Research Article

Triglyceride Glucose Index Predicting Cardiovascular Mortality in Chinese Initiating Peritoneal Dialysis: A Cohort Study

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Keywords

Triglyceride glucose index · Cardiovascular diseases · Mortality · Peritoneal dialysis · Prognostic factor

Abstract

Background: Insulin resistance (IR) is increased among people with end-stage renal disease (ESRD). The Triglyceride glucose (TyG) index is a marker of IR and is also associated with the prognosis of cardiovascular disease among patients initiating peritoneal dialysis (PD). This study was aimed at examining the associations between TyG index and cardiovascular deaths in patients initiating PD. **Methods and Results:** Three thousand fifty-four patients initiating PD between 2007 and 2014 were included in a prospective cohort derived from Henan PD Registry, TyG index alongside other baseline characteristics were measured when ESRD patients initiated PD. Logistic regression adjusting for age, gender, and major cardiovascular risk factors estimated the association between TyG index and subsequent cardiovascular mortality within 2 years since the initiation of PD. **Results:** TyG index was positively associated with cardiovascular mortality: adjusted incidence rates ratio (95% CI) comparing the highest vs. lowest TyG index quartile was 2.32 (2.12–2.55) in all, 2.22 (2.01–2.46) in those with body mass index (BMI) <25 kg/m², and 2.82 (2.24–3.54) in those with BMI ≥25 kg/m², respectively. Linear dose-response relationships were revealed in all and by BMI. **Conclusions:** TyG index might be a prognostic factor in predicting cardiovascular mortality among patients initiating PD.

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Published by S. Karger AG, Basel

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Introduction

Chronic kidney disease (CKD) has become a worldwide health problem [1]. In particular, end-stage renal disease (ESRD) triggers premature mortality and is a substantial health economic burden [1]. It has been estimated that >10.8% of Chinese adults (around 130 million) have CKD with dialysis needed at some point in their lives [2]. The Chinese medical insurance scheme has now increased its coverage, making dialysis, especially peritoneal dialysis (PD), more affordable among Chinese patients with ESRD [3].

Cardiovascular disease (CVD) is the main cause of death in PD patients [4], a situation that can be explained by a combination of traditional and non-traditional risk factors for CVD in these patients [5, 6]. Glucose and insulin homeostasis are altered in CKD patients even in the early stages of CKD, leading to insulin resistance (IR) by various pathways [7]. Several factors have been implicated in the pathogenesis of IR, including anemia, dyslipidemia, uremia, malnutrition, excess of parathyroid hormone, vitamin D deficiency, metabolic acidosis, and increase in plasma-free fatty acids and proinflammatory cytokines [8]. IR and dyslipidemia are observed and found to increase with the progression of CKD, playing an important role in the pathogenesis of hypertension and atherosclerosis [9]. Particularly in PD patients, exposure to glucose from dialysis fluid accentuates the foregoing metabolic abnormalities. IR and altered glucose metabolism are frequently observed in CKD, and perhaps alter PD patient survival [10].

IR is a pivotal component in the pathophysiology of Type 2 diabetes mellitus and has often existed 10–20 years prior to the diagnosis [10–12]. However, measurement of IR is costly and complex [13]. Therefore, a simple, reliable, and reproducible index to measure IR is needed.

Many recent studies have shown that the triglyceride glucose (TyG) index is associated with IR [14–17], as assessed by hyperinsulinemic (euglycemic) clamp testing and HOMA IR. The clamp is a complex method and not used in clinical practice. Similarly, HOMA IR cannot be used routinely due to cost of insulin assays (if not on insulin therapy), and lack of proof validity among patients treated with insulin therapy. Thus, the TyG index has been proposed as a reliable and simple surrogate marker of IR in clinical practice [14–17].

Consistent with these data, there is growing evidence to suggest that the TyG index is associated with CVD [18–20]. However, to the best of our knowledge few studies have examined the relationship between the TyG index and deaths mainly due to CVD in incident PD patients. Therefore, in the present study, we investigated the relationship between the TyG index and cardiovascular mortality among patients initiating PD.

Methods

Data Source and Study Population

Data from the Henan PD Registry (HPDR) were used. A province in Central China, the population of Henan is over 100 million. The First Affiliated Hospital of Zhengzhou University Department of Nephrology manages the HPDR providing an independent audit and analysis of renal care in the province.

