0130521
- Liu, S., Suzuki, H., Ito, H., Korenaga, T., Akatsu, H., Meno, K., et al. (2019). Serum levels of proteins involved in amyloid-beta clearance are related to cognitive decline and neuroimaging changes in mild cognitive impairment. *Alzheimer's Dement.* 11, 85–97. doi: 10.1016/j.dadm.2018.11.003
- Lv, Y. B., Yin, Z. X., Chei, C. L., Brasher, M. S., Zhang, J., Kraus, V. B., et al. (2016). Serum cholesterol levels within the high normal range are associated with better cognitive performance among Chinese elderly. *J. Nutr. Health Aging* 20, 280–287. doi: 10.1007/s12603-016-0701-6
- Ma, C., Yin, Z., Zhu, P., Luo, J., Shi, X., and Gao, X. (2017). Blood cholesterol in late-life and cognitive decline: a longitudinal study of the Chinese elderly. *Mol. Neurodegenerat.* 12:24. doi: 10.1186/s13024-017-0167-y
- Mapstone, M., Cheema, A. K., Fiandaca, M. S., Zhong, X., Mhyre, T. R., MacArthur, L. H., et al. (2014). Plasma phospholipids identify antecedent memory impairment in older adults. *Nat. Med.* 20, 415–418. doi: 10.1038/nm.3466
- Martins, I. J., Berger, T., Sharman, M. J., Verdile, G., Fuller, S. J., and Martins, R. N. (2009). Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. J. Neurochem. 111, 1275–1308. doi: 10.1111/j.1471-4159.2009.06408.x
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's Disease. *Neurology* 34, 939–944. doi: 10.1212/WNL.34.7.939
- Menotti, A., and Puddu, P. E. (2015). How the Seven Countries Study contributed to the definition and development of the Mediterranean diet concept: a 50-year journey. *Nutr. Metab. Cardiovasc. Dis.* 25, 245–252. doi: 10.1016/j.numecd.2014.12.001
- Merino-Serrais, P., Loera-Valencia, R., Rodriguez-Rodriguez, P., Parrado-Fernandez, C., Ismail, M. A., Maioli, S., et al. (2019). 27-hydroxycholesterol induces aberrant morphology and synaptic dysfunction in hippocampal neurons. *Cereb. Cortex* 29, 429–446. doi: 10.1093/cercor/bhy274
- Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339:b2535. doi: 10.1136/bmj.b2535
- Morley, J. E., and Banks, W. A. (2010). Lipids and cognition. J. Alzheimer's Dis. 20, 737–747. doi: 10.3233/JAD-2010-091576
- Mouzat, K., Chudinova, A., Polge, A., Kantar, J., Camu, W., Raoul, C., et al. (2019). Regulation of brain cholesterol: what role do liver X receptors play in neurodegenerative diseases? *Int. J. Mol. Sci.* 20:3858. doi: 10.3390/ijms201 63858
- Ohtani, R., Nirengi, S., Nakamura, M., Murase, N., Sainouchi, M., Kuwata, Y., et al. (2018). High-density lipoprotein subclasses and mild cognitive impairment: study of Outcome and aPolipoproteins in Dementia (STOP-Dementia) 1. J. Alzheimer's Dis. 66, 289–296. doi: 10.3233/JAD-180135
- Olesen, O. F., and Dago, L. (2000). High density lipoprotein inhibits assembly of amyloid beta-peptides into fibrils. *Biochem. Biophys. Res. Commun.* 270, 62–66. doi: 10.1006/bbrc.2000.2372
- Pappolla, M. A., Bryant-Thomas, T. K., Herbert, D., Pacheco, J., Fabra Garcia, M., Manjon, M., et al. (2003). Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. *Neurology* 61, 199–205. doi: 10.1212/01.WNL.0000070182.02537.84
- Patterson, C. (2018). The State of the Art of Dementia Research: New Frontiers. Alzheimer's Disease International (ADI) World Alzheimer Report (2018).
