TITLE PAGE

Title: Total / high-density lipoprotein cholesterol and cardiovascular disease (re)hospitalisation nadir in type 2 diabetes

Running title: TC/HDL predict CVD (re) hospitalisation in diabetes

Authors: Dahai Yu [1,2], Yamei Cai [1], Rui Qin [1], Jonathan Graffy [3], Daniel Holman [4], Zhanzheng Zhao [1*], David Simmons [5*]

Affiliations:

1. Department of Nephrology, the First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, China.

2. Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele ST5 5BG, UK.

3.Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, Cambridgeshire CB2 0SR, United Kingdom

4. Department of Sociological Studies, University of Sheffield, Sheffield S10 2TU, United Kingdom

5. Western Sydney University, Campbelltown, Sydney NSW 2751, Australia

***Correspondence 1:**
Professor Zhanzheng Zhao, Department of Nephrology, the First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, CHINA
Email: zhanzhengzhao@zzu.edu.cn
TEL: +86 139 3852 5666
FAX: +86 371 6698 8753

***Correspondence 2:**
Professor David Simmons, Macarthur Clinical School, School of Medicine, Western Sydney University, Locked Bag 1797, Campbelltown NSW 2751, AUSTRALIA
Email: dsworkster@gmail.com
TEL: (61+2) 4620 3899
FAX: (61+2) 4620 3890

Abbreviations: TC/HDL: Total cholesterol to high density lipoprotein cholesterol ratio; CVD: cardiovascular disease; CHD: coronary heart disease; UKPDS: UK Prospective Diabetes Study; LDL: low density lipoprotein; NHS: National Health Service; SUS: Secondary Uses Service; EMIS: Egton Medical Information Systems; GP: general practitioner; CONSORT: Consolidated Standards of Reporting Trials; CCG: Clinical Commissioning Group; A&E: Accident & Emergency; ICD: International Classification of Diseases; AIC: Akaike information criterion

Abstract (230 words); main text (3,080 words)

References (21); Tables (2); Figures (1); Appendix (1)

ABSTRACT

Total cholesterol to high density lipoprotein cholesterol ratio (TC/HDL) is an important prognostic factor for cardiovascular disease (CVD). This study used restricted cubic spline modelling to investigate the dose-response associations between TC/HDL and both CVD hospitalisation and CVD re-hospitalisation in two independent prospective cohorts. The East Cambridgeshire and Fenland (ECF) cohort includes 4,704 patients with type 2 diabetes from 18 general practices in Cambridgeshire. The RAndomised controlled trial of Peer Support In type 2 Diabetes (RAPSID) cohort comprises 1,121 patients with type 2 diabetes with post-trial follow-up data. TC/HDL and other demographic and clinical measurements were measured at baseline. Outcomes were CVD hospitalisation over 2 years, and CVD re-hospitalisation after 90 days of the prior CVD hospitalisation. Modelling showed nonlinear relationships between TC/HDL and risks of CVD hospitalisation and re-hospitalisation consistently in both cohorts (all $P < 0.001$ for linear tests). The lowest risks of CVD hospitalisation and re-hospitalisation were consistently found for TC/HDL at 2.8 (95% confidence interval: 2.6 to 3.0) in both cohorts and both overall and by gender. This is lower than the current lipid control target, 4.0 of TC/HDL. Reducing the TC/HDL target to 2.8 would include a further 33-44% patients with TC/HDL in the 2.8-4.0 range. Studies are required to assess the effectiveness and cost effectiveness of the earlier introduction of, and more intensive, lipid lowering treatment needed to achieve this new lower TC/HDL target.

KEY WORDS

Diabetes population; Hospitalisation; rehospitalisation; TC/HDL; Lipid

INTRODUCTION

The prevalence and cost of diabetes is growing rapidly worldwide (1). People with diabetes are twice as likely to be admitted to hospital, and at least 10% of those in hospital have diabetes at any one time (2). In some locations and age groups, it is as many as one in five (3). The associated costs of excess admissions, as well as increased costs per admission, are significant contributors to the financial burden borne by healthcare systems from diabetes and often reflect preventable morbidity suffered by patients (4).

As one of the most dominant risk factors, dyslipidaemia has been found to be associated with coronary heart disease (CHD) among people with type 2 diabetes in large prospective studies such as the UK Prospective Diabetes Study (UKPDS) (1, 2). Both total and low density lipoprotein (LDL) cholesterol have been found to correlate with risk of CHD consistently over different studies (5). Among various lipid profile measurements, the total cholesterol to high density lipoprotein cholesterol ratio (TC/HDL) has been widely used as a prognostic factor to predict the risk of CVD both in general (3) and diabetes populations, as applied in the UKPDS score reflecting its association both with CHD (6) and stroke in people with type 2 diabetes.