Over the study period, electronic information was routinely and prospectively collected from all nephrological units across Henan. Data reaching the HPDR are subjected to an algorithm which identifies suspicious records (e.g., body mass index [BMI] over 65 kg/m²), which are then further verified and corrected where necessary by contacting the nephrological unit (overall response rate 97.5%).

The present study was designed as a cohort study, which incorporated all incident PD patients aged >18 years who initiated PD between 2007 and 2014 and who had at least 2 years' follow-up. Patients who died, underwent transplant or whose kidney function recovered within 90 days after initiation of PD were dropped off (*n* = 16) to avoid a reverse causal association between exposures and outcome.

Ethics approval was granted by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants before inclusion.

Table 1. Baseline characteristics and their comparisons according to TyG index quartiles

	Quartile 1 (<8.10)	Quartile 2 (8.10–8.39)	Quartile 3 (8.39–8.69)	Quartile 4 (≥8.69)	p value
<i>Number</i>	766	760	766	762	–
Age, years	46 (35–56)	47 (37–56)	48 (39–61)	48 (39–60)	0.2356
Gender, male, n (%)	502 (65.5)	419 (55.1)	432 (56.4)	437 (57.3)	<0.001
Hemoglobin, g/L	88.7 (74.0–103.0)	93.0 (80.0–102.0)	95.0 (81.0–107.0)	94.0 (81.0–108.0)	<0.001
Packed cell volume	19.0 (1.7–28.0)	0.3 (0.2–25.1)	14.5 (0.3–28.5)	20.5 (0.3–30.1)	<0.001
Reticulocytes, %	34.0 (2.8–58.0)	58.0 (31.6–85.0)	49.5 (21.0–83.5)	55.0 (24.1–79.0)	<0.001
Phosphate, mg/dL	1.7 (1.4–2.1)	1.8 (1.4–2.1)	1.7 (1.4–2.0)	1.7 (1.4–2.1)	<0.001
Albumin, g/L	33.2 (29.5–36.5)	32.5 (30.1–36.8)	34.0 (30.2–37.0)	34.2 (30.9–38.7)	<0.001
Total iron binding capacity, μmol/L	42.2 (33.5–52.0)	52.0 (40.9–52.0)	52.0 (41.4–53.0)	47.1 (34.4–52.1)	<0.001
FeTIBC, mmol/L	26.0 (21.1–40.1)	23.1 (22.6–37.3)	23.1 (20.0–36.0)	23.1 (20.3–31.3)	<0.001
Estimated glomerular filtration rate, mL/min/1.73 m ²	1.6 (0.4–3.7)	1.5 (0.6–3.1)	1.4 (0.5–3.8)	1.5 (0.5–3.0)	<0.001
Transferrin, mg/dL	181.1 (75.1–36.5)	164.2 (106.0–258.0)	167.0 (100.4–308.3)	238.0 (154.0–405.4)	<0.001
Total protein, g/L	54.8 (50.4–60.1)	57.6 (52.2–60.4)	58.0 (53.6–62.3)	59.0 (54.5–64.4)	<0.001
Pre-albumin, mg/L	304.2 (221.0–350.0)	345.0 (246.0–409.0)	313.0 (250.0–406.0)	342.0 (257.0–395.0)	<0.001
Total cholesterol, mmol/L	3.9 (3.3–4.6)	4.3 (3.6–5.0)	4.5 (3.7–5.1)	4.9 (4.1–5.1)	<0.001
Triglyceride, mmol/L	0.8 (0.6–0.9)	1.0 (0.9–1.1)	1.1 (0.6–1.5)	1.8 (1.5–2.1)	<0.001
Low density lipoprotein, mmol/L	2.3 (1.3–2.8)	2.6 (2.0–3.1)	2.6 (2.0–3.2)	2.8 (2.1–3.4)	<0.001
High density lipoprotein, mmol/L	1.2 (1.0–1.4)	1.1 (1.0–1.3)	1.2 (1.0–1.3)	1.1 (0.9–1.3)	<0.001
Fasting glucose, mmol/L	4.2 (3.9–4.6)	4.6 (4.3–5.1)	4.9 (4.4–5.3)	5.0 (4.5–5.6)	<0.001
Sodium, mEq/L	141.0 (138.0–143.2)	141.0 (138.0–144.0)	140.3 (138.0–143.0)	140.0 (137.2–142.5)	<0.001
C-reactive protein, mg/dL	2.0 (1.0–6.1)	1.2 (0.6–2.8)	2.3 (1.0–5.8)	3.0 (1.3–5.2)	<0.001
BMI, kg/m ²	22.2 (20.6–24.1)	22.5 (20.8–24.6)	22.7 (20.8–25.1)	23.3 (21.1–25.2)	<0.001
Systolic blood pressure, mm Hg	140.0 (132.0–154.0)	142.0 (135.0–155.0)	145.0 (135.0–156.0)	145.0 (135.0–155.0)	<0.001
Diastolic blood pressure, mm Hg	89.0 (80.0–98.0)	86.0 (80.0–92.0)	85.0 (80.0–93.0)	85.0 (80.0–92.0)	<0.001
Cardiovascular diseases, n (%)	310 (40.5)	327 (43.0)	336 (43.9)	411 (53.9)	<0.001
Type 2 diabetes, n (%)	99 (12.9)	108 (14.2)	113 (14.8)	129 (16.9)	<0.001
Taking antihypertensive treatment, n (%)	333 (43.5)	320 (42.1)	315 (41.1)	289 (37.9)	<0.001
Taking antidiabetes agent, n (%)	96 (12.5)	105 (13.8)	108 (14.1)	120 (15.7)	<0.001
BMI, body mass index; TyG, triglyceride glucose.					

