Exploring the dynamics of triglyceride with stroke onset in the Chinese population through parameterized joint models

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Abstract

Background: Stroke has become one of the diseases with the highest mortality and disability rates in the world, especially in low-income and developing countries. Our objective was to discuss the relationship between the longitudinal dynamic changes of triglyceride and stroke onset in healthy populations by constructing different parametric joint models.

Methods: 298 participants aged 23 to 69 in Xijing hospital of Xi'an City in Shanxi Province from 2008 to 2015 were included. The Cox proportional hazards model was performed to analyze the correlation between triglyceride and stroke incidence at baseline. Different parameterized joint models were used to analyze the impact of dynamic changes of triglyceride on the incidence of stroke under longitudinal data.

Results: Of the 298 participants, a total of 70 (23.49%) subjects developed stroke during the study period. Cox proportional hazards model showed that the risk of disease increased by 1.056 times (95%*CI*=0.920-0.975) for each 1 unit of baseline age decrease. Each 1 mmol/L increase in sqrt(triglyceride) increased the risk by 1.816 times (95%*CI*=1.017-3.245). Joint model showed that the risk of sqrt(triglyceride) increased by 4.869 times (95%*CI*=3.987-8.857) for each 1 mmol/L increase in the longitudinal direction. The lagged effects (*HR*=5.284, 95%*CI*=4.397-9.680) and cumulative effects (*HR*=1.786, 95%*CI*=1.613-3.399) of sqrt(triglyceride) dynamic trajectory were also statistically related to the incidence of stroke.

Conclusions: Over time, the longitudinal growth of triglyceride levels in individuals will increase the risk of stroke even more. People should pay more attention to the dynamic changes of individual triglyceride values, as well as the lagged effect and cumulative effect, to reduce the incidence of stroke.

Background

Stroke is a group of acute cerebrovascular diseases caused by a variety of pathogenic factors, leading to cerebrovascular block, short-term blood that can not flow into the brain, or acute rupture of cerebral vessels caused by brain function damage [1]. Stroke is irreversible and difficult to treat. The high mortality, high disability rate, and high recurrence rate caused by stroke will bring a great disease burden to society, which has become one of the major public health problems in the world. However, stroke can be also prevented effectively [2,3]. Related research showed that 90.7% of global stroke was related to 10 correctable risk factors, such as hypertension, diabetes, dyslipidemia, smoking, drinking, and abdominal obesity [4]. Therefore, primary prevention of stroke is the fundamental measure.

Some studies showed that there was a correlation between the abnormal levels of TC, TG, LDL-C, and HDL-C and the incidence of stroke [5,6]. And blood pressure, blood lipid, blood glucose, BMI, and waist circumference are controllable factors [7,8]. It will have a better guiding significance for individuals to formulate intervention measures if factors are changed, which can make the assessment objects more intuitively see the reduced degree of disease risk. However, at present, the research conclusions are not completely unified and need to be further explored.

In recent years, most studies have focused on studying the relationship between the level of blood lipid indicators and the incidence of stroke through traditional statistical models, such as logistic regression, Cox proportional hazards model, random forest, and competitive risk model [9,10]. However, these studies lacked the consideration of the impact of the dynamic changes of longitudinal indicators, resulting in poor fitting effects and large errors [11]. To solve this problem, Faucett et al [12] proposed a joint modeling method for longitudinal data and survival data, which could describe the dynamic change trajectory of longitudinal variables.

The joint model was first used in clinical trials of AIDS to evaluate and compare the efficacy of different drugs in the treatment of AIDS [13]. At present, it has been widely applied in many research fields [14-19], such as cancer, cardiovascular and cerebrovascular diseases, kidney disease, liver disease, heart surgery, mental health, and other different diseases research. It has become a hot issue in the field of population health research and provides a mature and powerful method to solve longitudinal data research.

To the best of our knowledge, no previous studies have been conducted to explore the effect of dynamic triglyceride levels on stroke onset by the joint model. We hypothesized that the longitudinal growth of triglyceride levels in individuals, and the lagged effectively and the cumulative effect will increase the risk of stroke. The aim of this study was, therefore, to examine the influence of dynamic TG on stroke onset, and to comprehensively investigate the correlation of the lagged effect and cumulative effect of TG with the stroke onset.

