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Complete List of Authors:	Dai, Lingli; Jiangsu Province Geriatric Hospital Yu, Yun; Jiangsu Province Geriatric Hospital Wang, Kunling; Jiangsu Province Geriatric Hospital Hu, Cuining; Jiangsu Province Geriatric Hospital Wu, Dan; Jiangsu Province Geriatric Hospital Shan, Shan; Jiangsu Province Geriatric Hospital,
Keywords:	DIABETES & ENDOCRINOLOGY, General endocrinology < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY

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The TyG index on admission was associated with a better long-term mortality of critically ill patients

Lingli Dai[1],Yun Yu[1], Kunlin Wang[1],Cuining Hu[1],Dan Wu[1], Shan Shan[1]*

1.Department of Endocrinology and Metabolism, Jiangsu Province Official Hospital, Geriatric Hospital of Nanjing Medical University,210000 Nanjing, China.

*Corresponding to
Shan Shan, Department of Endocrinology and Metabolism, Jiangsu Province Official Hospital, Geriatric Hospital of Nanjing Medical University,210000 Nanjing, China. E-mail: shanshan@lista.cc

Abstract

Aim: To evaluate the association of triglycerides glucose (TyG) index on admission with outcomes of critically ill patients.

Methods: We conducted a retrospective study that included all intensive care unit (ICU) admissions extracted from the Medical Information Mart for Intensive Care III database (MIMIC III). The TyG index was calculated as ln [triglycerides (mg/dL) *glucose (mg/dL)/2]. The primary endpoint was 360-day mortality. Multivariable Cox regression analysis was used to explore the prognostic effect of TyG index.

Results: A total of 3902 patients with an average age of 63.1 ± 15.9 years old were enrolled, including 1623 (41.6%) females. The 360-day mortality were lower in a higher TyG group. Compared with the lowest TyG group, the hazards ratio of 360-day mortality was 0.79 (95% confidence interval [0.66, 0.95]; p=0.011) in the fully adjusted Cox model and 0.71 ([0.59, 0.85]; p<0.001) in the stepwise Cox model. In the subgroup analysis, an interaction effect was detected between TyG index and gender.

Conclusions: The TyG index was negatively associated with the risk of 360-day mortality in critically ill patients.

Keywords: TyG index; mortality; ICU; critically illness; cohort study

Introduction

The triglyceride glucose (TyG) index is calculated using fasting triglyceride and fasting glucose measurements. It has been suggested as a surrogate marker of insulin resistance (IR)[1, 2]. Critical illness is characterized by a hypermetabolic state associated with increased mortality due to enhanced IR[3, 4].

Several studies have examined the associations between IR and mortality in critically ill patients. Nathan found that IR was a predictor for mortality in traumatic brain injury[5] and increased the mortality of surgical care population[6]. Recently, a study concluded that the TyG index was a potential predictor for hospital and ICU mortality in critically ill stroke patients[7]. To the best of our knowledge, there is no research to evaluate the association of TyG index on intensive care unit (ICU) admission with long-term outcome of critically ill patients.

Thus, we performed a retrospective cohort study to clarify whether there is an association between admission TyG index and long-term outcomes in critically ill patients.

Materials and methods

Participants

This was a retrospective cohort study using data from the MIMIC database, which is a large publicly available database consisting of patients in the ICU of Beth Israel Deaconess Medical Center between 2001 and 2012. The database was approved from the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates.

Adult patients of first hospital and ICU admission with complete triglycerides and glucose records were included, but patients staying at ICU for < 24 hours were excluded. The selection process was shown in **Figure 1**. Our study was approved by the Review Boards of Jiangsu Province Official Hospital (201921A011).

Variables

We used PostgreSQL 13 to extract data from the database. The baseline characteristics within the first 24 hours after ICU admission included the following: age, gender, ethnicity, weight, severity measured by Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II) score, laboratory examination including white blood cell (WBC), platelet, potassium, sodium, triglycerides, and glucose, treatment including albumin infusion, mechanical ventilation, administration of vasopressors, and dialysis, comorbidities including coronary artery disease (CAD), hypertension (HBP), diabetes (DM) and chronic obstructive pulmonary disease (COPD), as well as the length of stay (LOS) in hospital and in ICU.

Outcomes

The primary exposure was the triglycerides and glucose (TyG) index, defined as ln (triglycerides*glucose/2). The outcomes of the present study were in-hospital mortality, 30-day

mortality and 360-day mortality.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables are shown as number (proportions). One way analysis of variance and the $\chi 2$ tests were used to compare the difference among groups. The Kaplan-Meier analysis was used to explore the association between TyG quartile and 30-day mortality and 360-day mortality. Multivariate modeling of the association between TyG index (as continuous and categorical variables) and 360-day mortality was performed with Cox regression. Baseline variables that were considered clinically relevant or associated with the TyG index ($P<0.05$) were entered into a multivariate Cox regression model, while all baseline variables were entered into a stepwise model. Subgroup analyses according to gender, age and mechanical ventilation were performed. All statistical analysis was performed by R software version 3.6.

Patient and Public Involvement

No patient involved.

Results

The present study included 3902 patients admitted into ICU. The baseline characteristics of the study population according to TyG quartile were shown in the **Table 1**. Participants with a higher TyG index tended to have a higher weight, WBC, platelet and more percentage of DM and mechanical ventilation, as well as longer LOS in hospital and LOS in hospital **(Figure 2A&B).** In addition (**Figure 3A**), there was less 360-day mortality (P=0.002) in a higher TyG group while no difference was observed in in-hospital mortality (P=0.866), and 30-day mortality (P=0.244).

