Article

Not peer-reviewed version

Non-fasting plasma triglycerides are positively associated with diabetes mortality

Yutang Wang * , Yan Fang , Xiulin Zhang , Na-Qiong Wu

Posted Date: 2 May 2024

doi: 10.20944/preprints202405.0137.v1

Keywords: Triglycerides; non-fasting; diabetes; mortality; risk factor

Article

Non-Fasting Plasma Triglycerides Are Positively Associated with Diabetes Mortality

Yutang Wang [1,*], Yan Fang [1], Xiulin Zhang [2] and Na-Qiong Wu [3]

[1] Discipline of Life Science, Institute of Innovation, Science and Sustainability, Federation University Australia, Ballarat, VIC, Australia
[2] Department of Urology, The Second Hospital of Shandong University, Jinan, China
[3] Cardiometabolic Center, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Science, Peking Union Medical College, Beijing, China
* Correspondence: yutang.wang@federation.edu.au

Abstract: This study aimed to investigate whether non-fasting plasma triglycerides were associated with diabetes mortality. It included 7,312 US adult participants. Diabetes mortality data were obtained via linkage to the National Death Index (NDI) records. Hazard ratios of non-fasting plasma triglycerides for diabetes mortality were assessed using Cox proportional hazards models, adjusting for age, gender, ethnicity, obesity, poverty-income ratio, education levels, physical activity, alcohol consumption, cigarette smoking status, survey period, hypercholesterolemia, hypertension, diabetes, and family history of diabetes. Among these participants, 1,180 had diabetes. A total of 420 diabetes-caused deaths were recorded during a mean follow-up of 16.8 years. A 1-natural-log-unit increase in non-fasting plasma triglycerides was associated with a 41% higher diabetes mortality risk (hazard ratio, 1.41; 95% confidence interval, 1.19-1.67). Participants with non-fasting plasma triglycerides in the highest quintile, versus those in the lowest quintile, had a 144% higher diabetes mortality risk (hazard ratio, 2.44; 95% confidence interval, 1.49-4.02). The positive association of non-fasting plasma triglycerides with diabetes mortality was independent of diabetes status at the baseline. In conclusion, this study demonstrated that non-fasting plasma triglycerides were positively associated with diabetes mortality, independent of diabetes status at the baseline. Non-fasting triglycerides may be a therapeutic target for diabetes-related complications.

Keywords: triglycerides; non-fasting; diabetes; mortality; risk factor

1. Introduction

According to the World Health Organization, diabetes affects 8.5% of adults aged 18 years and older and causes 1.5 million deaths per year [1]. The diabetes mortality rate has increased over time. The age-standardized mortality rate from diabetes is increased by 3% from 2000 to 2019 worldwide, whereas the increase is 13% in lower-middle-income countries [1]. Therefore, it is important to investigate the modifiable risk factors for diabetes mortality.

High triglycerides have been linked to cardiovascular events [2,3], cardiovascular mortality [4] and all-cause mortality [5]. Recently, baseline fasting plasma triglycerides have been shown positively associated with diabetes mortality [6], suggesting that triglycerides may play a crucial role in glycemic control. However, whether non-fasting triglycerides are associated with diabetes mortality is unknown.

The aim of this study was to investigate the association of non-fasting plasma triglycerides with diabetes mortality using US adults who attended the National Health and Nutrition Examination Survey (NHANES) from 1988 to 2014. This study may be of clinical relevance given that some guidelines have started to recommend non-fasting triglyceride tests for general screening and risk evaluation [7,8].

 doi:10.20944/preprints202405.0137.v1

2. Materials and Methods

2.1. Study Participants

A total of 7,490 adults aged ≥ 20 years attended the NHANES from 1988 to 2014 and had their non-fasting (fasting time <8h) plasma triglycerides available. The following participants with missing data were excluded from this study: follow-up time (N = 14), blood hemoglobin A1c (HbA1c, N = 38), plasma glucose (N = 31), serum insulin (N = 45), cigarette smoking status (N = 1), or education (N = 49). The remaining 7,312 participants were included in the final analysis. The study was conducted following the ethical standards as laid down in the Declaration of Helsinki. It was approved by the National Center for Health Statistics Research Ethics Review Board. All procedures were performed following the guidelines of the Declaration of Helsinki. The participants' records were anonymized before being accessed by the author.

