Research Paper

Serum lipid levels and suicidality: a meta-analysis of 65 epidemiological studies

Shunquan Wu, MD*; Yingying Ding, PhD*; Fuquan Wu, MD*; Guoming Xie, PhD; Jun Hou, PhD; Panyong Mao, PhD

Background: We conducted a systematic review and meta-analysis to determine the association between serum lipid levels and suicidality, as evidence from previous studies has been inconsistent. **Methods:** We identified relevant studies by searching Medline, Web of Science, EMBASE, and the Cochrane Database of Systematic Reviews (1980 to Dec. 5, 2014). Studies assessing the association between serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG) levels and suicidality were included. We used a random-effects model to take into account heterogeneity among studies. **Results:** We included 65 studies with a total of 510 392 participants in our analysis. Compared with the nonsuicidal patients, suicidal patients had significantly lower serum TC (weighted mean difference [WMD] –22.35, 95% confidence interval [CI] –27.95 to –16.75), LDL-C (WMD –19.56, 95% CI –26.13 to –12.99) and TG (WMD –23.40, 95% CI –32.38 to –14.42) levels, while compared with the healthy controls, suicidal patients had significantly lower TC (WMD –24.75, 95% CI –27.71 to –21.78), HDL-C (WMD –1.75, 95% CI –3.01 to –0.48) and LDL-C (WMD –3.85, 95% CI –7.45 to –0.26) levels. Furthermore, compared with the highest serum TC level category, a lower serum TC level was associated with a 112% (95% CI 40%–220%) higher risk of suicidality, including a 123% (95% CI 24%–302%) higher risk of suicide attempt and an 85% (95 CI 7%–221%) higher risk of suicide completion. The cut-off values for low and high serum TC level were in compliance with the categories reported in the original studies. **Limitations:** A major limitation of our study is the potential heterogeneity in most of the analyses. In addition, the suicidal behaviour was examined using different scales or methods across studies, which may further explain heterogeneity among the studies. **Conclusion:** We identified an inverse association between serum lipid levels and suicidality. More mechanistic studies are needed to further explain this association.

Introduction

Suicide is an important public health problem and is one of the leading causes of death worldwide.[1,2] Suicide can generate a wave of psychiatric events in affected families, cause a great burden for society and hurt others. Several factors, including mental disorders, aggression or impulsivity, family history of suicide, obesity, smoking, marital problems, work problems and poor physical health, have been correlated with suicidality.[3–7]

Many studies have confirmed that biological markers might be linked to suicidality, among which serum lipid levels might play an important role.[8–10] In the clinical setting, the level of serum lipids is evaluated based on total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). Experimental evidence indicates that the lipid fluidity markedly modulates the binding of serotonin (5-HT) in mouse brain membranes; therefore, with low cholesterol levels, the cellular membrane fluidity increases and 5-HT receptors are less exposed to 5-HT in the synaptic cleft.[11] There is also evidence for an association between reduced 5-HT activity and suicide.[12] However, there has been considerable controversy about the association between serum lipid levels and suicidality reported in observational and epidemiological studies. Some human studies showed that suicide attempters had lower cholesterol levels,[9,13,14] but others reported positive associations between cholesterol and completed suicide.[15–17] Some studies also indicated that there was no evidence for an association between serum cholesterol and suicidality.[18,19]

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Given the inconsistency in the literature, we conducted a meta-analysis to make a quantitative assessment of the role of serum lipid levels in suicidality.

Methods

Search strategy and eligibility criteria

We followed the guidelines published by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group to complete the meta-analysis (Appendix, Table S1, available at jpn.ca).[20] Two of us (S.W. and Y.D.) performed a systematic literature search of Medline, Web of Science, EMBASE and the Cochrane Database of Systematic Reviews (1980 to Dec. 5, 2014) to identify eligible articles published in English-language peer-reviewed journals using selected synonymous terms. The references of all retrieved articles and recent reviews were also manually reviewed. The search strategy was not limited by study design. We contacted the authors of the included studies to ask them for additional information and unpublished data as needed. We did not include the grey literature.

To be eligible for inclusion, studies had to meet the following criteria: 1) the study population consisted of participants with suicidal behaviour and healthy controls, or the studies used risk of suicidality as the outcome, with no age restriction for participants; 2) the association between serum lipid (TC, HDL-C, LDL-C, and/or TG) levels and suicidality was assessed; 3) the studies reported lipid levels as means ± standard deviation (SD), risk estimates of suicidality with confidence intervals (CIs), or sufficient information with which to calculate these; and 4) suicidality was evaluated based on suicidal ideation, suicide attempt, suicidal tendencies (defined as having shown suicidal ideation, threatened suicide, or having made a suicide attempt), or suicide completion. Cohort, case–control and cross-sectional studies were all included in the analysis. We excluded animal studies, reviews and mechanistic research. Two of us (S.W. and F.W.) selected the studies for inclusion in our analysis, and disagreements were resolved by consensus.

Data extraction and study quality evaluation

Two of us (F.W. and J.H.) extracted study characteristics independently. We extracted means ± SDs or risk estimates with 95% CIs for male and female participants separately when possible. If a study reported more than 1 measure of serum lipid level, each was extracted separately. We included the most adjusted estimate when a study reported more than 1 risk estimate. Two of us (F.W. and P.M.) assessed the quality of each study using the Newcastle–Ottawa Scale, as recommended by Wells and colleagues.[21] This scale judges each study based on 3 broad categories: selection of the study groups, the comparability of the groups and the ascertainment of the outcome of interest. Scores range from 1 to 9 stars for cohort and case–control studies and from 1 to 5 stars for cross-sectional studies.

Statistical analysis

For evaluation of the serum lipid levels between participants with and without suicidality, the effect size was estimated as weighted mean differences (WMDs) with 95% CIs. To evaluate the relative risk of suicidality, we estimated the effect size using odds ratios (ORs) with 95% CIs based on the lowest versus the highest serum lipid levels categories reported in each study, using the highest serum lipid levels as the reference group; if they were presented in a reverse order, we back-calculated the point estimates and 95% CIs using log ORs from the individual studies and corresponding standard errors (SEs; calculated from the confidence limits).[22]

We used a random-effects model, which takes into account heterogeneity among studies, because the study designs and measuring times were different across studies.[23] The I^2 and Q statistics were used to explore the heterogeneity among studies. A large I^2 value (> 50%) or a p value < 0.1 for the Q statistic suggests substantial heterogeneity among studies. We conducted subgroup analyses by stratifying the original data sets by several study-level factors. In the subgroup analyses, we used a cut-off of 40 years for mean age and distinguished studies published before and after 2005 based on the principle that each subgroup had an appropriate number of studies. We used funnel plots, the Egger regression test[24] and the Begg–Mazumdar test[25] to assess publication bias. Statistical analyses were conducted using Stata software version 12.0 (Stata Corp.).