Methods

Study population

In this study, the longitudinal data of 298 subjects who had health examinations from 2008 to 2015 in the health examination center of Xijing hospital in Xi'an City, Shanxi Province were used for analysis. The health examination of participants included a questionnaire survey, physical examination, and clinical physical and chemical index examination, etc. The main indicators included gender, date of birth, age, marital status, education level, height, weight, body mass index, personal history of diseases, family history of diseases, blood pressure, fasting blood glucose, uric acid, TC, TG, and LDL-C, etc.

Quality control measures for anthropometric and laboratory measurements included the participants in the physical examination from the same individual unit and all adopting the same test method. Before the physical examination, the subjects were required to be free of smoking, alcohol, coffee, and have a fasting stomach for more than 12 hours. Biochemical blood samples were collected 3-5ml from an antecubital vein of participants in the morning by the laboratory staff who had received unified training. Then, the samples were detected within 10-30 minutes after extraction.

All the study methods were performed by the Medical Ethics Committee of Weifang Medical University (NO.2021YX116). The participants provided their written informed consent to participate in this study.

Follow-Up and Outcomes

In this study, the trajectory of TG development over time was taken as the main research index. The unit of measurement of TG is mmol/L. The incidence of stroke was observed through follow-up, and the outcome and survival time were recorded, to analyze the relationship between TG trajectory and the occurrence of stroke.

The outcome variable of this study was a new stroke, which was defined as the sudden or rapid onset of a typical neurological deficit caused by vascular causes for the first time, lasting for more than 24 hours or until death [20]. The clinical doctor diagnosed it based on computed tomography (CT) and(or) magnetic resonance imaging (MRI) according to international clinical diagnostic standards.

Inclusion criteria: (1) The number of physical examinations ≥ 3 times; (2) There were no patients with diabetes, cardio-cerebrovascular disease, liver disease, and kidney disease at baseline; (3) No missing baseline diagnosis information. Exclusion criteria: (1) The number of physical examinations < 3 times; (2) Study subjects who already had a stroke at baseline.

The flow chart of cohort establishment in this study is shown in Figure 1. A total of 298 subjects were eventually included according to the inclusion and exclusion criteria of health check-ups, 70 of whom developed strokes during the follow-up period.

Statistical analysis

In our study, we developed joint models to explore the association between longitudinal TG and stroke onset. The standard joint model was used to capture the relationship between TG and stroke, which can be generalized to the case of three parameterization models [11,21,22] including lagged effects parameterization, time-dependent slopes parameterization, and cumulative effects parameterization. To better understand the lagged effects between the event and longitudinal parts in our model, we assumed that the risk of a terminal event in time depended on the value of TG in the previous 3 years [11]. Then, a time-dependent slopes parameterization joint model was also postulated, in which the risk depended on both the trajectory's current TG value and the true trajectory's slope at time *t*. However, in many cases, it may benefit by allowing the risk to depend on the longitudinal marker history, ie. the cumulative effect of TG.

The structure of the standard joint model included the longitudinal submodel established based on the longitudinal data and the survival submodel established based on the survival data. In this study, we assumed $y_i(t)$ to be the follow-up measurements (TG) for patient i (i=1,…,n) at time t, and we followed the framework of linear mixed effect model to fit the longitudinal outcomes [23]:

$$y_i(t) = m_i(t) + \varepsilon_i(t) = x_i^T(t)\beta + z_i^T(t)b_i + \varepsilon_i(t)$$

$$b_i \sim N(0, D), \varepsilon_i(t) \sim N(0, \sigma^2)$$

Among them, $x_i^T(t)$ is the time-varying covariate with corresponding fixed effect term β. $z_i^T(t)$ is the time-varying covariate with corresponding fixed effect term b_i. According to the distribution requirements of longitudinal observed variables, square root transformation of TG index was required to meet the normal distribution [11].

For the survival submodel, we perform the Cox proportional hazards model [24]:

$$h_i(t) = h_0(t)\exp\{\gamma^\top \omega_i + \alpha m_i(t)\}$$

$$h_i(t) = h_0(t)\exp[\gamma^\top \omega_i + \alpha m_i\{max(t-c,\ 0)\}]$$

$$h_i(t) = h_0(t)\exp\{\gamma^\top \omega_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)\}, m_i'(t) = \frac{dm_i(t)}{dt}$$

