Short Communication

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Serum cholesterol levels preceding to suicide death in Japanese workers: a nested case-control study

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Abstract

Objective: To investigate the association between suicide death and serum cholesterol levels as measured at times close to suicide death. *Methods:* We conducted a nested case-control study of 41 cases of suicide deaths and 205 matched controls with serum total cholesterol (TC) levels till 3 years before suicide death in a large cohort of Japanese workers. *Results:* Individuals in the lowest versus highest tertile/predefined category of TC in a Japanese working population had a three- to four-fold greater risk of suicide death. Each 10 mg/dl decrement of average TC was associated with an 18% increased chance of suicide death (95% confidence interval, 2–35%). Similar results were found for TC levels at each year. *Conclusion:* These results suggest that a low serum TC level in recent past is associated with an increased risk of suicide death.

Significant outcomes

- A lower averaged level of TC across 3 years before suicide death was significantly associated with an increased risk of suicide death.
- This association remained statistically significant when the averaged TC level was treated as a continuous or a categorical variable.
- Similar results were found for TC levels at each single year.

Limitations

- A relatively small number of cases.
- The possibility of bias due to residual confounding effects and unmeasured confounders.
- The limited generalisability of the results to populations with different backgrounds.

Introduction

Suicide is among the leading causes of death worldwide. In Japan, which has one of the highest global suicide rates, suicide is the top cause of death among young adults (Ministry of Health Labour and Welfare of Japan, 2018). Suicide, in addition to several psychiatric disorders (De Berardis *et al.*, 2012, 2017, 2014), has been linked to nutritional biomarkers including serum cholesterol (Mittendorfer & Wasserman, 2000). Low serum total cholesterol (TC) level has been found to be related to lower central nervous system serotonin activity (Steegmans *et al.*, 1996), a condition often observed in cases of depression and suicide. However, epidemiological evidence regarding the association between serum TC concentrations and the risk of suicide death is

conflicting, with some studies showing an inverse association (Lindberg *et al.*, 1992; Neaton *et al.*, 1992; Zureik *et al.*, 1996; Partonen *et al.*, 1999; Ellison & Morrison, 2001; Jee *et al.*, 2011) and others suggesting a null (Kromhout *et al.*, 1992; Smith *et al.*, 1992; Giltay *et al.*, 2010; Chang *et al.*, 2012) or even positive (Iribarren *et al.*, 1995; Tanskanen *et al.*, 2000; Svensson *et al.*, 2017) association. Furthermore, no data are available regarding circulating TC levels during the years immediately preceding suicide death. In this study, we examined serum TC levels as measured during the 3 years before suicide death among a large cohort of Japanese workers. We hypothesised that low levels of serum TC are associated with an increased risk of suicide death.

Materials and methods

Study design

We performed a case-control study nested in a cohort of the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study, which is an ongoing study among workers at multiple companies (Hu *et al.*, 2018). A total of 146 619 participants who attended health check-ups at least once between January 2008 and December 2016 or between April 2008 and March 2017 comprised the sample for the present study. The research protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine in Japan.

Measures

Ascertainment of suicide death and control selection

Using within-study registration, we ascertained participants' deaths and their causes of death since April 2012. The dataset was locked for the present study on 10 August 2018. Causes of deaths were confirmed based on death certificates, sick leave documents, family confirmation and other sources. The causes of deaths were classified according to the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10). Of the 60 suicide deaths (ICD-10 codes X60–X84) we ascertained, 19 cases were excluded owing to a lack of TC measurements conducted at any health check-up during the 3 years prior to suicide death, leaving 41 cases for analysis. Controls were selected by using the incidence density method. For each case of suicide death, we first created a pool of controls matched on sex, birthday (±2 years) and worksite. We then allocated the date of suicide death as an index date to matched controls. For a given case, we randomly selected five controls from the pool of eligible controls. We did not allow cases to be chosen as controls, nor did we allow a selected control to serve as a control of other cases.