Results

Search results

Our search strategy yielded 1206 citations. After removing the duplicate articles, 1091 articles remained for further assessment. After screening titles and abstracts, 91 full-text articles were assessed for eligibility (Fig. 1). Finally, a total of 65 studies met the inclusion criteria and were included in the meta-analysis: 8 cohort studies,[16,26–32] 8 case–control studies[13,17,33–38] and 49 cross-sectional studies,[9,10,14,15,18,19,39–81] involving 510 392 participants. The participants were categorized as follows: 1) patients with various psychiatric diseases (e.g., depression, schizophrenia, personality disorder, drug and alcohol addictions) with suicidality, who we defined as suicidal patients; 2) patients with various psychiatric diseases without suicidality, who we defined as nonsuicidal patients; and 3) healthy participants without any psychiatric disease and suicidality, who we defined as healthy controls. A total of 55 articles were available for assessing the serum lipid levels between suicidal patients and nonsuicidal patients/healthy controls (Appendix 1, Table S2). A total of 12 studies were available for assessing the risk of suicidality according to the lowest versus the highest serum TC level category, among which 6 assessed the risk of suicide attempt and 6 assessed the risk of suicide completion (Appendix 1, Table S3). Among the 65 included studies, 29 studies controlled for body mass index (BMI) and 3 studies controlled for depression. Because few studies assessed the risk of suicidality based on HDL-C, LDL-C and TG, these were not included

in the meta-analysis. The quality assessment of the included studies is presented in detail in Appendix 1, Tables S4–S6.

Serum TC levels between suicidal and nonsuicidal patients/ healthy controls

The serum TC level of suicidal patients was significantly lower than those of nonsuicidal patients (WMD –22.35, 95% CI –27.95 to –16.75; Fig. 2A) and healthy controls (WMD –24.75, 95% CI –27.71 to –21.78; Fig 2B). We observed significant heterogeneity for the pooled analyses (I^2 = 88.5%, p < 0.001, and I^2 = 96.7%, p < 0.001, respectively). The subtotal estimates were almost consistent for suicidal ideation, suicide attempt and suicidal tendencies. Exclusion of the studies with results that did not control for at least age or sex did not reduce the heterogeneity and did not significantly change the WMD estimates (WMD –17.04, 95% CI –22.51 to –11.57, and WMD –32.03, 95% CI –38.14 to –25.93, respectively; Appendix 1, Fig. S1). In the pooled subgroup analyses comparing suicidal with nonsuicidal patients, there were larger differences in mean serum TC level in women, younger participants (mean age < 40 yr) and patients with schizophrenia and in studies that used cross-sectional designs, were published before 2005 and had relatively low quality. In the subgroup analyses comparing suicidal patients with healthy controls, there were larger differences in mean serum TC levels in men, older participants (mean age ≥ 40 yr) and patients with schizophrenia and in studies that used cross-sectional designs, were published before 2005 and had relatively high quality (Table 1). Notably, when compared with controls, patients with violent suicide attempts had much larger mean serum TC level differences than those with nonviolent suicide attempts (WMD –51.54, 95% CI –67.45 to –35.63 v. WMD –18.13, 95% CI –27.22 to –9.04; Table 1).

Serum HDL-C levels between suicidal and nonsuicidal patients/healthy controls

The serum HDL-C levels between suicidal patients and nonsuicidal patients did not differ significantly (WMD –0.16, 95% CI –2.13 to 1.80; Fig. 3A), and there was no evidence of significant heterogeneity among studies (I^2 = 35.6%, p = 0.05). The subtotal estimates were consistent for suicidal ideation, suicide attempt and suicidal tendencies. When we performed subgroup analyses using several study-level factors, the WMDs between suicidal and nonsuicidal patients persistently showed no significant differences except in patients with schizophrenia (Table 1). However, suicidal patients had significantly lower serum HDL-C level than healthy controls (WMD –1.75, 95% CI –3.01 to –0.48, Fig. 3B), and there was significant heterogeneity among the studies (I^2 = 96.9%, p < 0.001). Subtotal estimates showed that patients who had attempted suicide had lower serum HDL-C levels than controls, but this difference did not reach statistical significance. Exclusion of the studies with results that did not control for at least age or sex reduced the heterogeneity (I^2 = 66.2%, p = 0.031) but did not significantly change the WMD estimate (WMD –1.44, 95% CI –6.06 to 3.17; Appendix 1, Fig. S2). Subgroup analyses showed that the significant differences were only in women, younger participants (mean age < 40 yr) and patients with schizophrenia and in studies published after 2005 and that had relatively low quality (Table 1).

Serum LDL-C levels between suicidal and nonsuicidal patients/healthy controls

The serum LDL-C level of suicidal patients was significantly lower than those of nonsuicidal patients (WMD –19.56, 95% CI –26.13 to –12.99; Fig. 4A) and healthy controls (WMD –3.85, 95% CI –7.45 to –0.26; Fig 4B). We found significant heterogeneity for the pooled analyses (I^2 = 78.5%, p < 0.001, and I^2 = 98.1%, p < 0.001, respectively). The subtotal estimates were almost consistent for suicidal ideation, suicide attempt and suicidal tendencies. Exclusion of the studies with results that did not control for at least age or sex reduced the heterogeneity (I^2 = 56.0%, p = 0.005, and I^2 = 92.4%, p < 0.001, respectively) but did not significantly change the WMD estimates (WMD –9.70, 95% CI –15.52 to –3.88, and WMD –14.00, 95% CI –32.75 to 4.75, respectively; Appendix 1, Fig. S3). Subgroup analyses showed that younger suicidal patients (mean age < 40 yr) but not older ones (mean age ≥ 40 yr) had significantly lower serum LDL-C level than nonsuicidal patients (WMD –22.81, 95% CI –30.79 to –14.83, and WMD –4.38, 95% CI –9.48 to 0.72, respectively; Table 1) and that patients with schizophrenia had larger mean serum LDL-C level differences than patients with other mental disorders. In addition,

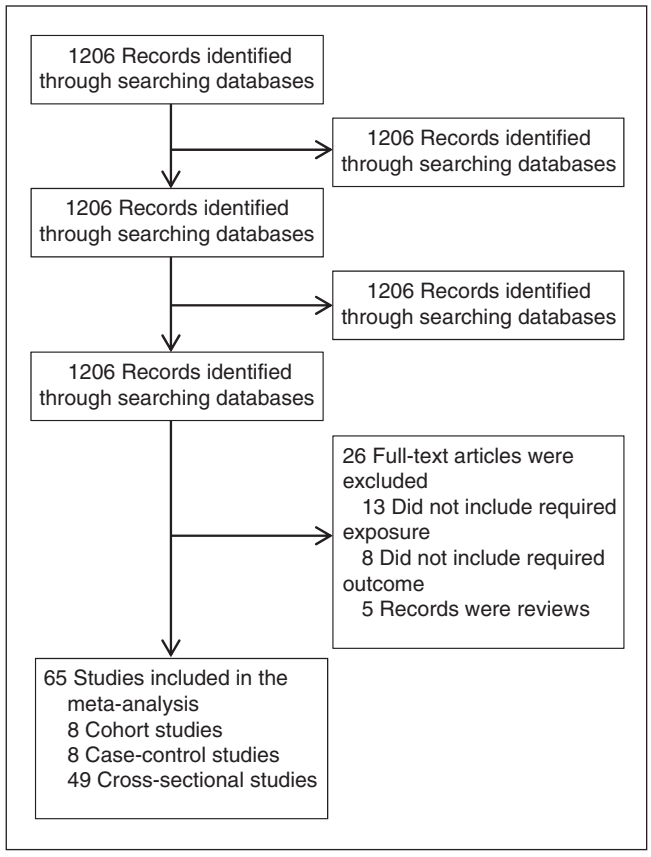

Fig. 1: Selection of eligible studies.