2.2. Definitions of Comorbidities

Diabetes was defined as HbA1c ≥ 6.5%, fasting plasma glucose ≥126 mg/dL, taking hypoglycemic drugs, or self-reported diagnosis [9]. Hypercholesterolemia was defined as total cholesterol ≥ 240 mg/dL or self-reported diagnosis of hypercholesterolemia [10]. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or prior diagnosis or treatment of hypertension [11].

2.3. Diabetes Mortality

Diabetes mortality was obtained from NHANES-linked mortality files and was defined as diabetes being listed as underlying cause of death [6]. Follow-up time was defined as the time (in months) from the time when the blood was drawn at the Mobile Examination Center until death, or until the end of follow-up (i.e., December 31, 2015), whichever occurred first.

2.4. Covariates

Confounding covariates of this study included age, gender, ethnic background (Hispanic, non-Hispanic black, non-Hispanic white, or other), obesity (underweight, normal, overweight, obese, or unknown) [12], education (< high school, high school, or > high school) [13], poverty-income ratio (< 130%, 130%-349%, ≥ 350%, or unknown) [14], and survey periods [15]. Lifestyle confounders included physical activity (inactive, insufficiently active, or active) [6], alcohol consumption (never, < 1 drink per week, 1-6 drinks per week, ≥ 7 drinks per week, or unknown), and cigarette smoking (smoker or non-smoker). Clinical confounding factors included hypercholesterolemia, hypertension, diabetes, and family history of diabetes [6].

2.5. Statistical Analyses

Data were presented as mean and standard deviation for continuous variables or percentages for categorical variables. Associations of nonfasting plasma triglycerides with diabetes markers (glucose, HbA1c, and insulin) were analyzed using linear regression. The association of plasma triglycerides with diabetes diagnosis was analyzed by binary logistic regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) of nonfasting plasma triglycerides for diabetes mortality were analyzed using Cox proportional hazards models [16]. All association analyses were adjusted for age, gender, ethnicity, obesity, poverty-income ratio, education levels, physical activity, alcohol consumption, cigarette smoking status, survey period, hypercholesterolemia, hypertension, diabetes, and family history of diabetes. Triglycerides, glucose, HbA1c, and insulin were natural log-transformed to improve the data distribution in all the analyses, which were conducted using SPSS (version 27.0). A two-sided P value of < 0.05 was considered as statistically significant.

 doi:10.20944/preprints202405.0137.v1

3. Results

This cohort included 7,312 US adult participants, among which 1,180 had diabetes. Baseline characteristics are described in Table 1. Non-fasting plasma triglycerides were positively associated with glucose, HbA1c, and insulin after adjustment for all the tested confounders, independent of diabetes diagnosis at the baseline (Table 2). A 1-natural-log-unit increase in non-fasting plasma triglycerides (e.g., from 80 to 217 mg/dL) was associated with a 130% higher diabetes diagnosis risk (adjusted odds ratio, 2.30; 95% CI, 2.01-2.63; P<0.001).

Table 1. Baseline characteristics of the study cohort.

	Without diabetes	With diabetes	All
Participant number	6,132	1,180	7,312
Nonfasting triglycerides, mg/dL, mean (SD)	147 (108)	220 (180)	159 (126)
Age, y, mean (SD)	48 (19)	62 (14)	50 (19)
PG, mg/dL, mean (SD)	94 (13)	176 (93)	107 (49)
HbA1c, %, mean (SD)	5.3 (0.5)	7.8 (1.9)	5.7 (1.3)
Insulin, μU/mL, mean (SD)	13.4 (15.3)	39.2 (89.1)	17.5 (39.6)
Gender (male), %	46.9	46.0	46.7
Ethnicity, %			
Hispanic	27.2	29.6	27.5
Non-Hispanic white	45.7	36.9	44.3
Non-Hispanic black	24.9	31.2	25.9
Other	2.3	2.3	2.3
Obesity, %			
Underweight	2.5	0.6	2.2
Normal	38.6	17.8	35.3
Overweight	34.7	36.4	35.0
Obese	23.5	43.4	26.7
Unknown	0.7	1.8	0.8
Poverty-income ratio, %			
< 130%	28.7	35.7	29.9
130%-349%	38.7	37.4	38.5
≥ 350%	23.6	15.3	22.3
Unknown	8.9	11.7	9.4
Education status, %			
< High School	37.6	56.9	40.7
High School	30.0	24.0	29.0
> High School	32.4	19.1	30.2
Physical activity, %			
Inactive	34.1	23.3	32.3
Insufficiently active	39.5	35.6	38.9
Active	26.5	41.1	28.8
Alcohol consumption, %			
0 drink/week	16.5	30.2	18.7
< 1 drink/week	12.9	8.3	12.2
1-6 drinks/week	19.6	7.8	17.7
≥ 7 drinks/week	13.3	5.9	12.1
Unknown	37.8	47.8	39.4
Cigarette Smoker, %	51.1	53.5	51.4
Hypercholesterolemia, %	30.7	48.2	33.5
Hypertension, %	36.3	69.6	41.6
Diabetes, %	0	100	16.1