Table 1. Baseline characteristics across the quartile of TyG index.

Variables	Q1 (n=963)	Q2 (n=987)	Q3 (n=969)	Q4 (n=983)	P
Age, years	66.84 (15.61)	64.63 (15.04)	62.82 (15.96)	58.22 (15.77)	<0.001
Female, %	400 (41.5)	441 (44.7)	395 (40.8)	387 (39.4)	0.105
Ethnicity, %					0.073
White	738 (76.6)	737 (74.7)	700 (72.2)	722 (73.4)	
Asian	30 (3.1)	18 (1.8)	19 (2.0)	17 (1.7)	
Black	6 (0.6)	5 (0.5)	3 (0.3)	2 (0.2)	
Hispanic	25 (2.6)	31 (3.1)	28 (2.9)	37 (3.8)	
Other	164 (17.0)	196 (19.9)	219 (22.6)	205 (20.9)	
Weight, kg	76.8 (21.6)	80.9 (23.1)	84.2 (24.5)	90.9 (29.3)	<0.001
CAD, %	321 (33.3)	334 (33.8)	324 (33.4)	299 (30.4)	0.345
HBP, %	402 (41.7)	455 (46.1)	429 (44.3)	431 (43.8)	0.285
DM, %	206 (21.4)	242 (24.5)	297 (30.7)	418 (42.5)	<0.001
COPD, %	16 (1.7)	15 (1.5)	16 (1.7)	15 (1.5)	0.99
SOFA score	3 [2, 6]	3 [1, 6]	4 [2, 6]	4 [2, 7]	<0.001
SAPS II score	35 [27, 45]	34[25,45.5]	34 [26, 44]	34 [25, 46]	0.7
WBC, 10^9/L	10.94 (6.14)	11.76 (5.59)	11.86 (6.54)	12.72 (9.96)	<0.001
Platelet, 10^9/L	219.4 (117.0)	238.0 (128.8)	240.9 (134.5)	245.3 (157.8)	<0.001
Potassium, mmol/L	4.02 (0.70)	4.03 (0.53)	4.04 (0.56)	4.04 (0.54)	0.937
Sodium, mmol/L	138.8 (4.90)	139.18 (4.52)	139.41 (4.70)	139.16 (5.05)	0.075
Triglycerides, mg/dL	68.0 (22.2)	107.6 (28.7)	152.5 (49.6)	337.1 (330.9)	<0.001
Glucose, mg/dL	106.8 (26.2)	122.8 (30.5)	138.2 (43.7)	176.8 (87.3)	<0.001
Albumin, g	38.2 (26.5)	39.5 (24.3)	43.9 (32.9)	42.1 (23.5)	0.750
Mechanical Ventilation, %	381 (39.6)	439 (44.5)	500 (51.6)	582 (59.2)	<0.001
Vasopressors, %	28 (2.9)	28 (2.8)	32 (3.3)	28 (2.8)	0.92

Dialysis, %	87 (9.0)	85 (8.6)	74 (7.6)	111 (11.3)	0.037
LOS in Hospital, day	8.2 [4.8, 18.1]	9.0 [4.7, 17.0]	10.6 [5.0, 20.1]	12.0 [5.6, 22.8]	<0.001
LOS in ICU, day	3.4 [2.0, 8.9]	4.2 [2.0, 10.0]	4.8 [2.1, 12.0]	6.1 [2.4, 13.4]	<0.001
In-hospital mortality, %	152 (15.8)	143 (14.5)	147 (15.2)	145 (14.8)	0.866
30-day mortality, %	149 (15.5)	167 (16.9)	140 (14.4)	136 (13.8)	0.244
360-day mortality, %	301 (31.3)	280 (28.4)	286 (29.5)	234 (23.8)	0.002

Q1: TyG<8.51, Q2: 8.51≤TyG<8.95, Q3: 8.95≤TyG<9.44, Q4: TyG≥9.44. CAD, coronary artery diseases; HBP, hypertension; DM, diabetes mellites; COPD, chronic obstructive pulmonary diseases; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; WBC, white blood cell; LOS, length of stay.

The Kaplan-Meier analysis was performed to explore the prognostic effect of TyG index on 30-day or 360-day mortality (**Figure 3B&C**). As shown, a higher TyG index was associated with a higher risk of 360-day mortality (P for log-rank=0.006).

As shown in **Table 2**, we constructed three models for analyzing the prognostic role of TyG index in 360-day mortality. When compared with the lowest quartile, the highest quartile of TyG decreased the risk of mortality (HR 0.79, 95% CI [0.66, 0.95]; P=0.011) in the multivariable-adjusted model. The stepwise model also showed the same trend (HR 0.71, 95%CI [0.59, 0.85]; P<0.001). Per 1-unit increasement of TyG was associated with 0.85-fold lower risk of mortality (HR 0.85, 95% CI [0.79, 0.92]; P<0.001).

Table 2. Multivariable Cox regression analyzing TyG index and 360-day mortality.