Serum total cholesterol and other variables

Serum TC levels were analysed enzymatically. Analyses of TC were performed by laboratories that hold a high rank (Rank A or Score > 95/100 according to external quality control agencies). Of 41 cases, 28 had three recorded TC measurements, 5 had two TC records, and 8 had only one TC measurement. We calculated a mean TC level using the available data. Covariates included smoking status, lipid-lowering treatment, diabetes and hypertension at 1 year prior to suicide death. If these data were not available, measurements obtained 2 or 3 years prior to death were used.

Statistical analyses

We built conditional logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI) of suicide death according to the 3-year average of TC levels. We used continuous (each 10 mg/dl decrement), tertile and predefined categories of averaged TC (<180 mg/dl, 180 to <200 mg/dl, 200 to <220 mg/dl and ≥220 mg/dl) as independent variables in separate models. We also adjusted for current smoking status, lipid-lowering treatment, diabetes and hypertension. We assessed trend association by assigning ordinal numbers to TC categories and modelling this as a continuous variable. We repeated the analyses using TC levels at single time points. We tested the interaction of smoking status on the potential association between TC and the risk of suicide death. We performed two sensitivity analyses: (1) excluding subjects who were undergoing lipid-lowering treatment and (2) using data comprising cases that had two or more TC measurements and their matched controls. Statistical analyses were performed using SAS version 9.4.

Results

There were no significant differences in the mean of body mass index, glycated hemoglobin, systolic blood pressure and diastolic blood pressure, nor in the rate of current smoker, lipid-lowering treatment, diabetes or hypertension between cases and controls (Table 1). Cases had significantly higher blood glucose levels than did controls.

The risk of suicide death increased with decreasing serum TC levels across the 3 years preceding suicide death (Table 2). Compared with the highest tertile (≥217 mg/dl), the adjusted OR (95% CI) was 1.49 (0.53, 4.16) for the middle tertile and 4.68 (1.67, 13.14) for the lowest tertile (<188 mg/dl) (*p* for trend = 0.003). In analyses using the predefined categories with TC levels ≥ 220 mg/dl as a reference, the adjusted OR (95% CI) was 1.72 (0.53, 5.55) for TC levels 200 to <220 mg/dl, 2.80 (0.96, 8.14) for TC levels 180 to <200 mg/dl and 3.29 (1.10, 9.85) for TC levels <180 mg/dl (*p* for trend = 0.02). Each 10 mg/dl decrement of average TC was associated with an 18% increased chance of suicide death (95% CI, 2–35%). The interaction between smoking status and average TC was not statistically significant (*p* for interaction = 0.17). The results were similar when examining the associations using TC levels recorded during each year before suicide/index date (Supplementary Table 1).

In sensitivity analyses, the exclusion of cases and controls who were undergoing lipid-lowering treatment did not materially change the results (Supplementary Table 2). Similar results were obtained when restricting analyses to cases with two or more TC measurements and their matched controls (data not shown).

Discussion

In the present case-control study nested in a large cohort study of a Japanese working population, we demonstrated that low serum TC levels during the years immediately preceding suicide were significantly associated with an increased risk of suicide death. To our knowledge, this is the first study to demonstrate this association using serum TC levels measured at time points close to suicide death.

A meta-analysis of seven Western cohort studies showed a two-fold increased risk of suicide death for the lowest versus highest TC (Wu *et al.*, 2016). In our study, individuals in the lowest versus

Table 1. Characteristics of suicide cases and controls at 1 year prior to suicide/index date

Characteristics	Cases	Controls	p*
N	41	205	
Age, mean ± SD, years	44.5 ± 11.4	44.7 ± 11.2	
Male, %	97.6	97.6	
Current smoker, %	46.3	38.0	0.32
BMI, mean ± SD, kg/m^2	23.4 ± 2.8	24.2 ± 3.9	0.21
Systolic blood pressure, mean ± SD, mmHg	124.3 ± 15.2	122.5 ± 14.8	0.46
Diastolic blood pressure, mean ± SD, mmHg	80.3 ± 15.2	76.1 ± 11.0	0.10
Fasting plasma glucose, mean ± SD, mg/dl	107.3 ± 32.0	98.5 ± 20.4	0.03
HbA1c, mean ± SD, %	5.7 ± 1.2	5.6 ± 0.6	0.35
Diabetes, %	12.2	9.3	0.56
Hypertension, %	29.3	21.0	0.24
Lipid-lowering treatment, %	7.3	9.3	0.69
History of cancer, %	2	0	–