 doi:10.20944/preprints202405.0137.v1

Family diabetes history, %	40.3	63.3	44.0

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; PG, plasma glucose; SD, standard deviation.

Table 2. Association of non-fasting plasma triglycerides with plasma glucose, blood hemoglobin A1c, and serum insulin.

	All participants (N=7,312)		Without diabetes (N = 6,132)		With diabetes (N = 1,180)	
	β	P value	β	P value	β	P value
Plasma glucose	0.106	<0.001	0.087	<0.001	0.235	<0.001
Blood hemoglobin A1c	0.067	<0.001	0.051	<0.001	0.163	<0.001
Serum insulin	0.286	<0.001	0.318	<0.001	0.247	<0.001

During 122,940 person-years of follow-up (mean follow-up, 16.8 years), 420 diabetes-caused deaths were documented. A 1-natural-log-unit increase in non-fasting plasma triglycerides was associated with a 41% higher risk of diabetes mortality, which was independent of diabetes status at the baseline (Table 3). Participants with non-fasting plasma triglycerides in the highest quintile, versus those in the lowest quintile, had a 144% higher risk of diabetes mortality (adjusted HR, 2.44; 95% CI, 1.49-4.02), which was also independent of diabetes status at the baseline (Table 4).

Table 3. Non-fasting plasma triglycerides and adjusted risk for diabetes mortality.

Participants	Hazard ratio	95% confidence interval	P value
All (N = 7,312)	1.41	1.19-1.67	<0.001
Without diabetes (N = 6,132)	1.62	1.10-2.38	0.014
With diabetes (N = 1,180)	1.33	1.10-1.61	0.004

Table 4. Non-fasting plasma triglycerides in quintiles and adjusted risk for diabetes mortality.

	All (N = 7,312)			Without diabetes (N = 6,132)			With diabetes (N = 1,180)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Q1	HR = 1 (reference)			HR = 1 (reference)			HR = 1 (reference)		
Q2	1.72	1.03-2.89	0.038	2.28	0.84-6.20	0.108	1.42	0.77-2.62	0.265
Q3	1.90	1.13-3.19	0.016	2.29	0.84-6.23	0.106	1.63	0.88-3.04	0.123
Q4	1.93	1.17-3.19	0.010	2.41	0.88-6.60	0.086	1.66	0.92-3.00	0.093
Q5	2.44	1.49-4.02	<0.001	3.13	1.14-8.55	0.026	2.02	1.13-3.61	0.018

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quintile (Q1=lowest quintile and Q5=highest quintile.).

4. Discussion

Using a representative cohort of US adults, this study found, for the first time, that non-fasting plasma triglycerides were positively associated with diabetes mortality. This study extended the previous finding that triglycerides are positively associated with diabetes mortality from the fasting state [6] to the non-fasting state. Similar to the previous finding [6], such an association was independent of diabetes status at the baseline. Therefore, non-fasting triglycerides might be used to detect those with a high risk of diabetes mortality.

The results of the study are clinically relevant because some guidelines have started to recommend the use of non-fasting triglycerides for general screening and risk evaluation [7,8]. This

 doi:10.20944/preprints202405.0137.v1

shift from fasting to non-fasting triglyceride tests is supported by various reasons. Non-fasting tests are more comfortable and convenient than fasting tests, and they may be safer as certain people may experience hypoglycemia when fasting [7,8]. In addition, non-fasting triglyceride levels are ~27 mg/dL above their fasting counterpart [7], and this difference is thought not clinically significant for most people [7]. Most importantly, non-fasting triglycerides seem to have similar or better prognostic value for general risk screening compared with their fasting counterpart [5,7].