- Popp, J., Lewczuk, P., Kolsch, H., Meichsner, S., Maier, W., Kornhuber, J., et al. (2012). Cholesterol metabolism is associated with soluble amyloid precursor protein production in Alzheimer's disease. J. Neurochem. 123, 310–316. doi: 10.1111/j.1471-4159.2012.07893.x

- Popp, J., Meichsner, S., Kolsch, H., Lewczuk, P., Maier, W., Kornhuber, J., et al. (2013). Cerebral and extracerebral cholesterol metabolism and CSF markers of Alzheimer's disease. *Biochem. Pharmacol.* 86, 37–42. doi: 10.1016/j.bcp.2012.12.007
- Querfurth, H. W., and LaFerla, F. M. (2010). Alzheimer's disease. *N. Engl. J. Med.* 362, 329–344. doi: 10.1056/NEJMra0909142
- Rantanen, K., Strandberg, A. Y., Salomaa, V., Pitkala, K., Tilvis, R. S., Tienari, P., et al. (2017). Cardiovascular risk factors and glucose tolerance in midlife and risk of cognitive disorders in old age up to a 49-year follow-up of the Helsinki businessmen study. Ann. Med. 49, 462–469. doi: 10.1080/07853890.2017.1290821
- Raygani, A. V., Rahimi, Z., Kharazi, H., Tavilani, H., and Pourmotabbed, T. (2006). Association between apolipoprotein E polymorphism and serum lipid and apolipoprotein levels with Alzheimer's disease. *Neurosci. Lett.* 408, 68–72. doi: 10.1016/j.neulet.2006.08.048
- Reitz, C., Tang, M. X., Schupf, N., Manly, J. J., Mayeux, R., and Luchsinger, J. A. (2010). Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. *Arch. Neurol.* 67, 1491–1497. doi: 10.1001/archneurol.2010.297
- Romero-Sevilla, R., Casado-Naranjo, I., Portilla-Cuenca, J. C., Duque-de San Juan, B., Fuentes, J. M., and Lopez-Espuela, F. (2018). Vascular risk factors and lesions of vascular nature in magnetic resonance as predictors of progression to dementia in patients with mild cognitive impairment. *Curr. Alzheimer Res.* 15, 671–678. doi: 10.2174/1567205015666180119100840
- Schonknecht, P., Lutjohann, D., Pantel, J., Bardenheuer, H., Hartmann, T., von Bergmann, K., et al. (2002). Cerebrospinal fluid 24S-hydroxycholesterol is increased in patients with Alzheimer's disease compared to healthy controls. *Neurosci. Lett.* 324, 83–85. doi: 10.1016/S0304-3940(02)00164-7
- Singh, N. K., Chhillar, N., Banerjee, B. D., Bala, K., Mukherjee, A. K., Mustafa, M. D., et al. (2012). Gene-environment interaction in Alzheimer's disease. *Am. J. Alzheimer's Dis. Other Dement.* 27, 496–503. doi: 10.1177/1533317512 456067
- Sittiwet, C., Simonen, P., Nissinen, M. J., Gylling, H., and Strandberg, T. E. (2018). Serum noncholesterol sterols in Alzheimer's disease: the Helsinki Businessmen Study. *Transl. Res.* 202, 120–128. doi: 10.1016/j.trsl.2018.07.002
- Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.* 25, 603–605. doi: 10.1007/s10654-010-9491-z
- Strand, B. H., Langballe, E. M., Hjellvik, V., Handal, M., Naess, O., Knudsen, G. P., et al. (2013). Midlife vascular risk factors and their association with dementia deaths: results from a Norwegian prospective study followed up for 35 years. J. Neurol. Sci. 324, 124–130. doi: 10.1016/j.jns.2012.10.018
- Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., et al. (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 283, 2008–2012. doi: 10.1001/jama.283. 15.2008