Outcome Definition

We defined our primary outcome as recorded death, on the HPDR, with clinically diagnosed CVD (including coronary heart disease, heart failure, myocardial infarction, arrhythmia or stroke) as the cause of death [6, 21].

Exposure Definition

TyG index was calculated as the $\ln$ (fasting triglyceride [mg/dL] $\times$ fasting glucose [mg/dL]/2) [14]. Patients were classified into 4 groups by quartiles of TyG index: Group 1 (TyG index <8.10), Group 2 (TyG index in 8.10–8.39); Group 3 (TyG index in 8.39–8.69), and Group 4 (TyG index $\geq$ 8.69).

Covariables and Missing Information

All available information, including demographic characteristics, self-reported comorbidities, and clinical measurements at the time of patients initializing the PD were evaluated [6]. For covariables, our cohort had missing information on BMI (13.51%), phosphorus (20.92%), albumin (19.92%), total protein (22.57%), total cholesterol (24.25%), low density lipoprotein (24.58%), fasting glucose (15.92%), sodium (8.02%), systolic blood pressure (4.82%), and diastolic blood pressure (4.82%). We used multiple imputation to replace missing values by using a chained equation approach based on all candidate predictors. We created 30 imputed datasets for missing variables that were then combined across all datasets by using Rubin's rule to obtain the final estimates.

Statistical Analysis

In descriptive analyses, differences in participant characteristics by TyG index categories were assessed by logistic regression model for categorical variables and generalized linear model for continuous variables.

Logistic regression was used to estimate crude and adjusted incidence rate ratios (IRRs) of cardiovascular mortality by TyG index categories, with adjustment of covariables (including clinical measurements, comorbidities, and treatments) presented in Table 1. The dose-response relationships between TyG index and risks of cardiovascular mortality were estimated using a linear model, a natural cubic spline model with 3 equally spaced knots determined from the levels of TyG index measures, and a quadratic spline model. The natural cubic spline model was chosen as the best-fit model for the relationship curve by its minimum Akaike information criterion compared with the linear model or quadratic spline model. The linear test was used in the natural cubic spline model to test the linearity of the relationship. The break-point test [11] was carried out to target the potential thresholds (P_5 to P_{95} of TyG index measures) by incorporating the piecewise term into the cubic spline model. The threshold with a significant break in the regression coefficients and achieving the minimum Akaike information criterion was chosen as the final threshold [22]. The 95% CI of the threshold was obtained from 1,000 bootstrap samples.

As the most important confounder, the role of the BMI in the association between TyG index and risks of cardiovascular mortality was examined by categorical analysis.

All analyses were performed using STATA (STATA/MP 15.0 StataCorp, College Station, TX, USA). All *p* values were calculated using two-tailed tests and a *p* value <0.05 was considered to be statistically significant.