$$h_i(t) = h_0(t)exp\{\gamma^T \omega_i + \alpha \int_0^t m_i(s)ds\}$$

Here, $h_0(t)$ donates the unspecified baseline risk function, γ^T is the time-varying covariate with corresponding fixed effect term ω_i. Most importantly, the shared parameter α represents the impact of longitudinal results $m_i(t)$ on event risk. In the lag effect joint model, the risk of the terminal event at a time depends on the real value of the longitudinal detection variable at time t-c, where c is the order of time delay. In the time-dependent slopes parameterization, the explanation of the parameter α_1 is the same as the shared parameter α in the standard joint model formula. If $m_i(t)$ is constant, the parameter α_2 measures the correlation between the slope of the longitudinal trajectory at time t and the risk of time end event at the same time point. And in the cumulative effects joint model, for any time point t, α quantifies the correlation between the area under the longitudinal trajectory from baseline to time point t and the terminal event at the same time point.

The main parameter estimation method of the joint model was the maximum likelihood estimation method [25]. EM algorithm [26] or Newton Raphson algorithm [27] can be used to solve the maximum solution of the log-likelihood function. As a general iterative algorithm, the EM algorithm is widely used.

In this study, quantitative data were calculated by means and standard deviation representation (), and qualitative data were expressed both in frequencies and percentages, i.e.. Kaplan-Meier method was used

for survival analysis, which was performed by survminer package of R 4.0.3 software. And the joint model was constructed by JM package of R 4.0.3 software. All tests were two-sided, and values of $P<0.05$ were considered statistically significant.

Results

Descriptive analysis

A total of 298 subjects were followed up and 1921 observational data were collected. Among them, the observation values of each research object include observation time, observation year, survival time, age, gender, TC, TG, HDL-C, LDL-C, and outcome status, etc. The dataset consisted of 204 males and 94 females, with a baseline age range of 23-69 years. And the median TG distribution at baseline was 1.57 (1.03,2.33) mmol/L.

The total population in this study was followed up for 3-8 years, with a mean of follow-up time 6.48±1.54 years. 41 people (13.76%) were followed up for 4 years, 27 people (9.06%) were followed up for 5 years, 45 people (15.10%) were followed up for 6 years and 67 people (22.48%) were followed up for 7 years. And 108 subjects (36.24%) were followed up for 8 years. A total of 70 subjects developed stroke during the study period, with an incidence density of 76.18 per 10,000 people per year. Among them, 58 were male and 12 were female, and the incidence density was 95.26 and 38.69 per 10,000 people per year, respectively. Figure. 2 showed the Kaplan-Meier plot of TG level and stroke cumulative incidence. The cumulative incidence of stroke was 23.49%.

Profile plot for TG biomarker were shown in Figure. 3. Figure.3 indicated that there were distinct differences in trajectories between those who had stroke during follow-up and those who did not. And at each time point, the change trajectory of the TG index had no obvious rule with observation time.

Results generated from Cox proportional hazards model

Table 1 presented the association between incident stroke and sqrt(TG) at baseline. As can be seen, there were statistically significant differences in the influence of baseline age and sqrt(TG) on the incidence of stroke ($P<0.05$). The risk of stroke increased by 0.946-fold (95%*CI*=0.920-0.975) for each 1 year decrease in baseline age. Similarly, the *HR* for sqrt(TG) predicting stroke was 1.816, which indicated that for every 1 mmol/L added to sqrt(TG) level for one subject, the increased risk for developing stroke was 1.816-fold (95%*CI*=1.017-3.245).

Table 1 Results of the Cox proportional hazards model

Variables	β	*SE*	*Z*	*P*	*HR*(95%*CI*)
Age	-0.055	0.015	-3.657	<0.001	0.946(0.920,0.975)
Sqrt(TG)	0.597	0.296	2.016	0.044	1.816(1.017,3.245)

β: The regression coefficients of the respective variables; *SE:*standard error; *Z:* Statistical quantity; *P:* significance level; *HR:* hazard ratio; 95%*CI:* 95% confidence interval. Nominally significant associations (*P* < 0.05) are highlighted in bold.

Results from standard joint model

The results of standard joint model were shown in table 2, which investigated the effect of dynamic change in sqrt(TG) on the hazard of stroke. In the longitudinal submodel, there was a significant difference in the influence of gender on sqrt(TG) (*P*<0.001), indicating that the average level of sqrt(TG) in males was 0.291 higher than that in females. The survival submodel in table 2 showed that there was a strong negative association between dynamic change in age and risk of stroke. A unit decrease in age is represented as a 0.946-fold (95%*CI*=0.931-0.960) increase in developing stroke. Most importantly, the results also reflected a strong positive association between longitudinal augments in sqrt(TG) and the risk of developing stroke, which implied a unit longitudinal augment in sqrt(TG) represented a 4.869-fold (95%*CI*=3.987-8.857) increase in the stroke.