- Testa, G., Staurenghi, E., Giannelli, S., Gargiulo, S., Guglielmotto, M., Tabaton, M., et al. (2018). A silver lining for 24-hydroxycholesterol in Alzheimer's disease: the involvement of the neuroprotective enzyme sirtuin 1. *Redox Biol.* 17, 423–431. doi: 10.1016/j.redox.2018.05.009
- Teunissen, C. E., Lutjohann, D., von Bergmann, K., Verhey, F., Vreeling, F., Wauters, A., et al. (2003). Combination of serum markers related to

several mechanisms in Alzheimer's disease. *Neurobiol. Aging* 24, 893–902. doi: 10.1016/S0197-4580(03)00005-8

- van den Kommer, T. N., Dik, M. G., Comijs, H. C., Jonker, C., and Deeg, D. J. (2012). Role of lipoproteins and inflammation in cognitive decline: do they interact? *Neurobiol. Aging* 33, 196.e1–12. doi: 10.1016/j.neurobiolaging.2010.05.024
- Wada, H. (2000). Analyses of serum concentrations of apolipoproteins in the demented elderly. *Int. Med.* 39, 220–222. doi: 10.2169/internalmedicine.39.220
- Watanabe, T., Koba, S., Kawamura, M., Itokawa, M., Idei, T., Nakagawa, Y., et al. (2004). Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. *Metabolism Clin. Exp.* 53, 476–482. doi: 10.1016/j.metabol.2003.11.020
- Wu, Y., Wang, Z., Jia, X., Zhang, H., Zhang, H., Li, J., et al. (2019). Prediction of Alzheimer's disease with serum lipid levels in Asian individuals: a metaanalysis. *Biomarkers* 24, 341–351. doi: 10.1080/1354750X.2019.1571633
- Xiao, Z., Wang, J., Chen, W., Wang, P., Zeng, H., and Chen, W. (2012). Association studies of several cholesterol-related genes (ABCA1, CETP and LIPC) with serum lipids and risk of Alzheimer's disease. *Lipids Health Dis.* 11:163. doi: 10.1186/1476-511X-11-163
- Yamamoto, H., Watanabe, T., Miyazaki, A., Katagiri, T., Idei, T., Iguchi, T., et al. (2005). High prevalence of *Chlamydia pneumoniae* antibodies and increased high-sensitive C-reactive protein in patients with vascular dementia. *J. Am. Geriatr. Soc.* 53, 583–589. doi: 10.1111/j.1532-5415.2005.53204.x
- Yassine, H. N., Feng, Q., Chiang, J., Petrosspour, L. M., Fonteh, A. N., Chui, H. C., et al. (2016). ABCA1-mediated cholesterol efflux capacity to cerebrospinal fluid is reduced in patients with mild cognitive impairment and Alzheimer's Disease. J. Am. Heart Assoc. 5:e002886. doi: 10.1161/JAHA.115.002886
- Zarrouk, A., Debbabi, M., Bezine, M., Karym, E. M., Badreddine, A., Rouaud, O., et al. (2018). Lipid biomarkers in Alzheimer's Disease. *Curr. Alzheimer Res.* 15, 303–312. doi: 10.2174/1567205014666170505101426
- Zengi, O., Karakas, A., Ergun, U., Senes, M., Inan, L., and Yucel, D. (2011). Urinary 8-hydroxy-2'-deoxyguanosine level and plasma paraoxonase 1 activity with Alzheimer's disease. *Clin. Chem. Lab. Med.* 50, 529–534. doi: 10.1515/cclm.2011.792
- Zhao, Z., Zhou, H., Peng, Y., Qiu, C. H., Sun, Q. Y., Wang, F., et al. (2014). Expression and significance of plasma 3-NT and ox-LDL in patients with Alzheimer's disease. *Genet. Mol. Res.* 13, 8428–8435. doi: 10.4238/2014.October.20.19
- Zheng, J., Yan, H., Shi, L., Kong, Y., Zhao, Y., Xie, L., et al. (2016). The CYP19A1 rs3751592 variant confers susceptibility to Alzheimer disease in the Chinese Han population. *Medicine* 95:e4742. doi: 10.1097/MD.00000000004742

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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