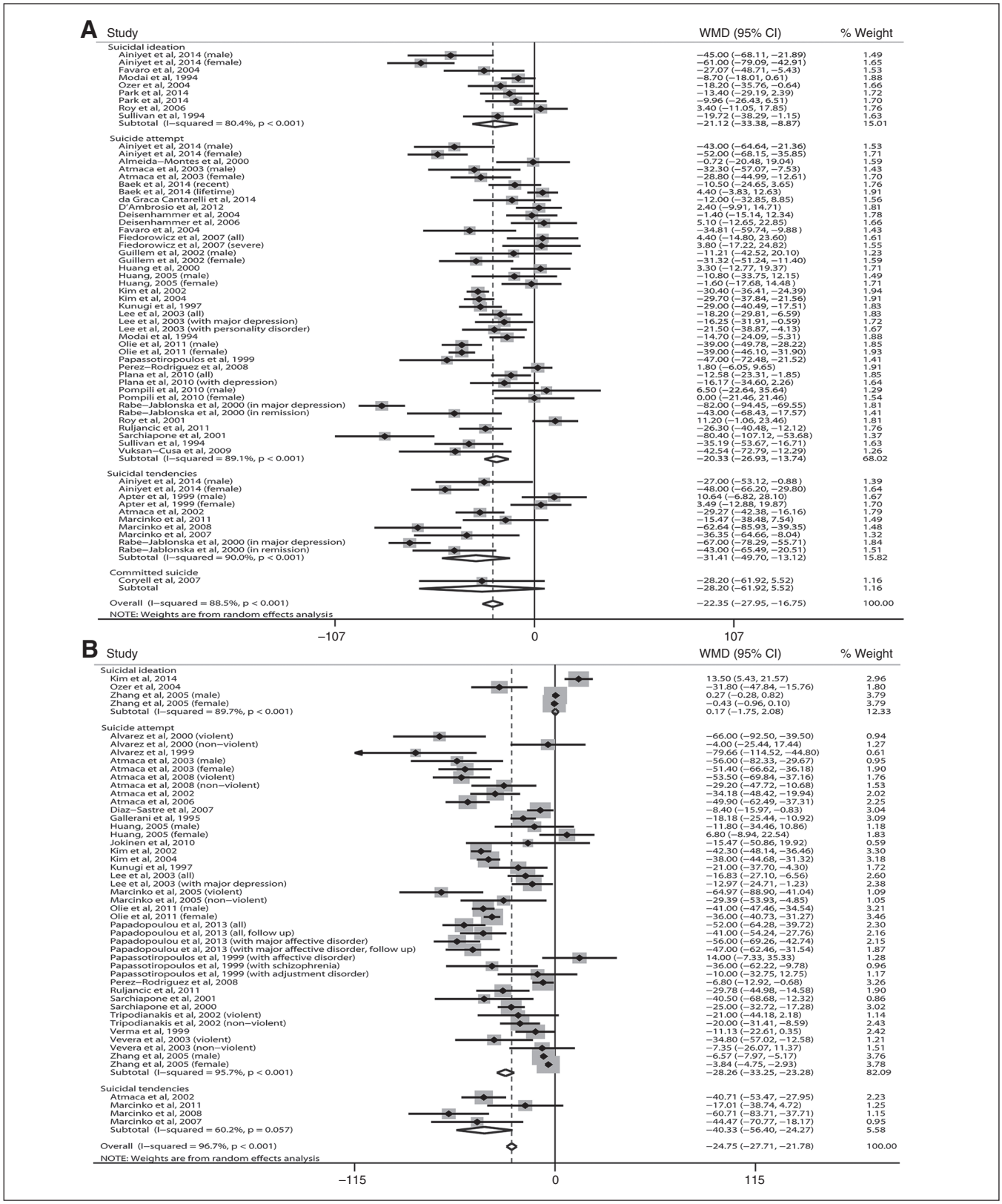

Fig. 2: Pooled summary estimates of serum total cholesterol (TC) levels in (**A**) suicidal versus nonsuicidal patients and (**B**) in suicidal patients versus healthy controls. *Defined according to the Hamilton Rating Scale for Depression, item 3 score. **Defined according to the Beck Depression Inventory, item 9 score. CI = confidence interval; WMD = weighted mean difference.

when comparing suicidal patients with healthy controls, significantly lower serum LDL-C level was seen only in participants younger than 40 years, in patients with schizophrenia and in studies published before 2005. Suicidal patients older than 40 years had significantly higher LDL-C level than their healthy peers based on 1 study (Table 1).

Serum TG levels between suicidal and nonsuicidal patients/healthy controls

Pooled results showed that suicidal patients had significantly lower serum TG level than nonsuicidal patients (WMD –23.40, 95% CI –32.38 to –14.42; Fig. 5A); their TG levels were also lower than those of controls, but this difference was not significant (WMD –9.53, 95% CI –19.75 to 0.69; Fig. 5B). There was significant heterogeneity for the pooled analyses (I^2 = 75.1%, $p < 0.001$, and I^2 = 81.0%, $p < 0.001$, respectively). The subtotal estimates were consistent for suicidal ideation, suicide attempt and suicidal tendencies. Exclusion of the studies with results that did not control for at least age or sex reduced the heterogeneity (I^2 = 67.5%, $p < 0.001$, and I^2 = 72.7%, p = 0.001, respectively) but did not significantly change the WMD estimates (WMD –15.59, 95% CI –24.53 to –6.65, and WMD –7.81, 95% CI –16.52 to 0.89, respectively; Appendix 1, Fig. S4). In the pooled analyses comparing suicidal patients with nonsuicidal patients, there were larger mean serum TG level differences in men, younger participants (mean age < 40 yr) and patients with schizophrenia and in studies that were published after 2005 and had relatively low quality. In the subgroup analyses comparing suicidal patients with healthy controls, we found significantly lower serum TG levels in men than women (WMD –29.11, 95% CI –44.78 to –13.43); a similar difference was not observed in the overall population (Table 1).