Results

Table 1 shows patient characteristics among patients with initiated PD by TyG index levels. Compared with those with a low level of TyG index (TyG index <8.10), patients with high levels of TyG index were more likely to be female, have existing CVD and/or type 2 diabetes, taking an antidiabetes agent, and be less likely to be taking antihypertensive treatment. Patients with high levels of TyG index were also more likely to have higher levels of hemoglobin, packed cell volume, reticulocytes, phosphate, albumin, total iron binding capacity, transferrin, total protein, pre-albumin, total cholesterol, low density lipoprotein, fasting glucose, C-reaction protein, systolic blood pressure and BMI, and a lower level of FeTIBC, estimated glomerular filtration rate, sodium, high density lipoprotein, and diastolic blood pressure.

Table 2. Incidence and IRR of cardiovascular mortality according to TyG index quartiles in all and by BMI status

	Outcome	Denominator	Incidence rate (95% CI)	IRR 1 (95% CI) [‡]	IRR 2 (95% CI) [§]	IRR 3 (95% CI) [¶]
All						
Quartile 1 (<8.10)	65	766	8.49 (6.55–10.82)	Reference	Reference	Reference
Quartile 2 (8.10–8.38)	96	760	12.63 (10.23–15.43)	1.49 (1.43–1.56)	1.63 (1.48–1.79)	1.62 (1.47–1.78)
Quartile 3 (8.39–8.68)	130	766	16.97 (14.18–20.15)	2.00 (1.86–2.16)	1.95 (1.78–2.14)	1.96 (1.79–2.15)
Quartile 4 (≥8.69)	146	762	19.16 (16.18–22.53)	2.26 (2.08–2.47)	2.34 (2.13–2.56)	2.32 (2.12–2.55)
BMI <25 kg/m²						
Quartile 1 (<8.10)	54	610	8.85 (6.65–11.55)	Reference	Reference	Reference
Quartile 2 (8.10–8.38)	82	596	13.76 (10.94–17.08)	1.55 (1.48–1.65)	1.48 (1.33–1.64)	1.48 (1.34–1.65)
Quartile 3 (8.39–8.68)	108	603	17.91 (14.69–21.62)	2.02 (1.87–2.21)	1.72 (1.55–1.91)	1.74 (1.57–1.93)
Quartile 4 (≥8.69)	105	542	19.37 (15.84–23.45)	2.19 (2.03–2.38)	2.23 (2.01–2.46)	2.22 (2.01–2.46)
BMI ≥25 kg/m²						
Quartile 1 (<8.10)	11	156	7.05 (3.52–12.62)	Reference	Reference	Reference
Quartile 2 (8.10–8.38)	14	164	8.54 (4.67–14.32)	1.21 (1.13–1.33)	1.19 (0.93–1.52)	1.18 (0.92–1.51)
Quartile 3 (8.39–8.68)	23	162	14.20 (9.00–21.30)	2.01 (1.69–2.56)	2.44 (1.93–3.07)	2.40 (1.90–3.03)
Quartile 4 (≥8.69)	40	221	18.10 (12.93–24.65)	2.57 (1.95–3.67)	2.81 (2.23–3.53)	2.82 (2.24–3.54)

[‡] Indicates unadjusted IRR.

[§] Indicates adjusted IRR in the model with adjustment of age and gender.

[¶] Indicates adjusted IRR in the model with adjustment of baseline characteristics presented in Table 1.

BMI, body mass index; TyG, triglyceride glucose; IRR, incidence rate ratio.

Fig. 1. Dose-response association between TyG and adjusted IRR of cardiovascular mortality in all and by BMI. In the left panel, covariables presented in Table 1 were adjusted. In the middle and the right panels, covariables presented in Table 1 except for BMI were adjusted. CVD, cardiovascular disease; BMI, body mass index; TyG, triglyceride glucose; IRR, incidence rates ratio.

Table 2 shows the cardiovascular mortality rates by TyG index groups. Patients with higher levels of TyG index were more likely to have higher cardiovascular mortality rates, such as 8.49% (of 766 patients), 12.63% (of 760 patients), 16.97% of (766 patients), and 19.16% (of 762 patients) for TyG index <8.10, 8.10–8.38, 8.39–8.68 and ≥8.69, respectively.