CVD hospitalisation and re-hospitalisation are important components of the increased costs of diabetes and the preventable morbidity suffered by people with diabetes (6). The TC/HDL management target among those with diabetes is an important risk factor for CVD hospitalisation and re-hospitalisation and might be useful in defining population risk of morbidity and increased health costs (7). Few studies have set out to investigate the associations between TC/HDL level and risk of CVD hospitalisation and re-hospitalisation in people with type 2 diabetes.

In our previous risk score to predict CVD hospitalisation and re-hospitalisation, TC and HDL were incorporated as 4 separated polynomial fractional terms to achieve a better model discrimination and calibration, which did not allow further examination of the association between the TC/HDL ratio and the risks of CVD hospitalisation and re-hospitalisation (8). For example, it is unclear whether or not there is a dose-response relationship between TC/HDL and the risk of hospitalisation in people with type 2 diabetes and if so, whether this is linear. If there is a non-linear relationship, and a potential threshold exists between TC/HDL and CVD hospitalisation, it could inform lipid management among people with type 2 diabetes in the primary care setting and thereby reducing hospitalisation and health payments.

The aim of this study was to investigate the dose-response relationships between TC/HDL and risks of CVD hospitalisation over the subsequent 2 years, and CVD re-hospitalisation up to 90 days, following a prior CVD related hospital stay in two independent prospective cohort studies.

METHODS

Data source and study population

East Cambridgeshire and Fenland **cohort**

In the East Cambridgeshire and Fenland (ECF) cohort patient lists from 18 general practices across Cambridgeshire, England, in 2008/2009 were collated and linked with hospital admissions (Secondary Uses Service (SUS)) data as part of an evaluation of diabetes care across the county by the local health board, National Health Service (NHS) Cambridgeshire. This cohort was limited to volunteer practices using the Egton Medical Information Systems (EMIS) general practitioner (GP) software system, from which a predefined set of data could be extracted. There was no systematic selection process for

these surgeries, and data extracted were for their entire diabetes population. Type 2 diabetes was defined based on GP diagnosis (9). All patients with diabetes had follow-up hospitalisation data to 2010–2011. Hospital admissions to NHS and private hospitals within and outside Cambridgeshire were followed-up. No personal identifiers were released to researchers, and all subsequent analyses were conducted on anonymised datasets.

RAndomised controlled trial of Peer Support In type 2 Diabetes **cohort**

The design and methods of the RAndomised controlled trial of Peer Support In type 2 Diabetes (RAPSID) trial have been published previously (7), as have its CONSORT (Consolidated Standards of Reporting Trials) diagram and the results of its primary outcomes (10). Briefly, RAPSID was a 2x2 factorial cluster RCT comparing 4 groups: Controls, 1:1 (individual) peer support, group peer support, and combined 1:1 and group peer support among patients with type 2 diabetes. Participants had their diabetes for at least 12 months and those with dementia or psychotic illness were excluded. Type 2 diabetes was defined based on GP diagnosis. Participants were recruited from communities across Cambridgeshire and neighbouring areas of Essex and Hertfordshire. Follow up data were only available for participants in Cambridgeshire and neighbouring areas of Hertfordshire that are served by the Cambridgeshire and Peterborough Clinical Commissioning Group (CCG). Clusters were defined by local government ('parish council') boundaries. The intervention was developed following a pilot (11), using a framework defined by Peers for Progress (12). Peers facilitating peer support were termed peer support facilitators and their selection, training, support and the overall programme are described elsewhere (13). The intervention lasted 8-12 months and was commenced and concluded, cluster by cluster, between 02/06/11 to 12/04/12. Ethics approval was received from the Cambridgeshire REC2 Committee (10/H0308/72), and signed consent included agreement for access to hospital data.

At baseline, demographic data, blood pressure, and HbA1c and lipid profile were collected. Each participant was followed up until June 2015 (0.91-4.07 years follow-up from beginning/entry into the trial). Hospitalisation (NHS hospitals & private hospitals), Accident & Emergency (A&E) and outpatient visits within/outside Cambridgeshire and the included areas of Hertfordshire were completely collected through Cambridgeshire and Peterborough Clinical CCG (14) including the elective/non-elective status, and International Classification of Diseases (ICD-10) codes (9).

Defining CVD hospitalisation and re-hospitalisation

The primary outcome of the study was having at least one hospitalisation with CVD as the primary diagnosis (ICD-10: I20–I25, I60–I69 and I73 in the first ICD field) over the 2-year follow-up and having at least one CVD re-hospitalisation after 90 days of prior CVD hospitalisation.