Risk of suicidality in the lowest versus the highest serum TC level category

We performed a meta-analysis for the risk of suicidality according to the lowest versus the highest serum TC level category only; the data for other types of serum lipids were insufficient

Table 1: Subgroup analyses for studies included in the analysis that assessed the serum lipid level in different groups (part 1 of 2)

	Suicidal v. nonsuicidal patients				Suicidal patients v. healthy controls			
Subgroup analysis	*n*	Pooled WMD (95% CI)	I^2, %	*p* value	*n*	Pooled WMD (95% CI)	I^2, %	*p* value
TC								
Sex								
Male	14	–23.72 (–37.48 to –9.96)	83.6	< 0.001	11	–26.06 (–33.67 to –18.46)	96.9	< 0.001
Female	11	–29.27 (–41.56 to –16.98)	84.2	< 0.001	7	–15.28 (–21.33 to –9.24)	98.0	< 0.001
Mean age, yr								
< 40	35	–22.69 (–28.87 to –16.50)	79.2	< 0.001	31	–19.45 (–22.38 to –16.53)	95.7	< 0.001
≥ 40	17	–14.84 (–24.53 to –5.15)	90.3	< 0.001	16	–32.21 (–42.83 to –21.58)	93.2	< 0.001
Type of suicide attempt								
Violent	0	—	—	—	6	–51.54 (–67.45 to –35.63)	63.4	0.018
Nonviolent	0	—	—	—	5	–18.13 (–27.22 to –9.04)	23.4	0.27
Type of disease								
Depression	18	–24.47 (-37.38 to –11.55)	92.9	< 0.001	6	–20.75 (–36.35 to –5.15)	86.2	< 0.001
Schizophrenia	9	–45.04 (-53.56 to –36.51)	37.2	0.12	6	–50.36 (–60.67 to –40.04)	21.4	0.27
Personality disorder	3	–24.57 (–34.09 to –15.04)	0.0	0.55	2	–30.56 (–53.54 to –7.57)	70.6	0.07
Mood disorder	4	–13.19 (–35.03 to 8.64)	69.9	0.019	0	—	—	—
Design								
Cohort	3	–2.16 (–18.74 to 14.42)	33.4	0.22	0	—	—	—
Case–control	5	–15.93 (–28.93 to –2.93)	83.6	< 0.001	8	–22.47 (–33.29 to –11.66)	79.9	< 0.001
Cross-sectional	53	–23.90 (–30.08 to –17.72)	88.9	< 0.001	41	–25.52 (–28.70 to –22.34)	97.1	< 0.001
Publication year								
Before 2005	30	–25.26 (–33.31 to –17.21)	89.5	< 0.001	24	–27.76 (–34.15 to –21.37)	81.4	< 0.001
2005 or later	31	–19.44 (–27.18 to –11.70)	86.9	< 0.001	25	–21.16 (–24.53 to –17.78)	97.3	< 0.001
Study quality†								
Relatively high	30	–16.24 (–22.52 to –9.96)	85.0	< 0.001	28	–30.93 (–37.91 to –23.95)	91.0	< 0.001
Relatively low	31	–28.53 (–38.51 to –18.55)	90.4	< 0.001	21	–13.33 (–16.31 to –10.35)	94.8	< 0.001
HDL-C								
Sex								
Male	7	–1.76 (–7.27 to 3.76)	51.5	0.05	4	–1.51 (–6.77 to 3.75)	97.9	< 0.001
Female	4	–3.15 (–6.51 to 0.21)	0.0	0.73	3	–3.91 (–6.69 to –1.13)	98.6	< 0.001
Mean age, yr								
< 40	13	–1.60 (–3.91 to 0.71)	6.9	0.38	9	–1.80 (–3.14 to –0.46)	97.2	< 0.001
≥ 40	7	2.59 (–0.19 to 5.37)	22.3	0.26	1	–1.30 (–4.11 to 1.51)	—	—

for this comparison. The cut-off values for low and high serum TC level were in compliance with the categories reported in the original studies. In the pooled analysis, we observed a potential adverse effect of lower serum TC level on suicidality. Compared with the highest serum TC level category, a lower serum TC level was associated with a 112% (95% CI 40%–220%)

Table 1: Subgroup analyses for studies included in the analysis that assessed the serum lipid level in different groups (part 2 of 2)

	Suicidal v. nonsuicidal patients				Suicidal patients v. healthy controls			
Subgroup analysis	*n*	Pooled WMD (95% CI)	I^2, %	*p* value	*n*	Pooled WMD (95% CI)	I^2, %	*p* value
HDL-C (cont'd)								
Type of disease								
Depression	9	1.56 (–1.70 to 4.81)	44.7	0.07	2	–3.59 (–13.89 to 6.71)	26.5	0.24
Schizophrenia	7	–2.51 (–6.33 to –1.31)	42.8	0.11	1	–12.76 (–22.50, –3.02)	—	—
Mood disorder	1	–0.89 (–7.58 to 5.80)	—	—	0	—	—	—
Publication year								
Before 2005	4	–0.71 (–5.97 to 4.54)	49.8	0.11	2	2.66 (–6.06 to 11.39)	62.3	0.10
2005 or later	18	–0.03 (–2.21 to 2.15)	35.7	0.07	8	–1.99 (–3.31 to –0.67)	97.6	< 0.001
Study quality†								
Relatively high	8	0.63 (–3.63 to 4.89)	60.9	0.013	3	–2.66 (–6.88 to 1.57)	62.7	0.07
Relatively low	14	–0.86 (–2.80 to 1.08)	0.2	0.45	7	–1.70 (–3.10 to –0.29)	97.9	< 0.001
LDL-C								
Sex								
Male	6	–28.67 (–40.00 to –17.35)	29.2	0.22	4	–9.62 (–19.85 to 0.62)	98.5	< 0.001
Female	4	–29.50 (–51.31 to –7.69)	88.1	< 0.001	3	–0.34 (–6.90 to 6.22)	99.2	< 0.001
Mean age, yr								
< 40	15	–22.81 (–30.79 to –14.83)	68.6	< 0.001	10	–5.82 (–9.56 to –2.07)	98.2	< 0.001
≥ 40	6	–4.38 (–9.48 to 0.72)	0.0	0.49	1	14.50 (7.48, 21.52)	—	—
Type of disease								
Depression	10	–13.35 (–23.04 to –3.66)	79.2	< 0.001	2	2.33 (–10.69 to 15.35)	20.3	0.26
Schizophrenia	7	–36.31 (–43.40 to –29.22)	0.0	0.72	1	–35.96 (–56.14 to –15.78)	—	—
Personality disorder	1	–17.19 (–30.31 to –4.07)	—	—	0	—	—	—
Mood disorder	1	–1.65 (–18.81 to 15.51)	—	—	0	—	—	—
Publication year								
Before 2005	9	–23.47 (–33.16 to –13.78)	73.5	< 0.001	3	–16.93 (–29.74 to –4.12)	69.5	0.038
2005 or later	17	–17.36 (–25.89 to –8.84)	79.3	< 0.001	8	–1.39 (–5.27 to 2.49)	98.6	< 0.001
Study quality†								
Relatively high	11	–17.42 (–26.13 to –8.72)	73.8	< 0.001	4	–9.38 (–28.68 to 9.91)	91.9	< 0.001
Relatively low	15	–20.92 (–30.74 to –11.10)	81.4	< 0.001	7	–3.86 (–7.92 to 0.20)	98.8	< 0.001
TG								
Sex								
Male	8	–38.05 (–54.58 to –21.52)	56.9	0.023	3	–29.11 (–44.78 to –13.43)	41.8	0.18
Female	6	–21.18 (–38.35 to –4.01)	67.7	0.008	2	9.58 (–34.15 to 53.30)	85.8	0.008
Mean age, yr								
< 40	16	–29.53 (–42.97 to –16.10)	79.7	< 0.001	5	–14.53 (–40.93 to 11.86)	79.2	0.001
≥ 40	11	–15.55 (–28.06 to –3.05)	67.3	0.001	4	–6.30 (–16.85 to 4.25)	83.8	< 0.001
Type of disease								
Depression	11	–22.33 (–36.02 to –8.64)	79.9	< 0.001	2	–5.53 (–82.92 to 71.86)	93.8	< 0.001
Schizophrenia	7	–45.60 (–56.52 – 34.68)	0.0	0.71	1	–24.74 (–60.14 to 10.66)	—	—
Mood disorder	3	–12.61 (–45.21 to 19.99)	67.8	0.045	0	—	—	—
Publication year								
Before 2005	6	–6.29 (–18.26 to 5.68)	47.8	0.09	3	–1.35 (–10.84 to 8.13)	38.6	0.20
2005 or later	21	–27.92 (–38.32 to –17.51)	70.5	< 0.001	6	–11.89 (–26.63 to 2.85)	78.1	< 0.001
Study quality†								
Relatively high	15	–14.96 (–24.68 to –5.25)	70.9	< 0.001	6	–7.08 (–15.77 to 1.61)	75.4	0.001
Relatively low	12	–36.07 (–48.92 to –23.23)	51.3	0.020	3	–15.37 (–71.56 to 40.82)	87.8	0.001