SD, standard deviation; BMI, body mass index; HbA1c, glycated hemoglobin.
*Comparisons between cases and controls using chi-square test for categorical variables, *t*-test for continuous variables.

Table 2. Associations between 3-year average of serum total cholesterol (TC) levels and the risk of suicide death

3-year average levels (mg/dl)		No. of cases/ controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Tertiles (range)†	Highest (≥217)	8/72	1.00	1.00
	Middle (188 to <217)	10/65	1.39 (0.52, 3.73)	1.49 (0.53, 4.16)
	Lowest (<188)	23/68	**4.17 (1.57, 11.10)**	**4.68 (1.67, 13.14)**
	p for trend‡		**0.004**§	**0.003**§
Predefined categories	≥220	7/63	1.00	1.00
	200 to <220	8/47	1.56 (0.52, 4.70)	1.72 (0.53, 5.55)
	180 to <200	11/43	2.43 (0.87, 6.89)	2.80 (0.96, 8.14)
	<180	15/52	**3.06 (1.08, 8.69)**	**3.29 (1.10, 9.85)**
	p for trend‡		**0.02**§	**0.02**§
Decrement of 10 mg/dl (continuous)			**1.17 (1.02, 1.34)**	**1.18 (1.02, 1.35)**

OR, odds ratio; CI, confidence interval.
*Adjusted for smoking (current smoker or not), lipid-lowering treatment (yes or no), diabetes (yes or no) and hypertension (yes or no).
†Tertiles were based on the distribution of TC levels among controls.
‡Trend association was assessed by assigning ordinal numbers to each tertile and treating this variable as a continuous variable.
§p <0.05.

highest tertile/predefined category had a three- to four-fold higher risk of suicide death. Our estimates were within the range of relative risks demonstrated in previous prospective studies showing an inverse association between TC and suicide death (approximately two- to six-fold higher risk for the lowest versus highest quartile/predefined category) (Lindberg *et al.*, 1992; Neaton *et al.*, 1992; Zureik *et al.*, 1996; Partonen *et al.*, 1999; Ellison & Morrison, 2001; Jee *et al.*, 2011). The present study, conducted in a Japanese working population, not only confirms previous findings among primarily Western populations but also provides additional evidence to link suicide risk to TC levels in the recent past.

A Finnish study reported a twofold increased risk of suicide death associated with a TC level ≥309 mg/dl (vs. <193 mg/dl) (Tanskanen *et al.*, 2000). A Japanese study showed an approximately twofold increased risk of suicide death associated with a TC level ≥220 mg/dl (vs. 180 to <220 mg/dl) in women but not

in men (Svensson *et al.*, 2017). In the present study, owing to the presence of few cases with a TC level of ≥240 mg/dl (*n*=4), we were unable to assess suicide risk associated with high TC levels.

The strengths of this study are its repeated measurements of serum TC levels and the prospective design in a well-defined cohort study. However, there are also some limitations to consider. First, the number of cases (*n*=41) was not large relative to that of previous studies. Despite this, we observed a statistically significant association between serum TC and the risk of suicide death. Second, we cannot rule out the possibility of bias due to residual confounding effects and unmeasured confounders, such as job stress. Third, as participants were employees at large companies in a Japanese context, we urge caution in generalising the results to populations with different backgrounds.

In conclusion, our findings among a Japanese working population add evidence to support the hypothesis that low serum TC level in the

recent past is associated with an increased risk of suicide death. The potential of monitoring serum TC level as a target metric for suicide prevention interventions needs to be further explored.

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