Table 2 Results of the standard joint model

Variables	*β*	*SE*	*Z*	*P*	*HR* (95%*CI)*
Longitudinal submodel					
Fixed effects					
Intercept	1.553	0.119	13.038	<0.001	
Obstime	-0.009	0.014	-0.637	0.525	
Age	0.003	0.002	1.540	0.124	
Gender	-0.291	0.045	-6.423	<0.001	
Obstime:gender	0.008	0.010	0.766	0.444	
Random effects					
α_{b00}	0.266				
σ_{b01}	0.040				
ε	0.348				
Survival submodel					
Age	-0.055	0.015	-3.820	<0.001	0.946(0.931,0.960)
	1.583	**0.450**	**3.519**	**<0.001**	**4.869(3.987,8.857)**

β: The regression coefficients of the respective variables; *SE:*standard error; *Z:* Statistical quantity; *P:* significance level; *HR:* hazard ratio; 95%*CI:* 95% confidence interval. Nominally significant

associations ($P < 0.05$) are highlighted in bold. , shared parameter, represents the impact of longitudinal observation variable (TG) on event (stroke) risk.

Results from parameterized joint models

Three paramaterized joint models results were shown in table 3, with a significant negative association between dynamic change in age and risk of stroke in three submodels. However, the effect of age is not quite remarkable in time-dependent slopes parameterization joint model ($P>0.05$). Additionally, shared parameters were statistically significant in the lagged effect joint model ($P<0.001$), which demonstrated that one unit longitudinal increase in sqrt(TG) level three years earlier was associated with a 5.284-fold (95%*CI*=4.397-9.680) increase in the risk of developing the disease. Similarly to the above analyses, we observed that sqrt(TG) remains strongly related with the risk for stroke ($P<0.001$). In particular, a unit increase in the area under the sqrt(TG) longitudinal profile corresponds to a 1.786-fold (95%*CI*=1.613-3.399) increase in the risk for stroke onset. In the time-dependent slopes parameterization joint model submodel, although the slope of the trajectory was not strongly associated with onset ($P>0.05$), a unit longitudinal increase in sqrt(TG) still increased the risk of the onset ($P<0.001$).

Table 3 Results of the survival submodels of three parameterized joint models

Models	Variables	*β*	*SE*	*Z*	*P*	*HR* (95%*CI)*
Lagged effects	Age	-0.058	0.0145	-3.922	<0.001	0.944(0.930,0.957)
	(lag=3)	**1.665**	**0.452**	**3.679**	**<0.001**	**5.284(4.397,9.680)**
Time-dependent slopes parameterization	Age	-0.188	1.830	-0.103	0.918	0.829(-0.910,2.567)
		1.607	**0.450**	**3.570**	**<0.001**	**4.986(4.104,9.090)**
		-0.455	6.244	-0.073	0.942	0.634(-5.297,6.566)
Cumulative effects	Age	-0.065	0.016	-4.109	<0.001	0.937(0.922,0.952)
		0.580	**0.088**	**6.594**	**<0.001**	**1.786(1.613,3.399)**

β: The regression coefficients of the respective variables; *SE:*standard error; *Z:* Statistical quantity; *P:* significance level; *HR:* hazard ratio; 95%*CI:* 95% confidence interval. Nominally significant associations ($P < 0.05$) are highlighted in bold. , shared parameter, represents the impact of longitudinal observation variable (TG) on event (stroke) risk.

Discussion

In recent years, the incidence of stroke has been increasing worldwide. However, the risk factors for stroke are still not clear [28,29]. At present, age, gender, hypertension, diabetes, dyslipidemia, heart disease, unhealthy diet and other factors are recognized as the main risk factors for stroke, and different risk factors have different effects on stroke. In this study, we conducted a preliminary analysis of the association between longitudinal TG trajectories and stroke onset. Although dyslipidemia as a risk factor

for stroke has been controversial, more and more epidemiological evidence supports the role of dyslipidemia in increasing the risk of stroke and represents a potential target for therapeutic intervention [30]. Therefore, we hope that this study can provide a methodological basis for the exploration of the etiology of such chronic diseases.