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; WMD = weighted mean difference.
*Heterogeneity *Q* test.
†We defined studies as relatively high quality if they had 8 stars or more for cohort and case–control studies and 4 stars or more for cross-sectional studies based on the Newcastle–Ottawa Scale, otherwise, we considered them to be relatively low quality.

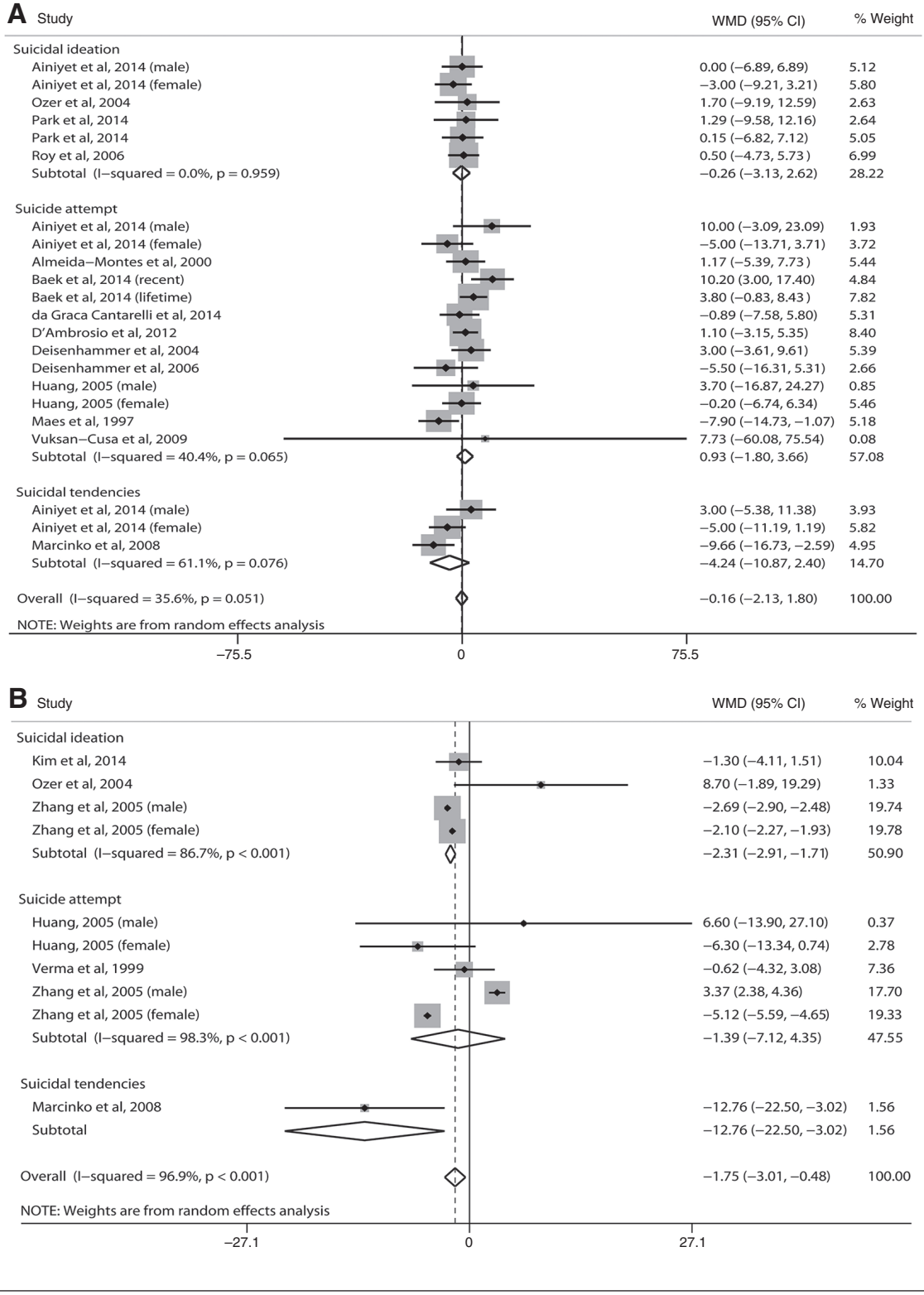

Fig. 3: Forest plot displaying the pooled summary estimates of serum high-density lipoprotein cholesterol levels in the suicidal patients versus nonsuicidal patients (**A**), and in the suicidal patients versus normal controls (**B**). *Defined according to the Hamilton Rating Scale for Depression, item 3 score. **Defined according to the Beck Depression Inventory, item 9 score. CI = confidence interval; WMD = weighted mean difference.