	Cases	N	Unadjusted		Adjusted#		Stepwise*	
			HR	P	HR	P	HR	P
Q1	301	963	Ref	-				
Q2	280	987	0.91 [0.77, 1.07]	0.259	0.97 [0.82, 1.14]	0.717	0.95 [0.81, 1.12]	0.548
Q3	286	969	0.93 [0.79, 1.10]	0.412	1.04 [0.88, 1.23]	0.633	0.98 [0.83, 1.16]	0.857
Q4	234	983	0.74 [0.63, 0.88]	0.001	0.79 [0.66, 0.95]	0.011	0.71 [0.59, 0.85]	<0.001
Continuous	1101	3902	0.89 [0.82, 0.96]	0.003	0.93 [0.86, 1.00]	0.063	0.85 [0.79, 0.92]	<0.001

Adjusted for age, gender, ethnicity, weight, CAD, COPD, HBP, DM, SOFA score, SAPSII score, WBC, platelet, creatine, ventilation, vasopressors, and dialysis.

*All variables except for outcomes were entered.

Subgroup analysis (**Table 3**) showed that an interaction was observed between TyG index and gender (P=0.03). In male patients, TyG was negative associated with 360-day mortality (HR 0.86, 95% CI [0.78,0.95]; P=0.004) while the association was reversed in female subgroup (HR 1.03, 95% CI [0.91,1.16]; P=0.681).

Table 3. Subgroup analysis of TyG index and 360-day mortality.

	HR	P for trend	P for interaction
Gender			0.03
female	1.03 [0.91, 1.16]	0.681	
male	0.86 [0.78, 0.95]	0.004	
Age			0.13
≤65	0.83 [0.73, 0.94]	0.003	
>65	0.96 [0.87, 1.07]	0.472	
Ventilation			0.357
No	1.01 [0.87, 1.17]	0.868	
Yes	0.91 [0.83, 1.00]	0.057	

Discussion

This is the first study to evaluate the association of the TyG index with long-term mortality in critically ill patients. We found that TyG index was negatively associated with 360-day mortality, not in-hospital or 30-day mortality of critically ill patients.

The TyG index has been well-recognized as a simple and reliable surrogated of IR [8]. It does not require levels of insulin and may be applicable to all of the patients and healthy population. Several studies reported that TyG index predicted outcomes in patients with acute coronary syndrome [9] and ischemic stroke [10]. Only one study found that TyG index was linearly associated with short-term mortality in ICU stroke after adjusting for confounding factors [7]. However, we did not find a positive

correlation between TyG index and in-hospital and 30-day mortality. Contrary, we demonstrated that TyG could be a protective predictor in long-term mortality in critically ill patients. The difference could be that we included more diseases in ICU and followed a longer time.

The mechanism underlying the relationship between the TyG index and critically illness is not fully elucidated. Insulin resistance is an adaptive mechanism that prioritizes utilization of energy for immune response in the presence of infection or injury[11]. However, the underlying molecular mechanisms involved in this association should be further investigated in the future study.

Our study still has some limitations. First, this was a retrospective analysis derived from an observational study, which could not definitively establish causality. Second, we did not measure HOMA-IR because the examination of insulin levels is not included. Third, we only included the baseline levels of plasma glucose and triglyceride, which could be affected by the use of antidiabetic and lipid-lowering drugs. Therefore, it is unknown whether the change in the TyG index could have predicted the mortality.

Conclusions

We found that TyG index was negatively associated with 360-day mortality, which could be a protective predictor in the long-term outcome in critically ill patients.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Institutional Review Board of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates and no new data was added. All methods were carried out in accordance with Helsinki regulations. The need for informed

consent was waived off by the Institutional Review Board of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates. Our study was approved by the Review Boards of Jiangsu Province Official Hospital (201921A011).

Consent for publication

Yes

Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Competing interests

The authors have nothing to disclose regarding conflict of interest with respect to this manuscript.

Funding

None.

Authors' contributions

D LL and Y Y made the statistical analysis; W KL and H CN wrote the original manuscript; S S and W D designed the study. All authors approved it.

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None.

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Figure legends

Figure 1. The flow diagram of study population.

Figure 2. The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.

Figure 3. The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day mortality (B), and 360-day mortality (C).