In the Cox proportional hazards model, we found that low age and high TG levels at baseline were associated with the risk of stroke, which was not completely consistent with other research results. Mi T et al [31]. indicated that TG was an independent risk factor for carotid plaque, thus identifying a high risk of stroke. This finding was consistent with other previous studies [32]. However, Gainey J et al [33]. found that old age was one of the risk factors for stroke through Cox regression analysis. The inconsistent finding may be related to the rapid rise and younger incidence of stroke in China [34]. The average age of stroke in China was about 65 years old, lower than that in developed countries, about 75 years old [35]. In fact, due to the relative improvement of risk awareness in the elderly from China, combined with lifestyle changes and lipid-lowering drugs, the risk of dyslipidemia and the incidence of cardiovascular and cerebrovascular diseases can be reduced to a certain extent. On the contrary, more and more young people were attacked by cardiovascular and cerebrovascular diseases because of drinking, smoking, excessive nightlife, high-fat diet, hypertension, and other risk factors [36].

In addition, there were many reasons for inconsistent results. The traditional statistical model did not consider the dynamic changes of individual indicators over time and the influence of other covariates, which may lead to some biases in the results. In this study, we used the joint model to dynamically analyze the association between TG and stroke incidence, considering the influence of dynamic changes of the index on disease progression, so as to more accurately analyze the rule of index values changing over time from the perspective of individuals. Our findings demonstrated that there was a strong positive association between longitudinal augments in sqrt(TG) and the risk of stroke onset. More importantly, the dynamic increase of TG level in individuals had a greater impact on stroke than at baseline, which may be due to the simultaneous consideration of baseline and longitudinal dynamic changes of indicators. This result was the most significant feature of the present study and corresponded with our purpose. It was consistent that Lee j et al [37]. in a 17.7-year prospective cohort study in the United States found that adults with high TG had a higher risk of stroke (*HR*=1.32, 95%*CI*=1.06-1.64). Interestingly, Wang Y [38] stratified the primary prevention population of stroke in China, and compared the correlation between the blood lipid level and the incidence of stroke among different levels. He believed that the incidence of stroke increased with the increase of age and TG level, and the correlation between the risk of stroke and serum TG level was greater in the population with the highest age, which was an inconclusive one from our research. In consequence, the relationship between age and stroke onset needed to be further explored.

Our study also constructed other different parameterized joint models for longitudinal data, to further analyze the correlation between different parameterization longitudinal marker sqrt(TG) and stroke onset. And we concluded that the longitudinal observation sqrt(TG) had a time lag effect and cumulative effect on the disease outcome. This was unexpected and novel, as other studies had found lagged associations

between some climatic factors, environmental factors as well as social factors and stroke onset [39-41]. The lag effect of dyslipidemia on stroke needed to be further explored. However, this study can provide new ideas for the etiological inference and prognosis of such diseases. Similarly, the cumulative effect joint model can also provide a feasible parameterization method for the construction of the etiology exploration model of stroke to a certain extent. Because, so far, a common feature of the parameterization we had seen was that they assumed the risk of a specific time event depended only on the longitudinal trajectory characteristics of a single point in time. However, some scholars believed that this hypothesis was not always true. In many cases, we can benefit from the more detailed function of allowing the risk of an event to depend on the longitudinal observation history [42,43].

We had expected that the slope term of sqrt(TG) longitudinal trajectory would have an effect on the outcome of the disease. However, we failed to find the association between them, and only the real level of sqrt(TG) at the same time point on the risk of stroke was found. The reason may be that the TG of the human body changed with the function of the immune system. Nevertheless, up to now, the time-dependent slopes parameterization joint model had been mostly used in the study of the relationship between biomarkers and risk of chronic diseases, used to capture the trajectory slope of observation indicators and the degree of risk [44]. In future study, it is necessary to determine the specific applicable diseases and indicators of this kind of parametric joint model, as well as the parameter setting in the modeling process.

Nevertheless, this study also had some limitations. First, due to the limitation of data collection, the influence of TG observation value on the stroke onset was only analyzed, instead of considering comprehensive factors, such as inflammatory factors, living habits, occupation, marriage, education level, and so on. In future study, more covariates should be considered to infer the risk factors of stroke onset. Second, the incidence of stroke was the result of long-term dynamic development, so the follow-up period of this study was still limited, which may lead to the deviation of model fitting. Third, the joint model established in this study can only deal with a single longitudinal marker. The related researches showed that multiple longitudinal results are modeled simultaneously, which can enhance model prediction ability and facilitate the guidance model for predicting stroke onset risk [45]. Therefore, it can be extended to the multivariable joint model dealing with multiple longitudinal markers in future research.