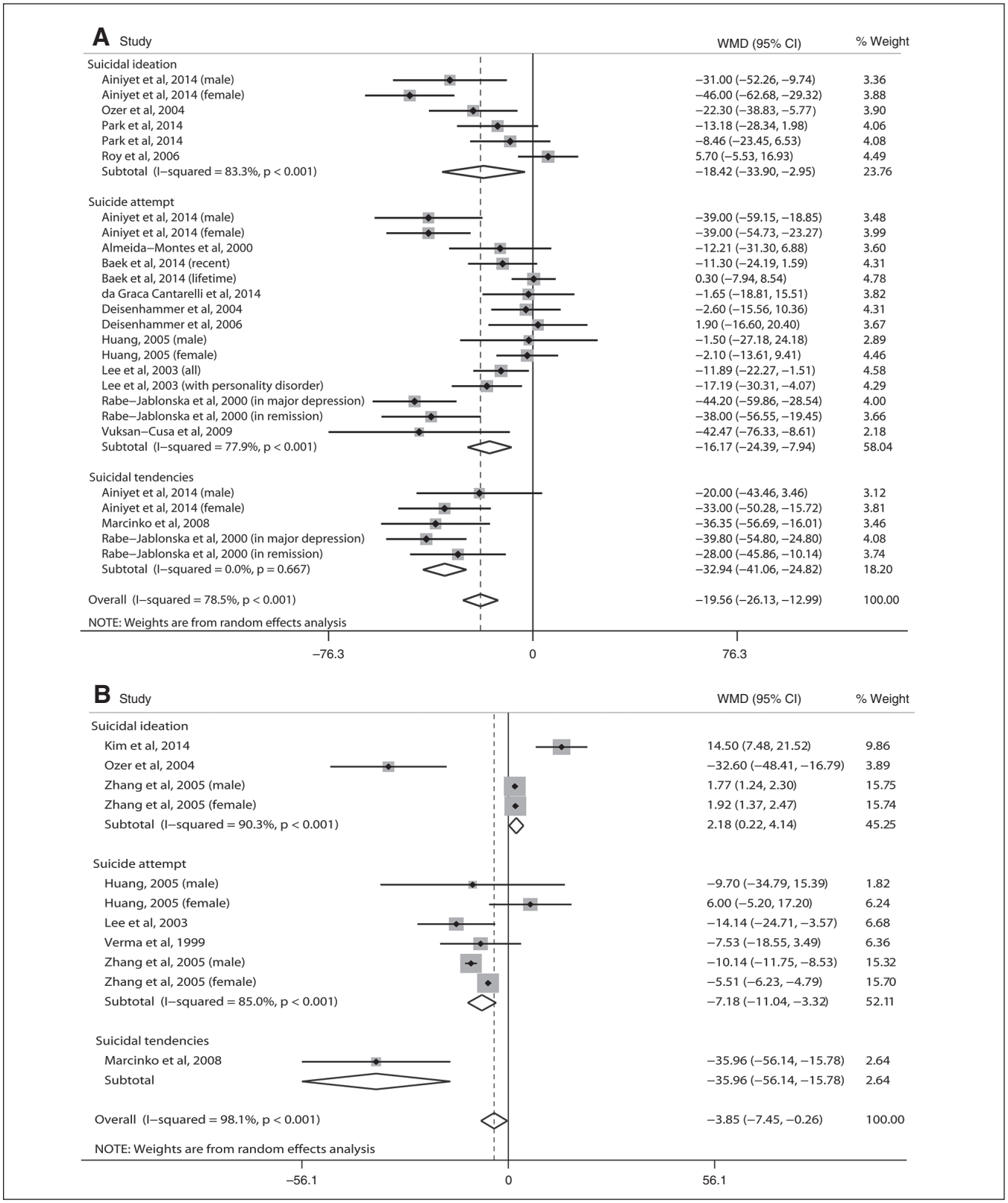

Fig. 4: Pooled summary estimates of serum low-density lipoprotein cholesterol levels in the (**A**) suicidal versus nonsuicidal patients and (**B**) in the suicidal patients versus healthy controls. *Defined according to the Hamilton Rating Scale for Depression, item 3 score. **Defined according to the Beck Depression Inventory, item 9 score. CI = confidence interval; WMD = weighted mean difference.

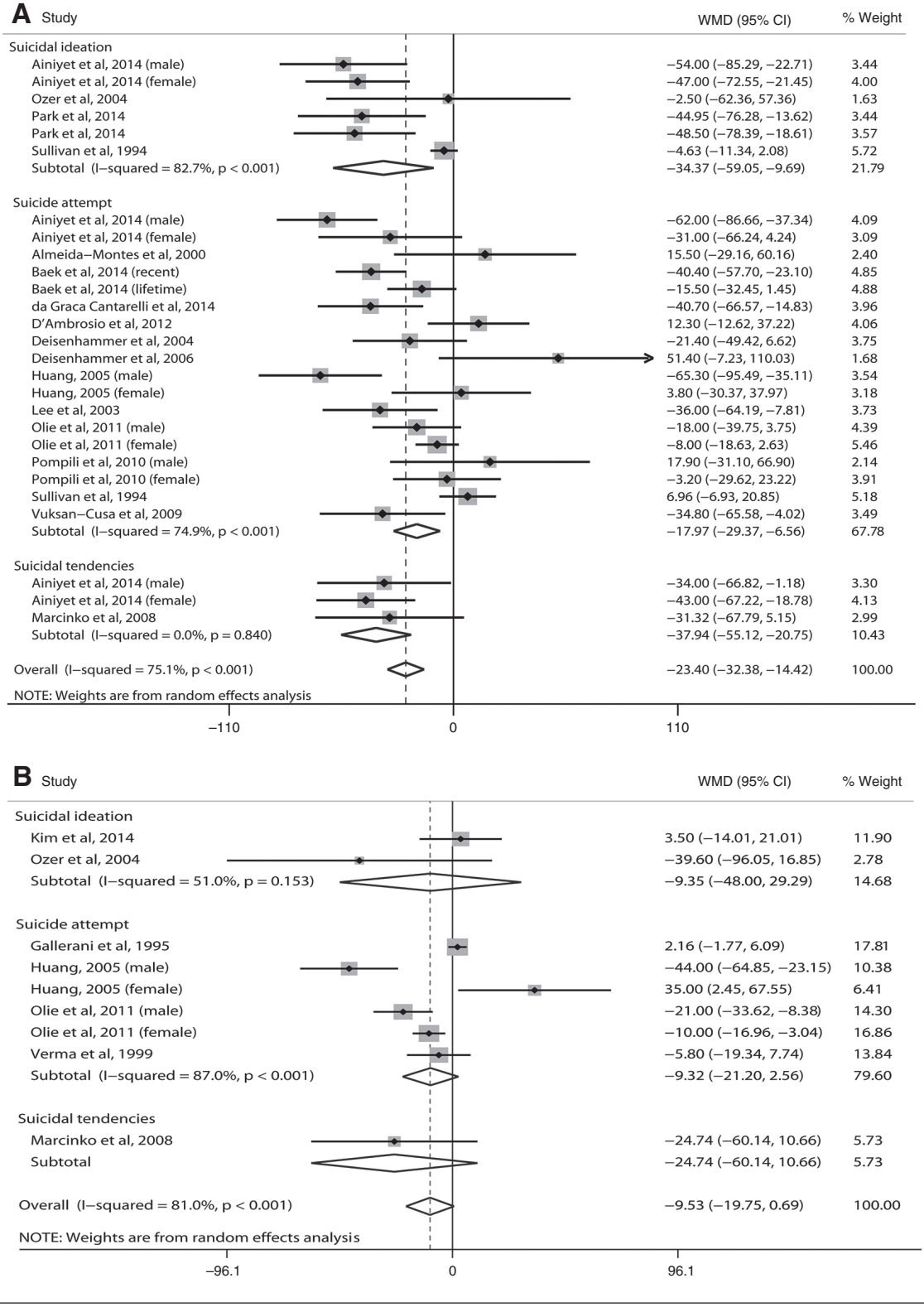

Fig. 5: Pooled summary estimates of serum triglycerides levels in (**A**) suicidal versus nonsuicidal patients and (**B**) in suicidal patients versus healthy controls. *Defined according to the Hamilton Rating Scale for Depression, item 3 score. **Defined according to the Beck Depression Inventory, item 9 score. CI = confidence interval; WMD = weighted mean difference.