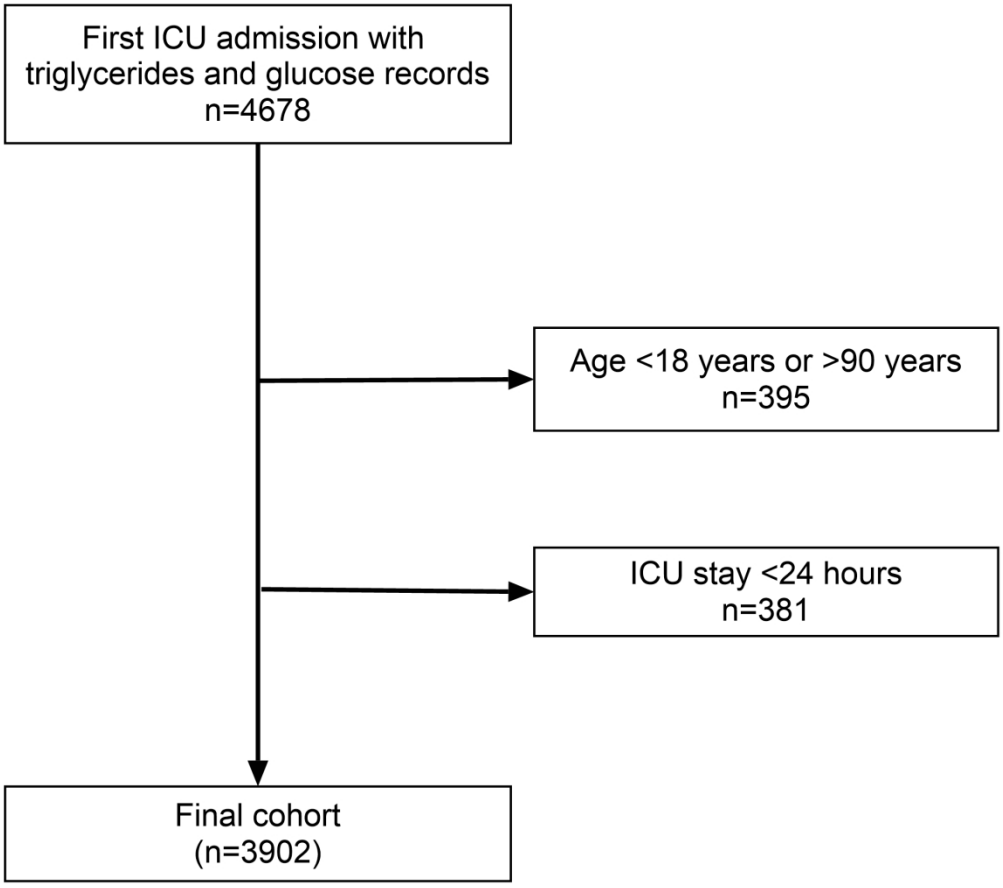

Figure 1. The flow diagram of study population.

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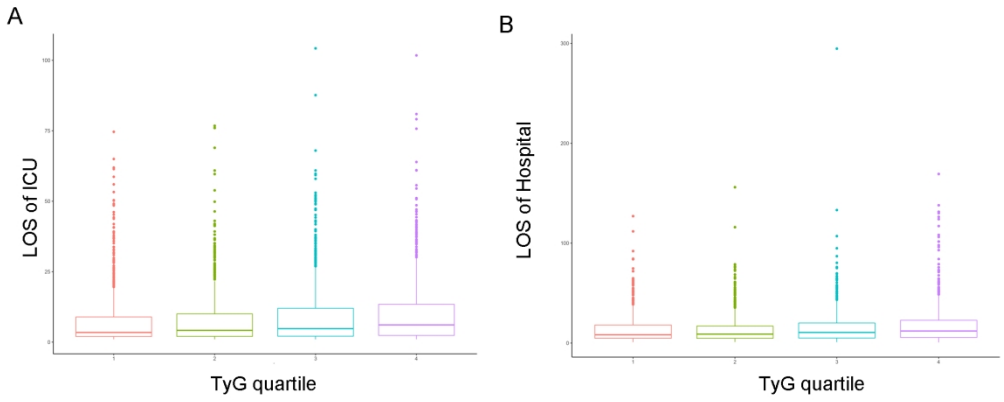

Figure 2. The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.

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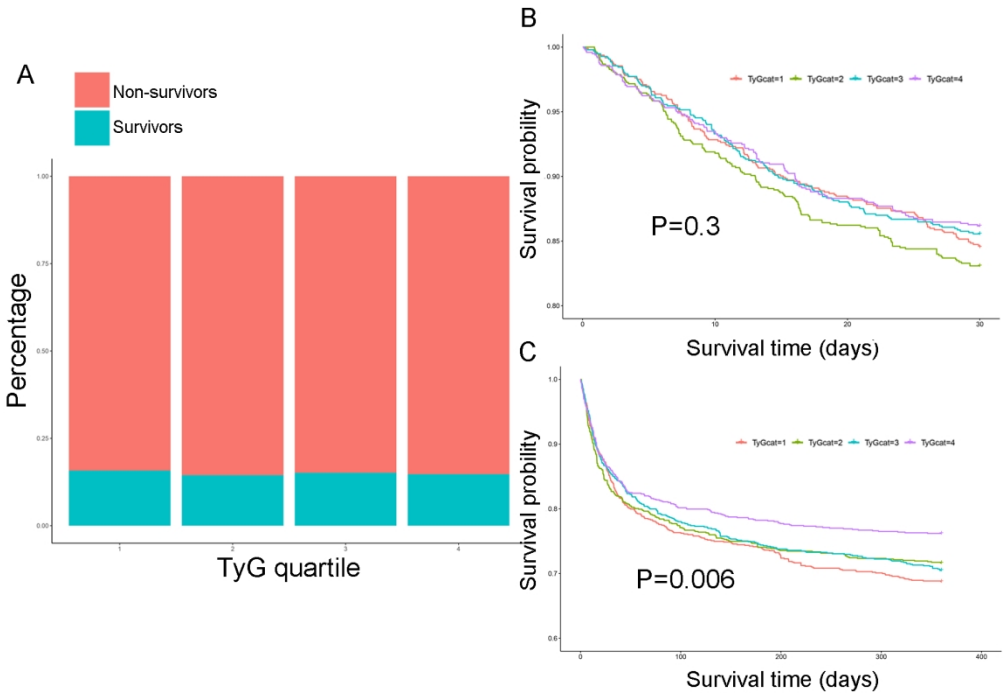

Figure 3. The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day mortality (B), P <0.05: Q2 vs. Q1, Q2 vs. Q3, Q2 vs. Q4; and 360-day mortality (C), P<0.05: Q1 vs. Q2, Q1 vs. Q3, Q1 vs. Q4, Q2 vs. Q4, Q3 vs. Q4.

160x115mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	5

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*6*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Association between TyG index and long-term mortality of critically ill patients: a retrospective study based on the MIMIC database

Lingli Dai[1], Yun Yu[1], Kunlin Wang[1], Cuining Hu[1], Dan Wu[1], Shan Shan[1]*

1.Department of Endocrinology and Metabolism, Jiangsu Province Official Hospital, Geriatric Hospital of Nanjing Medical University,210000 Nanjing, China.