The mechanism underlying the positive association between triglycerides and diabetes mortality is unclear. A few hypotheses have been put forward. For example, triglycerides promote inflammation [17]. Additionally, higher triglycerides may co-exist with other morbidities, such as hypercholesterolemia, hypertension, and diabetes [18]; however, after adjustment of these co-morbidities, our results showed that triglycerides remained positively associated with diabetes mortality.

The present study has a number of strengths, e.g., a large sample size (N = 7,312) derived from a nationally representative adult sample, prospective study design, and adjustment for many confounders. Limitations of the current study included lack of multiple triglyceride measurements throughout the study and possible misclassification of mortality. Mortality was ascertained by a probabilistic match via linkage to the National Death Index (NDI) records. Nevertheless, a prior validation study demonstrated that this probabilistic match yielded a high accuracy of 98.5% [19,20].

5. Conclusions

Non-fasting triglycerides were positively associated with diabetes mortality, suggesting that non-fasting triglycerides might be used to detect those with a high risk of diabetes mortality.

Author Contributions: Conceptualization, Y.W..; formal analysis, Y.W.; Data curation, Y.F.; writing—original draft preparation, Y.W., X.Z., N.W.; writing—review and editing, Y.W., Y.F., X.Z., N.W.; funding acquisition, Y.W. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by National Health and Medical Research Council of Australia, grant number 1062671.

Institutional Review Board Statement: The National Center for Health Statistics Research Ethics Review Board (ERB) approved all study protocols (ERB Numbers: NHANES III, NHANES Protocol #98–12, NHANES Protocol #2005–06, and NHANES Protocol #2011–17).

Informed Consent Statement: All participants provided written informed consent.

Data Availability Statement: The datasets supporting the conclusions of this article are publicly available on the NHANES website, https://www.cdc.gov/nchs/nhanes/index.htm.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. World Health Organization, Diabetes. **2023,** Available from https://www.who.int/news-room/fact-sheets/detail/diabetes. Accessed on 31 August 2023.
2. Nordestgaard, B. G.; Varbo, A., Triglycerides and cardiovascular disease. *The Lancet* **2014,** 384, (9943), 626–635.
3. Raposeiras-Roubin, S.; Rosselló, X.; Oliva, B.; Fernández-Friera, L.; Mendiguren, J. M.; Andrés, V.; Bueno, H.; Sanz, J.; Martínez de Vega, V.; Abu-Assi, E.; Iñiguez, A.; Fernández-Ortiz, A.; Ibáñez, B.; Fuster, V., Triglycerides and Residual Atherosclerotic Risk. *J. Am. Coll. Cardiol.* **2021,** 77, (24), 3031–3041.
4. Wang, Y.; Fang, Y.; Magliano, D. J.; Charchar, F. J.; Sobey, C. G.; Drummond, G. R.; Golledge, J., Fasting triglycerides are positively associated with cardiovascular mortality risk in people with diabetes. *Cardiovasc. Res.* **2023,** 119, (3), 826–834.
5. Fang, Y.; Wang, Y., Fasting status modifies the association between triglyceride and all-cause mortality: A cohort study. *Health Sci Rep* **2022,** 5, e642.
6. Wang, Y., Higher fasting triglyceride predicts higher risks of diabetes mortality in US adults. *Lipids Health Dis.* **2021,** 20, (1), 181.
7. Mach, F.; Baigent, C.; Catapano, A. L.; Koskinas, K. C.; Casula, M.; Badimon, L.; Chapman, M. J.; De Backer, G. G.; Delgado, V.; Ference, B. A.; Graham, I. M.; Halliday, A.; Landmesser, U.; Mihaylova, B.; Pedersen, T.

 doi:10.20944/preprints202405.0137.v1

R.; Riccardi, G.; Richter, D. J.; Sabatine, M. S.; Taskinen, M.-R.; Tokgozoglu, L.; Wiklund, O.; Group, E. S. D., 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur. Heart J.* **2019,** 41, (1), 111–188.