higher risk of suicidality, including a 123% (95% CI 24%–302%) higher risk of suicide attempt and an 85% (95 CI 7%–221%) higher risk of suicide completion (Fig. 6). There was potential heterogeneity among studies (I^2 = 86.8%, p < 0.001). Exclusion of the studies with results that did not control for at least age or sex did not reduce the heterogeneity and did not significantly change the OR estimate (OR 2.30, 95% CI 1.39–3.81; Appendix 1, Fig. S5). In the subgroup analyses, the inverse association between serum TC level and risk of suicidality was found in men but not in women (OR 2.89, 95% CI 1.90–4.39 v. OR 2.26, 95% CI 0.87–5.87, respectively, Table 2). In addition, this inverse association was found only in the studies published before 2005 (Table 2).

Publication bias

Visual assessment of funnel plots (Appendix 1, Fig. S6) showed that the studies were distributed fairly symmetrically about the combined effect size in most of the pooled analyses, which suggests little publication bias. The Egger regression test and the Begg–Mazumdar test also showed that there was no potential publication bias in most of the meta-analyses (Appendix 1, Fig. S6). However, the Egger regression test showed that there was potential publication bias when assessing the serum TC level according to suicidal patients compared with healthy controls (p < 0.001; Appendix 1, Fig. S6B) and serum TG level between suicidal patients and nonsuicidal patients (p = 0.033, Appendix 1; Fig. S6G). Both the Egger regression test and the Begg–Mazumdar test showed that there was potential publication bias when assessing serum LDL-C level between suicidal and nonsuicidal patients (p = 0.003 and p = 0.045, respectively, Appendix 1, Fig. S6E). After using the trim and fill approach, we found that no trimming was performed and the pooled results had not been changed in these analyses.

Discussion

To the best of our knowledge, this is the first meta-analysis to comprehensively assess the association between various serum lipid levels and suicidality. The present study revealed that the serum TC and serum LDL-C levels were significantly lower in suicidal patients than in both nonsuicidal patients and healthy controls, that the serum HDL-C level was significantly lower in suicidal patients than in healthy controls and that the serum TG level was significantly lower in suicidal patients than in nonsuicidal patients. In addition, we found a borderline significant 112% higher risk of suicidality for those in the lowest serum TC level category than in those in the highest serum TC level category.

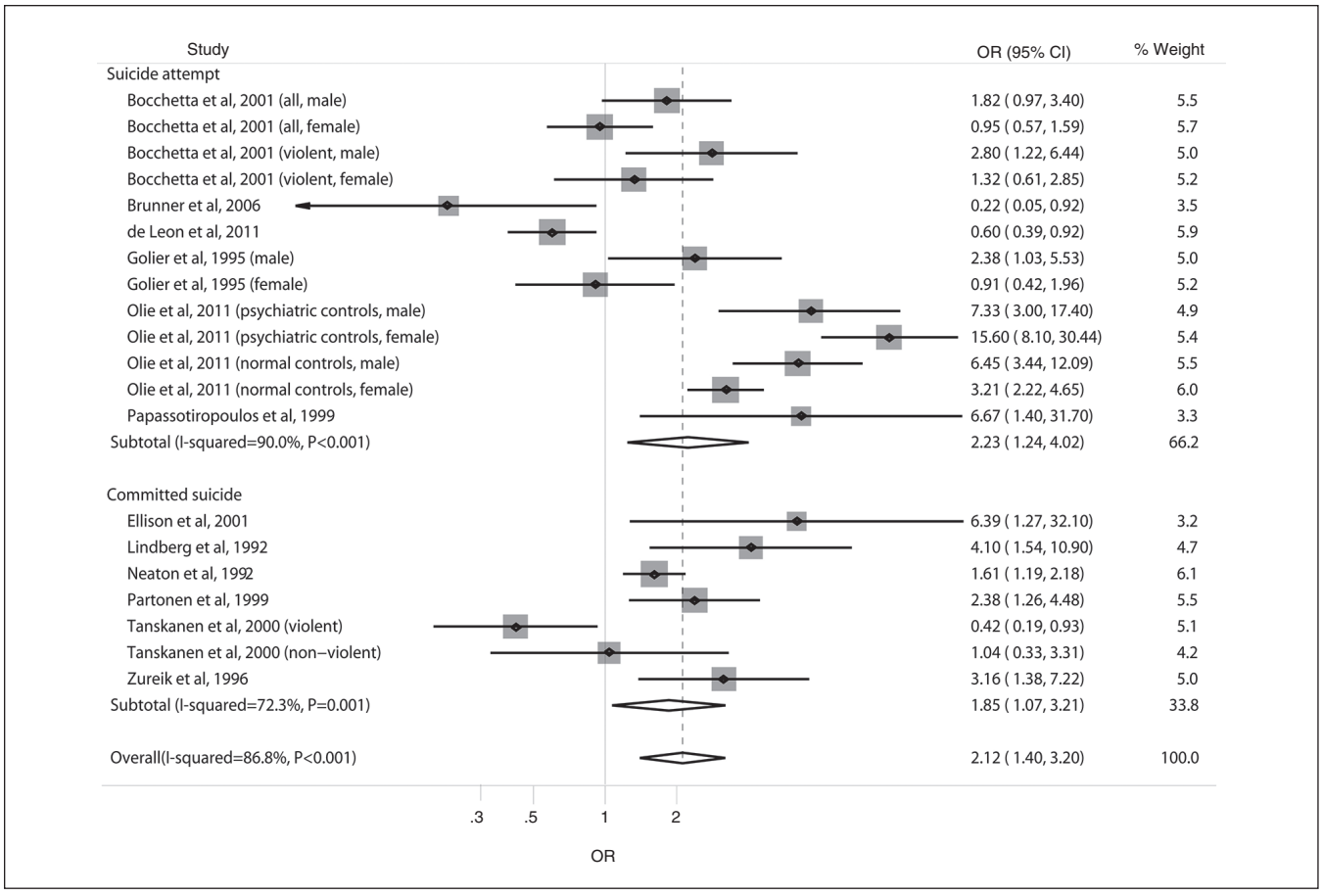

Fig. 6: Pooled relative risk of suicidality based on the lowest v. highest serum total cholesterol level category. CI = confidence interval; OR = odds ratio.

Previous studies have produced conflicting results when exploring the potential association between lipid levels and suicidality, because the assessment of suicidality has differed among studies. In our meta-analysis, we included patients with various suicidal behaviours, including suicidal ideation, suicide attempts, suicidal tendencies and suicide completion. Overall, the tendencies of serum lipid levels were consistent across different types of suicidal behaviours, which means that low serum lipid level is an interesting predictive marker not only for suicidal acts, but also for suicidal ideation, suicide attempt and even suicidal tendencies. In addition, an increasing number of reports raise the possibility that statins, a class of lipid-lowering agents, may be associated with deleterious cognitive,[82–84] mood and behavioural adverse effects, including violence,[85] depression and suicide,[86] which have been attributed to the effect of statins' cholesterol level reduction on brain function. These results were consistent with ours.