*Corresponding to
Shan Shan, Department of Endocrinology and Metabolism, Jiangsu Province Official Hospital, Geriatric Hospital of Nanjing Medical University,210000 Nanjing, China. E-mail: shanshan@lista.cc

Abstract

Objective To evaluate the association of triglycerides glucose (TyG) index on admission with outcomes of critically ill patients.

Design A retrospective study.

Setting A population-based cohort study of Medical Information Mart for Intensive Care III database (MIMIC III).

Participants: All intensive care unit (ICU) admissions were extracted from MIMIC III.

Main outcome measures The TyG index was calculated as ln [triglycerides (mg/dL) *glucose (mg/dL)/2]. The primary endpoint was 360-day mortality.

Results A total of 3902 patients with an average age of 63.1±15.9 years old were enrolled, including 1623 (41.6%) females. The 360-day mortality was lower in a higher TyG group. Compared with the lowest TyG group, the hazards ratio of 360-day mortality was 0.79 (95% confidence interval [0.66, 0.95]; p=0.011) in the fully adjusted Cox model and 0.71 ([0.59, 0.85]; p<0.001) in the stepwise Cox model. In the subgroup analysis, an interaction effect was detected between TyG index and gender.

Conclusions A lower TyG index was associated with the risk of 360-day mortality in critically ill patients, which could be a predictor of long-term survival of critically ill patients.

Keywords: TyG index; mortality; ICU; critically illness; cohort study

Strengths and limitations of this study

To the best of our knowledge, this is the first study assessing the association between TyG index and long-term mortality of critically ill patients.

This was a retrospective analysis, which could not definitively establish causality.

We only included the baseline levels of plasma glucose and triglyceride, which could be affected by the use of antidiabetic and lipid-lowering drugs.

Introduction

The triglyceride glucose (TyG) index is calculated using fasting triglyceride and fasting glucose measurements. It has been suggested as a surrogate marker of insulin resistance (IR)[1, 2] and has been found associated to bladder cancer that is widespread among men[3]. Critical illness is characterized by a hypermetabolic state associated with increased mortality due to enhanced IR[4, 5].

Several studies have examined the associations between IR and mortality in critically ill patients. Nathan found that IR was a predictor for mortality in traumatic brain injury[6] and increased the mortality of surgical care population[7]. Recently, a study concluded that the TyG index was a potential predictor for hospital and ICU mortality in critically ill stroke patients[8]. To the best of our knowledge, there is no research to evaluate the association of TyG index on intensive care unit (ICU) admission with long-term outcomes of critically ill patients.

Thus, we performed a retrospective cohort study to clarify whether there is an association between TyG index and long-term outcomes in critically ill patients.

Materials and methods

Participants

This was a retrospective cohort study using data from the MIMIC database, which is a large publicly available database consisting of patients in the ICU of Beth Israel Deaconess Medical Center between 2001 and 2012. The database was approved from the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates.

Adult patients of first hospital and ICU admission with complete triglycerides and glucose records were included, but patients staying at ICU for < 24 hours were excluded. The selection process was shown in **Figure 1**. Our study was approved by the Review Boards of Jiangsu Province Official Hospital (201921A011).

Variables

We used PostgreSQL 13 to extract data from the database. The baseline characteristics within the first 24 hours after ICU admission included the following: age, gender, ethnicity, weight, severity measured by Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II) score, laboratory examination including white blood cell (WBC), platelet, potassium, sodium, triglycerides, and glucose, treatment including albumin infusion, mechanical ventilation, administration of vasopressors, and dialysis, comorbidities including coronary artery disease (CAD), hypertension (HBP), diabetes (DM), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) as well as the length of stay (LOS) in hospital and in ICU.

Outcomes

The primary exposure was the triglycerides and glucose (TyG) index, defined as In

(triglycerides*glucose/2). The outcomes of the present study were in-hospital mortality, 30-day mortality and 360-day mortality.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables are shown as number (proportions). One way analysis of variance and the $\chi 2$ tests were used to compare the difference among groups. The Kaplan-Meier analysis was used to explore the association between TyG quartile and 30-day mortality and 360-day mortality. Multivariate modeling of the association between TyG index (as continuous and categorical variables) and 360-day mortality was performed with Cox regression. Baseline variables that were considered clinically relevant or associated with the TyG index ($P<0.05$) were entered into a multivariate Cox regression model, while all baseline variables were entered into a stepwise model. Subgroup analyses according to gender, age and mechanical ventilation were performed. All statistical analysis was performed by R software version 3.6.

Patient and public involvement

Patients and the public were not directly involved in the design or implementation of this study, since we used previously collected data.

Results

The present study included 3902 patients admitted into ICU. The baseline characteristics of the study population according to TyG quartile were shown in the **Table 1**. Participants with a higher TyG index tended to have a higher weight, WBC, platelet and more percentage of DM and mechanical ventilation, as well as longer LOS in ICU and LOS in hospital **(Figure 2A&B).** In addition (**Figure 3A**), there was less 360-day mortality (P=0.002) in a higher TyG group while no difference was observed in in-hospital mortality (P=0.866), and 30-day mortality (P=0.244).

The Kaplan-Meier analysis was performed to explore the prognostic effect of TyG index on 30-day or 360-day mortality (**Figure 3B&C**). As shown, a higher TyG index was associated with a lower risk of 360-day mortality (P for log-rank=0.006).