8. Pearson, G. J.; Thanassoulis, G.; Anderson, T. J.; Barry, A. R.; Couture, P.; Dayan, N.; Francis, G. A.; Genest, J.; Grégoire, J.; Grover, S. A.; Gupta, M.; Hegele, R. A.; Lau, D.; Leiter, L. A.; Leung, A. A.; Lonn, E.; Mancini, G. B. J.; Manjoo, P.; McPherson, R.; Ngui, D.; Piché, M. E.; Poirier, P.; Sievenpiper, J.; Stone, J.; Ward, R.; Wray, W., 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can. J. Cardiol.* **2021,** 37, (8), 1129–1150.
9. American Diabetes Association, 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. *Diabetes Care* **2021,** 44, (Supplement 1), S15–S33.
10. Liu, L.; Miura, K.; Kadota, A.; Fujiyoshi, A.; Gracely, E. J.; Xue, F.; Liu, Z.; Takashima, N.; Miyagawa, N.; Ohkubo, T.; Arima, H.; Okayama, A.; Okamura, T.; Ueshima, H., The impact of sex on risk of cardiovascular disease and all-cause mortality in adults with or without diabetes mellitus: A comparison between the U.S. and Japan. *J. Diabetes Complications* **2019,** 33, (6), 417–423.
11. Chobanian, A. V.; Bakris, G. L.; Black, H. R.; Cushman, W. C.; Green, L. A.; Izzo, J. L., Jr.; Jones, D. W.; Materson, B. J.; Oparil, S.; Wright, J. T., Jr.; Roccella, E. J., Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* **2003,** 42, (6), 1206–52.
12. Urrutia, I.; Martín-Nieto, A.; Martínez, R.; Casanovas-Marsal, J. O.; Aguayo, A.; Del Olmo, J.; Arana, E.; Fernandez-Rubio, E.; Castaño, L.; Gaztambide, S., Incidence of diabetes mellitus and associated risk factors in the adult population of the Basque country, Spain. *Sci. Rep.* **2021,** 11, (1), 3016.
13. Al-Mawali, A.; Al-Harrasi, A.; Jayapal, S. K.; Morsi, M.; Pinto, A. D.; Al-Shekaili, W.; Al-Kharusi, H.; Al-Balushi, Z.; Idikula, J., Prevalence and risk factors of diabetes in a large community-based study in the Sultanate of Oman: STEPS survey 2017. *BMC Endocr. Disord.* **2021,** 21, (1), 42.
14. Alam, M. S.; Dyck, R.; Janzen, B.; Karunanayake, C.; Dosman, J.; Pahwa, P., Risk factors, incidence, and prevalence of diabetes among rural farm and non-farm residents of Saskatchewan, Canada; a population-based longitudinal cohort study. *J Diabetes Metab Disord* **2020,** 19, (2), 1563–1582.
15. Wang, Y., Stage 1 hypertension and risk of cardiovascular disease mortality in United States adults with or without diabetes. *J. Hypertens.* **2022,** 40, (4), 794–803.
16. Tao, C.; Hu, N.; Liu, Y.; Wang, H.; Wang, Z.; Zhang, K.; Wang, L.; Chen, B.; Wu, F.; Rong, W.; Wu, J., Long-term outcome of adjuvant radiotherapy upon postoperative relapse of centrally located hepatocellular carcinoma: a real-world study. *Sci. Rep.* **2024,** 14, (1), 8506.
17. Aung, H. H.; Lame, M. W.; Gohil, K.; An, C. I.; Wilson, D. W.; Rutledge, J. C., Induction of ATF3 gene network by triglyceride-rich lipoprotein lipolysis products increases vascular apoptosis and inflammation. *Arterioscler. Thromb. Vasc. Biol.* **2013,** 33, (9), 2088–96.
18. Pradhan, A. D., A New Beginning for Triglyceride-Lowering Therapies. *Circulation* **2019,** 140, (3), 167–169.
19. National Center for Health Statistics. Office of Analysis and Epidemiology, The Linkage of National Center for Health Statistics Survey Data to the National Death Index – 2015 Linked Mortality File (LMF): Methodology Overview and Analytic Considerations. **2019,** Available from https://www.cdc.gov/nchs/data-linkage/mortality-methods.htm.
20. Menke, A.; Muntner, P.; Batuman, V.; Silbergeld, E. K.; Guallar, E., Blood lead below 0.48 micromol/L (10 microg/dL) and mortality among US adults. *Circulation* **2006,** 114, (13), 1388–94.