Conclusion

The joint model can be used to better understand the disease progression by analyzing longitudinal monitoring variables. In this study, we found that the longitudinal increase of individual TG level over time would increase the risk of stroke. People should pay close attention to the changing trend of TG and various other blood lipid indicators, and the growth of indicators in the normal range can not be ignored, while maintaining a healthy lifestyle, such as a healthy diet and active exercise. In addition, we found that the true longitudinal trajectory of TG, the lagged effect, and the cumulative effect three years ago were all strongly correlated with the stroke onset. In future research on stroke etiology, we should pay more

attention to the lagged effect and cumulative effect of TG. Future studies should be further developed to clarify how the slope of the TG locus affects the incidence of stroke.

Abbreviations

TG: triglyceride; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; BMI: body mass index; HR: hazard ratio; CI: confidence interval; AIDS: acquired immunodeficiency syndrome; EM: expectation maximization; SE: standard error; SD: standard deviation.

Declarations

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Author Contributions

QM, WG and YY: structural design and manuscript writing. LY: data collection and the basic data analysis. FS and SW: adjusted the modeling program and reviewed the manuscript. QM, WG and YY: discussed and performed the modeling analysis codes. HC and LW: data collection and consolidation. YX: reviewed the structural design and writing problems. All authors read and approved the final manuscript.

Declaration of Competing interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

The study was approved by Medical Ethics Committee of Weifang Medical University (NO.2021YX116). All the participants read and signed informed consent. All methods were carried out in accordance with relevant guidelines and regulations complied with the Helsinki declaration.

Consent for publication

Not applicable.

Availability of data and materials

The database used and analyzed in the present study is not publicly available as its information may compromise the participants' privacy and consent involved in the research. However, the datasets during the current study are available from the corresponding author on reasonable request.