Clinical measurements and missing data

Objective clinical measurements were used as predictors in the model, including body mass index (BMI), blood pressure (systolic (SBP) and diastolic (DBP)) and the metabolic variables glycated haemoglobin (HbA1c) and lipid profile. We also included demographic characteristics, (age and gender) and whether the patient was on lipid lowering treatment. Patients with diabetes were invited to have their blood pressure and metabolic variables measured at least once a year after the diagnosis of diabetes and the most recent was taken before 1 April 2009 (a minimum of 50 days before the first admission). Diabetes duration was not universally recorded, and hence was not usefully available for analysis. Diabetes therapy was not included in the dataset. The TC/HDL was defined as the ratio of total cholesterol to high density lipoprotein cholesterol.

ECF cohort had missing information on body mass index (3.17%), systolic blood pressure (9.95%), diastolic blood pressure (9.95%), total cholesterol (12.35%), high density

lipoprotein (14.56%), and low density lipoprotein (16.27%). We used multiple imputation to replace missing values by using a chained equation approach based on all candidate predictors and outcomes. We created 16 imputed datasets for missing variables that were then combined across all datasets by using Rubin's rule to obtain final model estimates. Limited information was missing (<1%) in RAPSID and the complete dataset was used in our analysis.

Ethical approval

The derivation cohort work had approval from the Cambridgeshire research ethics committee as part of a wider service evaluation. Ethics approval for the validation cohort was received from the Cambridgeshire REC2 Committee (10/H0308/72), and signed consent included agreement for access to hospital data.

Statistical analysis

We used 'incidence occurrence of CVD hospitalization after the first 90 days since the start of follow-up', and the 'incident occurrence of CVD re-hospitalisation', as binary outcome measures. Multivariable logistic regression model was used to explore the prospective association between TC/HDL and risks of CVD hospitalisation and re-hospitalisation with adjustment of co-variables presented in the **Table-1**. The adjusted incidence rates ratio was estimated as $adjusted\ IRR = \exp(\hat{\beta})$, with estimated regression coefficients ($\boldsymbol{\beta}$) from the multivariable logistic regression model.

The dose-response relationships between TC/HDL and risks of CVD hospitalisation and re-hospitalisation were estimated using a linear model, a natural cubic spline model with three equally spaced knots determined from the levels of TC/HDL 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 (AIC) 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 test11 was carried out to target the potential thresholds (P5 to P95 of TC/HDL 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 AIC was chosen as the final threshold. The 95% CI of the threshold was obtained from 1000 bootstrap samples. As the most important confounder, the role of the lipid lowering agents in the association between TC/HDL and risks of CVD hospitalisation and re-hospitalisation was also presented. In the first sensitivity analyses, all analyses were carried out in the continuous measurement data-rich range (covering > 95% people). In the second analysis, all analyses were carried out in men and women separately.

RESULTS

Study participants

In the ECF cohort, we analysed information on 4,704 type 2 diabetes patients with 588 CVD hospitalisations within 2 years and 316 re-hospitalisations after 90 days since a prior CVD hospitalisation. Our RAPSID cohort had information on 1,121 type 2 diabetes patients with 183 CVD hospitalisations and 78 re-hospitalisations. **Table-1** summarises the basic characteristics and potential predictors of the study population at baseline. Patients with type 2 diabetes in both cohorts had similar age, gender, blood pressure and total cholesterol. Patients in the RAPSID cohort had a higher level of high density lipoprotein, low density lipoprotein, and HbA1c. Compared with the ECF cohort, those in the RAPSID cohort were more likely to be prescribed lipid lowering medicine and had more CVD hospitalisation and re-hospitalisation.

Dose-response relationships between TC/HDL and CVD hospitalisation and re-hospitalisation

In both the ECF and RAPSID cohorts, non-linear ("J-shape") relationships were found between TC/HDL and risks of CVD hospitalisation (both P-values for linearity test < 0.0001) and re-hospitalisation (both P-values for linearity test < 0.0001). Relationship curves were derived from the natural cubic spline models with adjustment of covariates in **Figure 1**. Similar dose-response relationships were revealed in the sensitivity analyses modelling the associations within the data rich range (5^{th} percentile to 95^{th} percentile of the above measurements) as shown as **Supplemental Figure S1** for both the ECF and RAPSID cohorts. In another sensitivity analysis modelling the associations by gender, similar dose-response relationships were identified in men and women for both the ECF and RAPSID cohorts (**Supplemental Figure S2**).