Our subgroup analyses showed that the association between lower serum lipid levels and suicidality was stronger in participants younger than 40 years than in older participants in most analyses. Fiedorowicz and Coryell[16] reported that in the high cholesterol group, younger patients made more suicide attempts than older patients, which is the opposite of the results of our meta-analysis. We have also confirmed that sex plays an important role. Compared with healthy controls, suicidal women, but not men, had significantly lower HDL-C levels; however, other authors have reported an association between low cholesterol and suicidality only in men.[50,56] Other studies have also reported that male sex is associated with lower cholesterol levels in various psychiatric disorders.[87,88] The results of our meta-analysis are not consistent with those of others. Overall, measurement limitations as well as the types of serum lipid measured, the types of suicidality observed and the differences in sample selections may have led to the inconsistency in the observed results. More studies are needed to further explain the impact of age and sex on the differences in serum lipid levels between suicidal and nonsuicidal participants. We also found that suicidal men had significantly lower TG levels than healthy male controls, but we found no statistical difference in female participants. In addition, when compared with healthy controls, patients with violent suicide attempts had much larger mean serum TC level differences than those with nonviolent suicide attempts. This result indicates that patients with violent suicide attempts had lower TC levels than those with nonviolent suicide attempts, as the individual studies[34,38,41,46] revealed. However, 1 study found there was no difference between patients with violent and nonviolent suicide attempts.[78]

The mechanism that may link serum lipids with suicidality is still unclear. It is possible that low peripheral cholesterol in individuals with psychiatric disorders accompanies (by a common regulatory mechanism) the cholesterol changes that may occur in specific synaptic lipid rafts, which could cause the hypoactivity of serotonergic communication and, in turn, lead to impulsivity and violent suicidal behaviour.[89] In addition, Penttinen[90] has suggested that low cholesterol concentration and suicidality are connected with interleukin-2, a cytokine produced by T cells that causes a decrease in serum cholesterol and an increase in serum TG level; however, our finding that suicidal patients had a significantly lower serum TG level than nonsuicidal patients is contrary to his hypothesis. Other researchers have suggested that individuals with suicidal behaviour may have had depressive episodes that influenced their appetites and caused weight loss and, in turn, resulted in lower serum lipid levels.[81] Other possible mechanisms have described a central role for fatty acids, particularly docosahexaenoic acid.[91]

The possibility of publication bias is always a concern in a meta-analysis. In our study, there was no potential publication bias in most analyses, and only 3 pooled results showed potential publication bias. We further used the trim and fill method to adjust for publication bias. Nevertheless, results showed that meta-analyses with or without the trim and fill did not yield different effect estimates. More importantly, there were a wide range of articles included in our study, and the inverse associations between serum lipid levels and suicidality appeared to be consistent across most studies. Thus, the likelihood that these findings are largely a result of selective publication seems to be minimal. Taken together, our results are sound and reliable.

The strengths of this meta-analysis are that we included a broad range of studies to quantitatively assess serum lipid levels and suicidality, as the literature diverges on whether suicidal patients had lower serum lipid levels and on whether participants with lower TC levels had higher risk of suicidality. Compared with results of individual studies, the pooled results of the meta-analysis were more precise with more narrow CIs owing to the much larger sample size.

Table 2: Subgroup analyses for studies included in the analysis that assessed the risk of suicidality according to the lowest versus highest serum total cholesterol level category

		Risk estimates of suicidality		
Subgroup analysis	*n**	Pooled OR (95% CI)	I^2, %	*p* value†
Sex				
Male	8	2.89 (1.90–4.39)	70.4	0.001
Female	5	2.26 (0.87–5.87)	92.6	< 0.001
Geographical area				
North America	4	1.71 (1.03–2.85)	47.7	0.13
Europe	16	2.16 (1.28–3.65)	88.9	< 0.001
Design				
Cohort	7	1.62 (1.15–2.29)	48.0	0.07
Case–control	1	1.32 (0.61, 2.85)	—	—
Cross-sectional	12	2.41 (1.21–4.79)	91.1	< 0.001
Publication year				
Before 2005	14	1.73 (1.25–2.40)	61.9	0.001
2005 or later	6	2.79 (0.94–8.30)	94.9	< 0.001
Study quality‡				
Relatively high	15	2.19 (1.30–3.68)	89.4	< 0.001
Relatively low	5	1.73 (1.03–2.91)	56.5	0.06

CI = confidence interval; OR = odds ratio.
*Number of estimates in included studies.
†Heterogeneity *Q* test.
‡We defined studies as relatively high quality if they had 8 stars or more for cohort and case–control studies and 4 stars or more for cross-sectional studies based on the Newcastle–Ottawa Scale, otherwise, we considered them to be relatively low quality.

Limitations

A major limitation of our study was the potential heterogeneity in most of the analyses. Although we performed random-effects and subgroup analyses and excluded the studies that did not control for at least age or sex, we are unlikely to have fully accounted for heterogeneity. Therefore, the results of the meta-analysis must be interpreted with caution. Because of potential additional heterogeneity in the study designs, populations and analyses of the various studies, we assumed that the true effect being estimated would vary among the studies. Although the studies included in our analysis were heterogeneous, the associations we observed were largely consistent. Another important limitation was the poor quality of some studies included in the meta-analysis, which affected the comparability of groups on the basis of the design or analysis. However, the consistency of our results across studies and settings suggests that the findings of lower serum lipid levels in suicidal patients and increased risk of suicidality in patients with lower serum TC levels are robust. In addition, suicidality was examined using different scales or methods across studies, and this may be another explanation of the heterogeneity that existed among the studies. Some included studies did not adjust or adjusted only for a few important factors; genetic factors, alcohol consumption and cigarette smoking, for example, may contribute to the alterations in serum lipid levels in suicidal patients. Moreover, it is rather difficult to elucidate the cause and effect between serum lipids and suicidality, as most studies used a cross-sectional or case–control design. Further studies are needed to explain the association between serum lipid levels and suicidality and elucidate the cause–effect relationship. The time elapsed between lipid assessment and suicidal act was reported rarely among the included studies, and this may be another limitation of our study. Finally, the lipid levels were examined only once in most of the studies, whereas we now feel that estimation should occur at least twice,[92] because the serum lipid levels may fluctuate over time.

Conclusion

The results of our meta-analysis suggest that compared with nonsuicidal patients, suicidal patients had significantly lower serum TC, LDL-C and TG levels, while compared with the healthy controls, suicidal patients had significantly lower TC, HDL-C and LDL-C levels. Furthermore, compared with the highest serum TC level category, a lower serum TC level was associated a 112% higher risk of suicidality, including a 123% higher risk of suicide attempt and an 85% higher risk of suicide completion. More mechanistic studies are needed to further explain the association between serum lipid levels and suicidality.

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