The cardiovascular mortality rates by TyG index groups were the same pattern in patients with a BMI <25 kg/m² and patients with BMI ≥25 kg/m². Among patients with BMI <25 kg/m², cardiovascular mortality rate was 8.85% (of 610 patients), 13.76% (of 596 patients), 17.91% (of 603 patients), and 19.37% (of 542 patients) for TyG index <8.10, 8.10–

8.38, 8.39–8.68 and ≥ 8.69 , respectively. Among patients with BMI ≥ 25 kg/m², cardiovascular mortality rate was 7.05% (of 156 patients), 8.54% (of 164 patients), 14.20% (of 162 patients), and 18.10% (of 221 patients) for TyG index < 8.10 , 8.10–8.38, 8.39–8.68 and ≥ 8.69 , respectively.

Table 2 also shows that the risks of cardiovascular mortality increased significantly with increasing TyG index compared to those with the lowest TyG index group (TyG index < 8.10): adjusted IRR for cardiovascular mortality 1.62 (95% CI 1.47–1.78), 1.96 (1.79–2.15), and 2.32 (2.12–2.55) for TyG index in 8.10–8.38, 8.39–8.68, and ≥ 8.69 , respectively. The adjusted IRRs were the same pattern in patients with BMI < 25 kg/m² and patients with BMI ≥ 25 kg/m². Among patients with BMI < 25 kg/m², the adjusted IRR was 1.48 (1.34–1.65), 1.74 (1.57–1.93), and 2.22 (2.01–2.46) for TyG index in 8.10–8.38, 8.39–8.68, and ≥ 8.69 , respectively. Among patients with BMI ≥ 25 kg/m², the adjusted IRR was 1.18 (0.92–1.51), 2.40 (1.90–3.03), and 2.82 (2.24–3.54) for TyG index in 8.10–8.38, 8.39–8.68, and ≥ 8.69 , respectively.

A linear relationship between TyG index and cardiovascular mortality was found (p values for linear test > 0.05). Relationship curves were derived from the natural cubic spline models with adjustment of covariates in Figure 1. Similar linear relationships were revealed in the sensitivity analyses modeling the associations in patients with BMI < 25 kg/m² (p values for linear test > 0.05), as shown in the middle panel of Figure 1 and in patients with BMI ≥ 25 kg/m² (p values for linear test > 0.05), as shown in the right panel of Figure 1.

Discussion

In this large prospective cohort of patients initiating PD in a province of China, we provide evidence that TyG index may be a prognostic factor for subsequent risk of cardiovascular mortality, the most common reason for death among patients with ESRD. To our knowledge, this is the first study to identify TyG index measured in the initiation of PD as an independent risk factor of cardiovascular mortality. Increased levels of TyG index were associated with a greater risk of cardiovascular mortality, even after adjusting for potential confounders such as eGFR, comorbidities, blood pressure, and other lipid measurements. The TyG index, a marker indicating the severity of IR, among patients in the highest quartile showed a 2.32-fold increased risk of cardiovascular mortality compared with patients in the lowest quartile.

Although TyG index is a good surrogate of IR, prior studies have mostly focused on its relationship to the risk of development of type 2 diabetes [8, 23–25]. To date, these have reported significant associations between the TyG index level and risk of incident diabetes in both general and metabolically high-risk populations [23–25]. Some other studies also reported significant associations between TyG index and arterial stiffness [26], subclinical atherosclerosis [27], coronary artery calcification (CAC) [28], and cardiac autonomic neuropathy [29], which suggest that the TyG index is a surrogate for IR, which in turn contributed to the development and prognosis of CVDs. Notably, in our study, we identified the TyG index, a commonly used proxy of IR [23], as a novel prognostic factor for cardiovascular mortality in patients initializing PD. Although the TyG index has not been previously examined in the relationship with the risk of cardiovascular mortality among PD patients, our findings are consistent with others showing an increased level of measures of glucose and cardiovascular risk factors (e.g., elevated fasting glucose, C-reaction protein) among patients with higher levels of the TyG index. Taken together, these findings suggest that higher level of TyG index, which could result from impaired insulin and metabolism status, could be related to the prognosis of CVDs in patients with ESRD.