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Figures

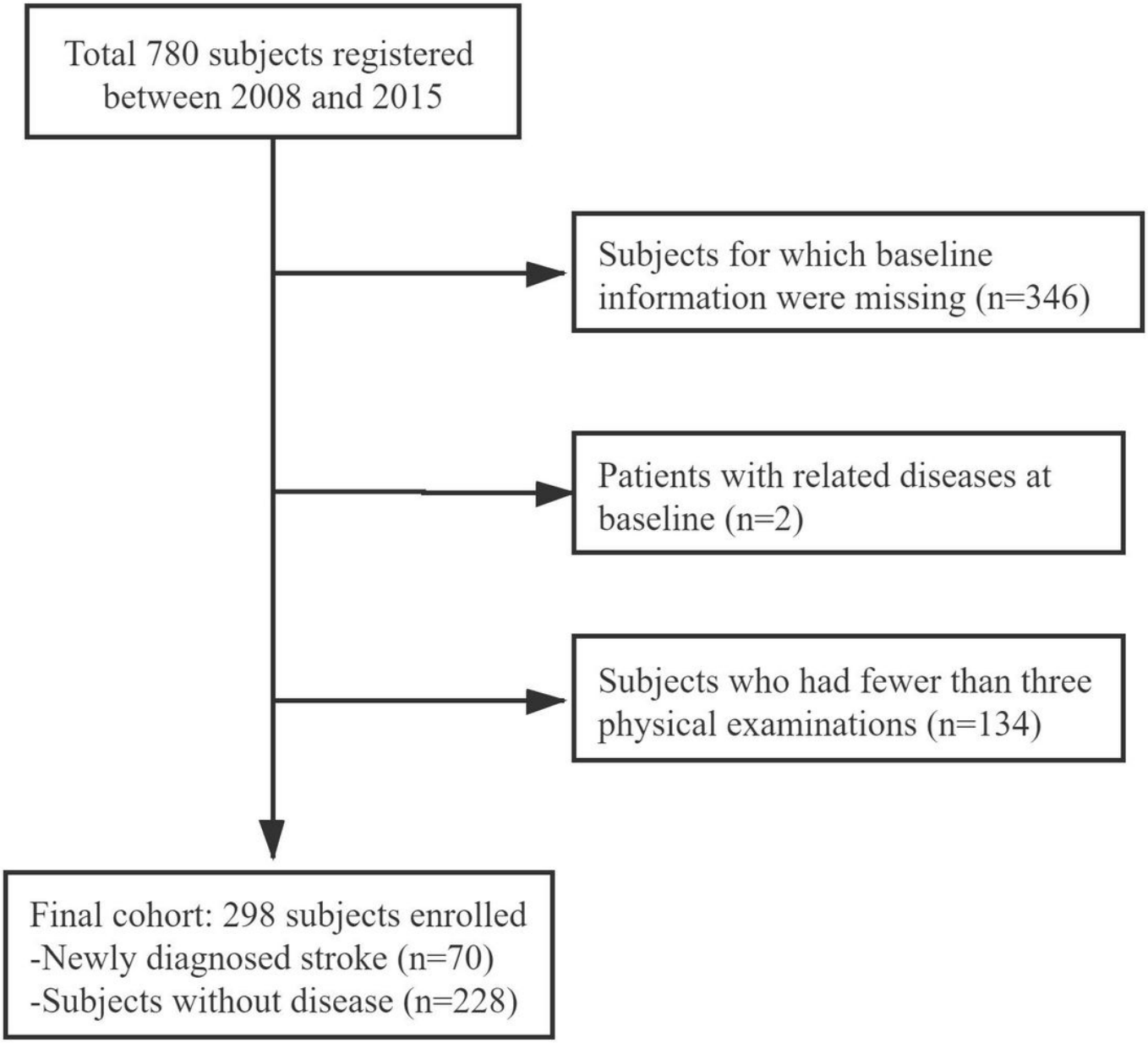

Figure 1

Flow chart of subjects selection.

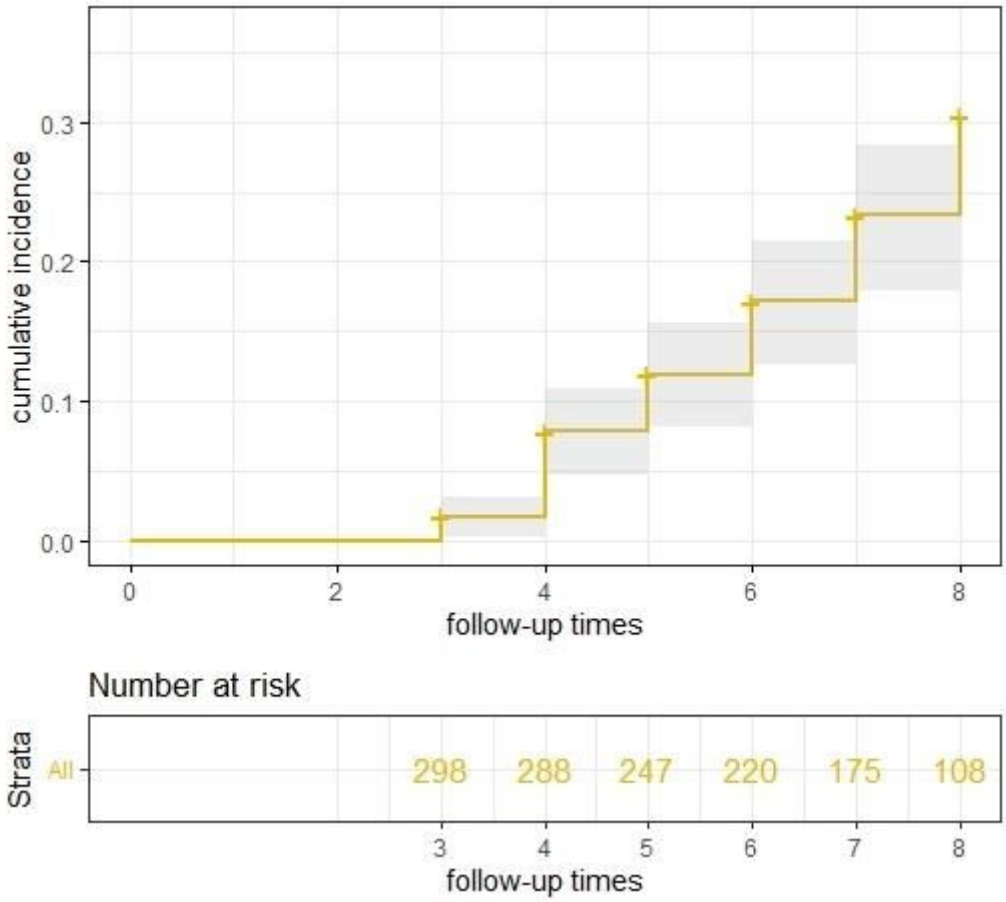

Figure 2

Kaplan-Meier curve for cumulative incidence. The yellow line represents the cumulative incidence at each point in time. The gray shaded areas represent the 95%*CI*.