As shown in **Table 2**, we constructed three models for analyzing the prognostic role of TyG index in 360-day mortality. When compared with the lowest quartile, the highest quartile of TyG decreased the risk of mortality (HR 0.79, 95% CI [0.66, 0.95]; P=0.011) in the multivariable-adjusted model. The stepwise model also showed the same trend (HR 0.71, 95%CI [0.59, 0.85]; P<0.001). Per one-unit increasement of TyG was associated with 0.85-fold lower risk of mortality (HR 0.85, 95% CI [0.79, 0.92]; P<0.001).

Subgroup analysis (**Table 3**) showed that an interaction was observed between TyG index and gender (P=0.03). In male patients, TyG was negative associated with 360-day mortality (HR 0.86, 95% CI [0.78,0.95]; P=0.004) while the association was reversed in female subgroup (HR 1.03, 95% CI [0.91,1.16]; P=0.681).

Discussion

This is the first study to evaluate the association of the TyG index with long-term mortality in critically ill patients. We found that TyG index was negatively associated with 360-day mortality, not in-hospital or 30-day mortality of critically ill patients.

The TyG index has been well-recognized as a simple and reliable surrogate of IR [9]. It does not require levels of insulin and may be applicable to all of the patients and healthy population. Several studies reported that TyG index predicted outcomes in patients with acute coronary syndrome [10] and ischemic stroke [11]. Only one study found that TyG index was linearly associated with short-term mortality in ICU stroke after adjusting for confounding factors [8]. However, we did not find a positive correlation between TyG index and in-hospital and 30-day mortality. Contrary, we demonstrated that TyG could be a protective predictor in long-term mortality in critically ill patients. The difference could be that we included more diseases in ICU and followed a longer time. Besides, a higher TyG index may be related to a good nutrition status and be compensatory for the development of various diseases.

The mechanism underlying the relationship between the TyG index and critically illness is not fully elucidated. Insulin resistance is an adaptive mechanism that prioritizes utilization of energy for immune response in the presence of infection or injury[12]. However, the underlying molecular mechanisms involved in this association should be further investigated in the future study.

Our study still has some limitations. First, this was a retrospective analysis derived from an observational study, which could not definitively establish causality. Secondly, we only included the baseline levels of plasma glucose and triglyceride, which could be affected by the use of antidiabetic and lipid-lowering drugs. Therefore, it is unknown whether the change of the TyG index

could predict the mortality.

Conclusions

We found that TyG index predicted a better long-term prognosis of critically ill patients, regardless of other risk factors. However, no association was observed in respect to in-hospital or 30-day mortality.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Institutional Review Board of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates and no new data was added. All methods were carried out in accordance with Helsinki regulations. The need for informed consent was waived off by the Institutional Review Board of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates. Our study was approved by the Review Boards of Jiangsu Province Official Hospital (201921A011).

Consent for publication

Yes.

Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Competing interests

The authors have nothing to disclose regarding conflict of interest with respect to this manuscript.

Funding

None.

Authors' contributions

D LL and Y Y made the statistical analysis; W KL and H CN wrote the original manuscript; S S and W D designed the study. All authors approved it.

Acknowledgements

None.

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Table 1. Baseline characteristics across the quartile of TyG index.

Variables	Q1 (n=963)	Q2 (n=987)	Q3 (n=969)	Q4 (n=983)	P
Age, years	66.84 (15.61)	64.63 (15.04)	62.82 (15.96)	58.22 (15.77)	<0.001
Female, %	400 (41.5)	441 (44.7)	395 (40.8)	387 (39.4)	0.105
Ethnicity, %					0.073
White	738 (76.6)	737 (74.7)	700 (72.2)	722 (73.4)	
Asian	30 (3.1)	18 (1.8)	19 (2.0)	17 (1.7)	
Black	6 (0.6)	5 (0.5)	3 (0.3)	2 (0.2)	
Hispanic	25 (2.6)	31 (3.1)	28 (2.9)	37 (3.8)	
Other	164 (17.0)	196 (19.9)	219 (22.6)	205 (20.9)	
Weight, kg	76.8 (21.6)	80.9 (23.1)	84.2 (24.5)	90.9 (29.3)	<0.001
CAD, %	321 (33.3)	334 (33.8)	324 (33.4)	299 (30.4)	0.345
HBP, %	402 (41.7)	455 (46.1)	429 (44.3)	431 (43.8)	0.285
DM, %	206 (21.4)	242 (24.5)	297 (30.7)	418 (42.5)	<0.001
COPD, %	16 (1.7)	15 (1.5)	16 (1.7)	15 (1.5)	0.99
CKD, %	36 (3.7)	35 (3.5)	40 (4.1)	45 (4.6)	0.689
SOFA score	3 [2, 6]	3 [1, 6]	4 [2, 6]	4 [2, 7]	<0.001
SAPS II score	35 [27, 45]	34[25,45.5]	34 [26, 44]	34 [25, 46]	0.7
WBC, 10^9/L	10.94 (6.14)	11.76 (5.59)	11.86 (6.54)	12.72 (9.96)	<0.001
Platelet, 10^9/L	219.4 (117.0)	238.0 (128.8)	240.9 (134.5)	245.3 (157.8)	<0.001
Potassium, mmol/L	4.02 (0.70)	4.03 (0.53)	4.04 (0.56)	4.04 (0.54)	0.937
Sodium, mmol/L	138.8 (4.90)	139.18 (4.52)	139.41 (4.70)	139.16 (5.05)	0.075
Triglycerides, mg/dL	68.0 (22.2)	107.6 (28.7)	152.5 (49.6)	337.1 (330.9)	<0.001
Glucose, mg/dL	106.8 (26.2)	122.8 (30.5)	138.2 (43.7)	176.8 (87.3)	<0.001
Albumin, g	38.2 (26.5)	39.5 (24.3)	43.9 (32.9)	42.1 (23.5)	0.750
Mechanical Ventilation, %	381 (39.6)	439 (44.5)	500 (51.6)	582 (59.2)	<0.001
Vasopressors, %	28 (2.9)	28 (2.8)	32 (3.3)	28 (2.8)	0.92
Dialysis, %	87 (9.0)	85 (8.6)	74 (7.6)	111 (11.3)	0.037
LOS in Hospital, day	8.2 [4.8, 18.1]	9.0 [4.7, 17.0]	10.6 [5.0, 20.1]	12.0 [5.6, 22.8]	<0.001
LOS in ICU, day	3.4 [2.0, 8.9]	4.2 [2.0, 10.0]	4.8 [2.1, 12.0]	6.1 [2.4, 13.4]	<0.001
In-hospital mortality, %	152 (15.8)	143 (14.5)	147 (15.2)	145 (14.8)	0.866
30-day mortality, %	149 (15.5)	167 (16.9)	140 (14.4)	136 (13.8)	0.244
360-day mortality, %	301 (31.3)	280 (28.4)	286 (29.5)	234 (23.8)	0.002