In prior studies, IR measured by HOMA-IR was documented to be associated with parameters of metabolic disorders such as BMI, impaired fasting glucose, and triglyceride, among patients with prevalent PD. In addition, increased HOMA-IR was significantly associated with new-onset cardiovascular events. For example, in a Chinese PD case cohort study, patients with a HOMA-IR between 2.85 and 19.5 compared with those with HOMA-IR between 0.83 and 2.71 had a 17-fold increased risk of new-onset cardiovascular events [30]. In a Korean PD case cohort, there was an 18% increased risk of new-onset major cardiovascular events in PD patients with an average HOMA-IR of 4.7 compared with PD patients with an average HOMA-IR of 2.6 [31]. Consistent with previous findings, among patients initiating PD we observed that more severe IR measured by the TyG index was significantly associated with higher risk of cardiovascular mortality after adjusting for potential confounders. In particular, compared with incident PD patients who had a TyG index <8.10, incident PD patients who had TyG index >8.69 had an almost threefold greater risk of cardiovascular mortality.

Although the mechanism underlying the relationship between the TyG index and CAC has not been clarified, it may be linked to IR. Some studies have suggested that IR leads to chronic inflammation, altered coagulation, and atherosclerosis [32, 33]. Furthermore, an independent association between IR and CAC has been reported [34, 35]. Both the HOMA-IR and the TyG index are well known representative markers of IR, and they are closely related to each other. However, our findings showed that the TyG index was better associated with the presence of coronary artery atherosclerosis than was HOMA-IR, and this result may be explained by the fact that the 2 indices reflect different aspects of IR. While the TyG index reflects IR mainly in the muscle [36, 37], HOMA-IR indicates IR mainly in the liver [38, 39], which may have caused the difference. Peripheral IR may be a very useful surrogate of coronary artery atherosclerosis [40]. Moreover, it has been suggested that IR, inflammation, and malnutrition complex interact closely with the progress of atherosclerosis among dialysis patients [41].

As an observational study, it is difficult to prove a causal association between TyG index and cardiovascular mortality among incident PD patients. However, prior studies among dialysis patients have suggested that the progression of IR and associated subsequent cardiovascular events could be altered by intervening with, for example, strict dietary management, intense antihypertensive treatments, anti-diabetes treatments, and lipid lowering treatments [42, 43]. As a useful prognostic factor, TyG index as the surrogate of IR might be used to routinely screen high cardiovascular risk patients for tailored interventions and treatments in the PD clinic.

There are several strengths to our study. First, our study uses a prospective case cohort design, incorporating incident PD patients with a relatively large sample size. The HPRD is the only PD registry data in Henan including all patients receiving PD care in Henan who will be followed up for their lifetime; therefore, selection bias and respondent bias were relatively small in this study. Second, the HPRD is located in Henan, the province with the largest population size in China, suggesting our study is likely to be a representative sample. Third, because other metabolic risk factors may influence IR and the onset of cardiovascular events, an additional strength of this study was that most metabolic risk factors were measured and accounted for in our primary analyses. There are some limitations in our study. First, there was some distinctive differences between the patients in our study and other non-Chinese ESRD patients, typical European ESRD patients, for example, young age, lower BMI, lower prevalence of comorbidities, and lower percentage of treatment, which suggests that potential adjustments might be needed when examining the association between TyG index and cardiovascular mortality in external non-Chinese ESRD populations, especially European ESRD populations. Second, some traditional risk factors, like

smoking and prior health information were not accessible in our study. Third, the relatively high missing percentage of some variables, for example, phosphate and albumin might have some impact on extrapolation of our findings, especially in the external population.

Conclusions

In summary, findings from this cohort study suggest that incident PD patients with IR, namely with higher TyG index levels, are more prone to suffer from cardiovascular events. This study also adds an important piece of evidence that TyG index might be a good prognostic factor in predicting cardiovascular deaths among patients initiating PD.

Acknowledgement

We thank the First Affiliated Hospital of Zhengzhou University for approving this study. We thank HPDR for providing the data for this study. This work was supported by the National Natural Science Foundation of China (Grant Nos. 81570690, 81873611 and 81700633), Science and Technology Innovation Team of Henan (Grant No. 17IRTSTHN020); Foundation and Frontier Technology Research Program of Henan Province (Grant No. 142300410211). Dr. Dahai Yu would like to thank Public Health England for his Honorary Public Health Academic Contract.

Disclosure Statement

The authors declare that they have no competing interests.

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