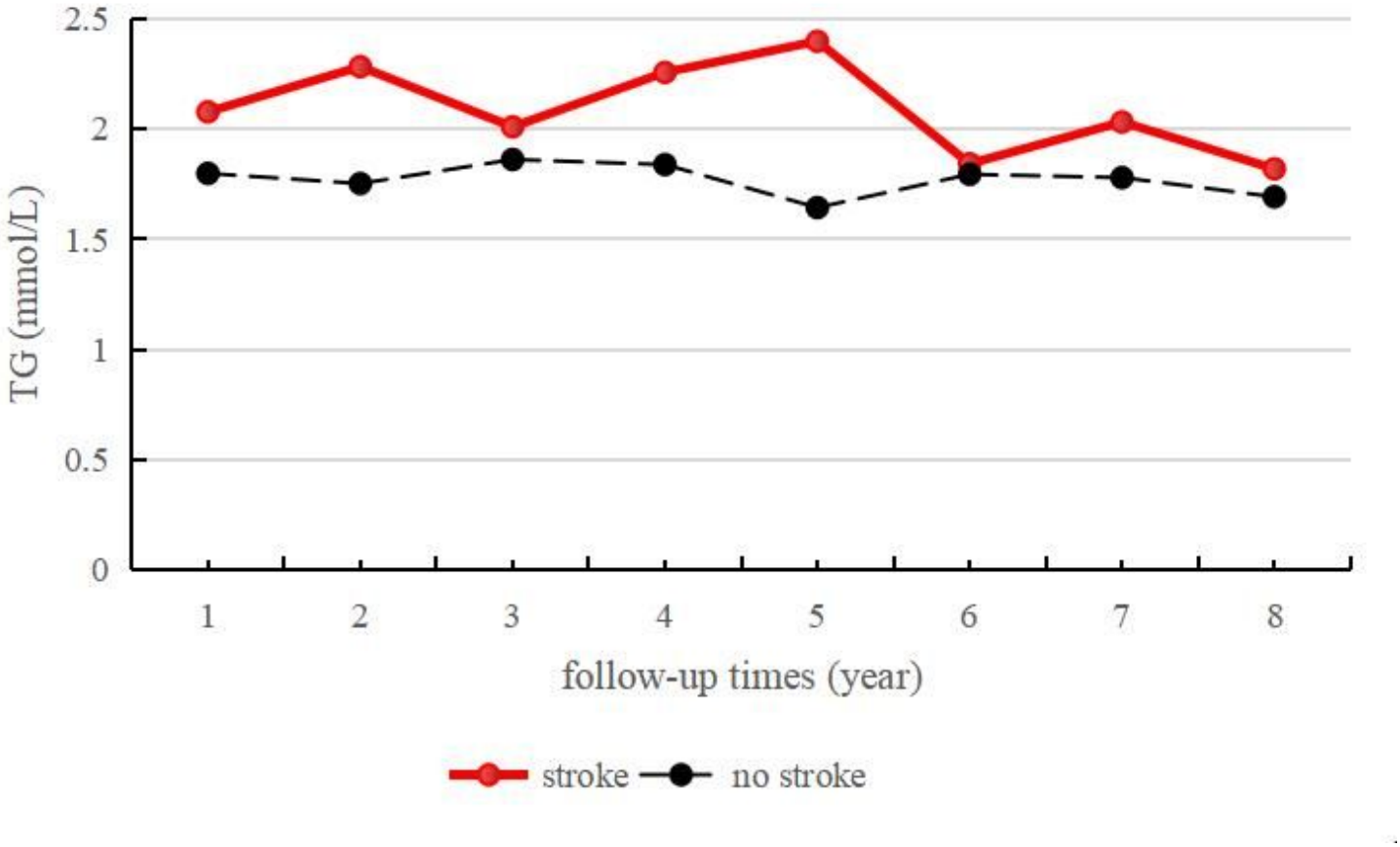

Figure 3

Longitudinal trajectory plot of TG. The y-axis measures the TG level of the subjects. The x-axis measures the time point of follow-up. The black line represents the non-infected group. The red line represents the patients.