Q1: TyG<8.51, Q2: 8.51≤TyG<8.95, Q3: 8.95≤TyG<9.44, Q4: TyG≥9.44. CAD, coronary artery diseases; HBP, hypertension; DM, diabetes mellites; COPD, chronic obstructive pulmonary diseases; CKD, chronic kidney disease; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; WBC, white blood cell; LOS, length of stay.

Table 2. Multivariable Cox regression analyzing TyG index and 360-day mortality.

	Cases	N	Unadjusted		Adjusted[#]		Stepwise*	
			HR	P	HR	P	HR	P
Q1	301	963	Ref	-				
Q2	280	987	0.91 [0.77, 1.07]	0.259	0.97 [0.82, 1.14]	0.717	0.95 [0.81, 1.12]	0.548
Q3	286	969	0.93 [0.79, 1.10]	0.412	1.04 [0.88, 1.23]	0.633	0.98 [0.83, 1.16]	0.857
Q4	234	983	0.74 [0.63, 0.88]	0.001	0.79 [0.66, 0.95]	0.011	0.71 [0.59, 0.85]	<0.001
Continuous	1101	3902	0.89 [0.82, 0.96]	0.003	0.93 [0.86, 1.00]	0.063	0.85 [0.79, 0.92]	<0.001

Adjusted for age, gender, ethnicity, weight, CAD, COPD, HBP, DM, SOFA score, SAPSII score, WBC, platelet, creatine, ventilation, vasopressors, and dialysis.

*All variables except for outcomes were entered.

Table 3. Subgroup analysis of TyG index and 360-day mortality.

	HR	P for trend	P for interaction
Gender			0.03
female	1.03 [0.91, 1.16]	0.681	
male	0.86 [0.78, 0.95]	0.004	
Age			0.13
≤65	0.83 [0.73, 0.94]	0.003	
>65	0.96 [0.87, 1.07]	0.472	
Ventilation			0.357
No	1.01 [0.87, 1.17]	0.868	
Yes	0.91 [0.83, 1.00]	0.057	

Figure legends

Figure 1. The flow diagram of study population.

Figure 2. The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.

Figure 3. The in-hospital mortality between TyG groups (A). The Kaplan-Meier analysis of 30-day mortality (B), P <0.05: Q2 vs. Q1, Q2 vs. Q3, Q2 vs. Q4; and 360-day mortality (C), P<0.05: Q1 vs. Q2, Q1 vs. Q3, Q1 vs. Q4, Q2 vs. Q4, Q3 vs. Q4.

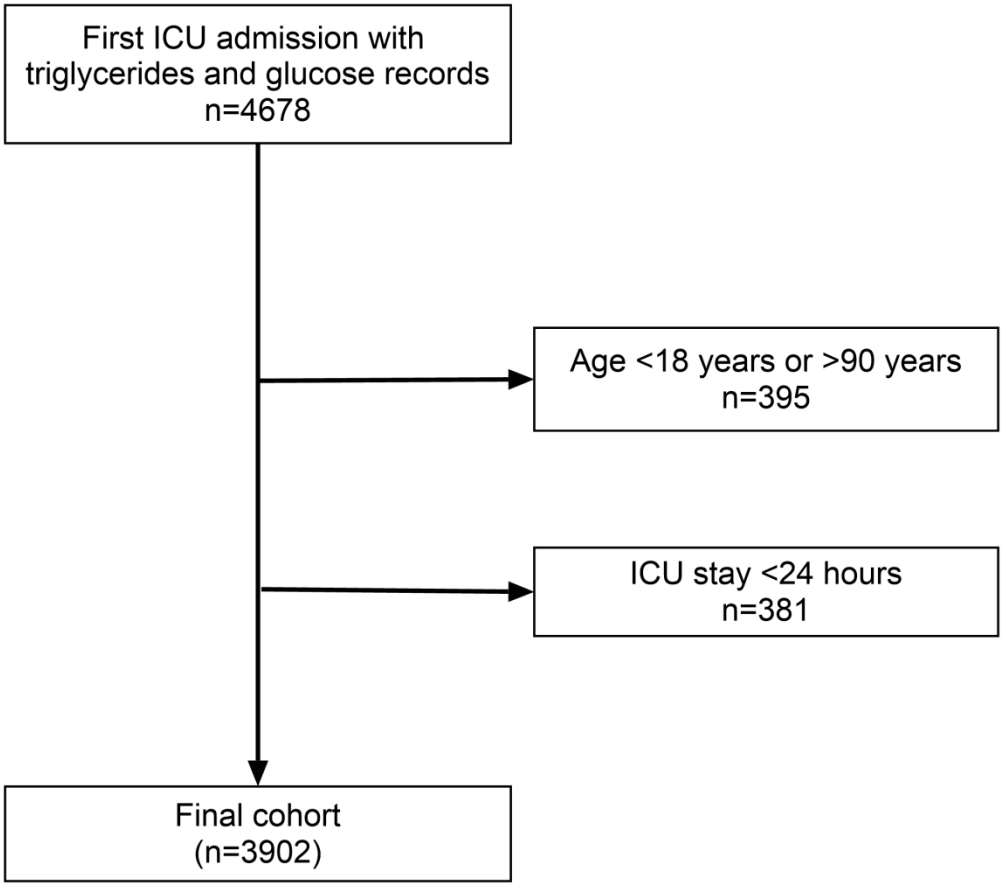


Figure 1. The flow diagram of study population.

277x244mm (192 x 192 DPI)

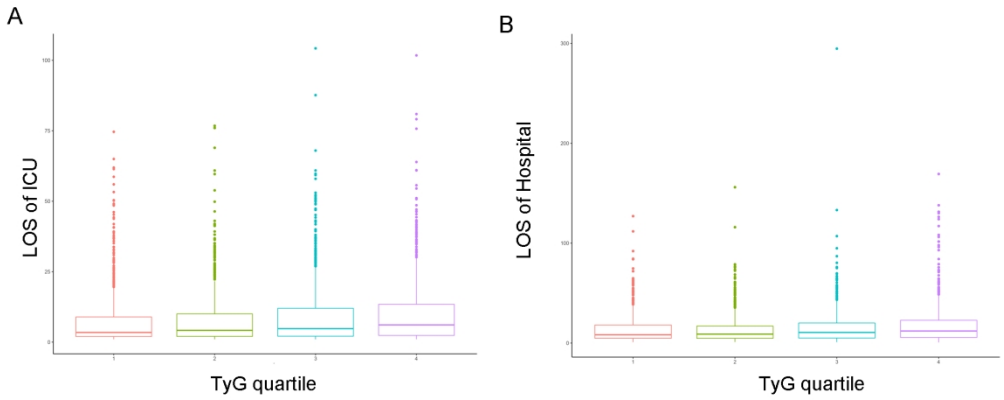
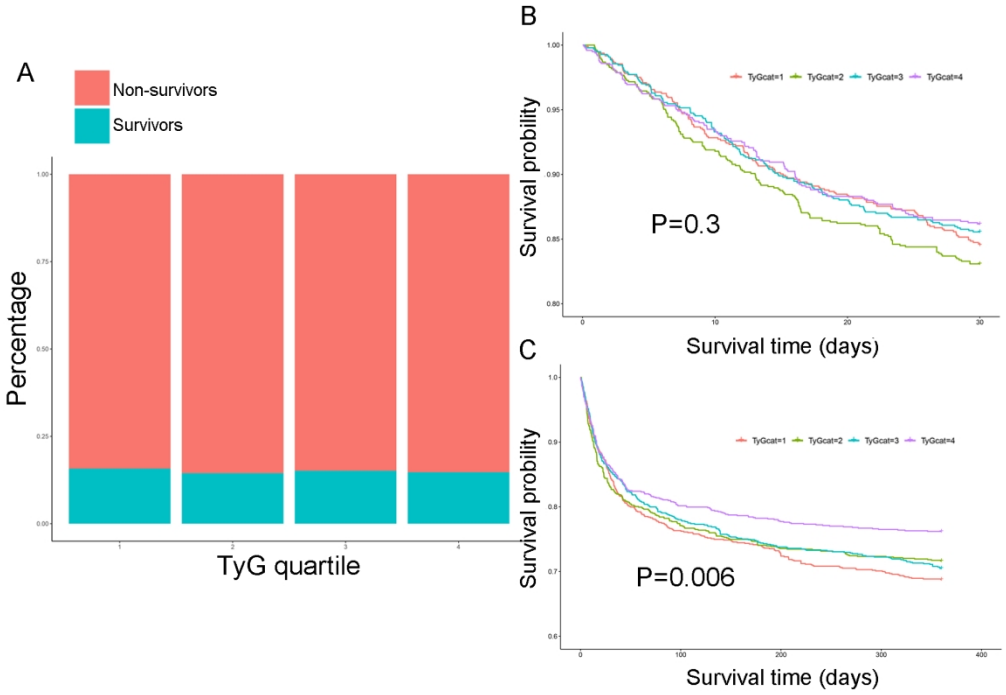


Figure 2. The LOS of ICU (A) and LOS (B) of hospital across TyG quartiles. LOS, los of stay.

180x76mm (300 x 300 DPI)



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160x115mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5
		(*e*) Describe any sensitivity analyses	5

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*6*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.