For both CVD hospitalisation and re-hospitalisation, a TC/HDL below 2.8 (95% confidence interval: 2.6 to 3.0) was estimated to be associated with the lowest risk of CVD hospitalisation and re-hospitalisation both in ECF and RAPSID cohorts, as tested by linear threshold models. The thresholds are the same among men and women. **Table 2** shows the CVD hospitalisation and rehospitalisation rates below and above the threshold. In the ECF cohort, the CVD hospitalisation rates below and above the threshold were 9.8% (of 2,211 participants) and 14.9% (of 2,493 participants) respectively and in the RAPSID cohort, 14.5% (of 269 patients) and 16.9% (of 852 patients) respectively. Similarly, CVD rehospitalisation rates below and above the threshold were 4.1% and 9.0% in the ECF cohort and 6.6% and 7.2% in the RAPSID cohort. **Table 2** also shows the risks of CVD hospitalisation and re-hospitalisation increase significantly with 1 unit increase of TC/HDL above the TC/HDL threshold (2.8) in both the ECF and RAPSID cohorts**:** adjusted incidence rates ratio (IRR) per TC/HDL unit for CVD hospitalisation 1.39 (95% CI: 1.37 to 1.41, P < 0.0001) in ECF and 1.18 (1.15 to 1.22, P=0.012) in RAPSID; adjusted IRR for CVD

rehospitalisation 1.20 (1.17 to 1.23, P < 0.0001) in ECF and 1.17 (1.13 to 1.21, P=0.040) in RAPSID. The risks of CVD hospitalisation and re-hospitalisation do not increase significantly with 1 unit increase of TC/HDL bellow the TC/HDL threshold (2.8) in either the ECF or RAPSID cohorts: adjusted IRR for CVD hospitalisation 1.05 (0.97 to 1.14, P=0.062) in ECF and 1.00 (0.85 to 1.19, P=0.595) in RAPSID; adjusted IRR for CVD rehospitalisation 1.04 (0.94 to 1.17, P=0.272) in ECF and 0.90 (0.72 to 1.12, P=0.385) in RAPSID. Findings were similar in men and women (**Supplemental Table S1**).

Lipid lowering agent was not a significant entrant into the model and the distribution of the TC/HDL ratio was not significantly different between patient with and without lipid lowering agent in each cohort (adjusted IRR for CVD hospitalisation: 1.01 (0.96 to 1.06) and 0.99 (0.89 to 1.09) for ECF and RAPSID cohorts, respectively; IRR for rehospitalisation: 0.99 (0.93 to 1.05) and 1.00 (0.98 to 1.01) for ECF and RAPSID cohorts, respectively). Similar findings were found in men and women: IRR for CVD hospitalisation: 1.01 (0.90 to 1.14) and 1.01 (0.97 to 1.04) in men and 1.00 (0.99 to 1.01) and 0.99 (0.97 to 1.02) in women for ECF and RAPSID cohorts, respectively; IRR for CVD rehospitalisation: 1.00 (0.98 to 1.01) and 1.00 (0.96 to 1.05) in men and 1.00 (0.99 to 1.02) and 0.98 (0.94 to 1.02) in women for ECF and RAPSID cohorts, respectively.

DISCUSSSION

Our study was undertaken to relate TC/HDL to the risks of CVD hospitalisation and re-hospitalisation in two independent cohorts of patients with type 2 diabetes. We focused our investigation on the dose-response relationships assessing the evidence for non-linear and particular in the existence of a threshold. In all our analyses, we found evidence that the associations are non-linear. Threshold analysis provided evidence of a TC/HDL threshold: 2.8 (2.6 to 3.0). The significantly higher risks of CVD admissions and re-admissions were found above 2.8 of TC/HDL.

Heart UK has recommended that a TC/HDL above 6 be regarded as a major risk factor for heart disease (15). However, Diabetes UK recommends a lower treatment goal of below 4 in diabetes patients (16). There are some other studies which set the TC/HDL ratio target below 4 for patients with type 2 diabetes (17). However, based on our findings, comparing patients with TC/HDL at 2.8, for people with TC/HDL at 4.0, there was 55.2% and 24.0% increased risks of CVD hospitalisation within 2 years and re-hospitalisation after 90 days of prior CVD hospitalisation, respectively.

Our results extend previous findings, suggesting a `J-shaped' non-linear association between TC/HDL and risks of both CVD hospitalisation and re-hospitalisation among people with type 2 diabetes. The existence of a non-linear relationship between TC/HDL and CVD outcomes has not been investigated before. In most previous studies, the association between TC/HDL and CVD outcomes were analysed by 1 unit or 1 standard deviation increase, assuming linearity (consistent slope), which may have led to an underestimate of the risk of CVD events (18,19). In other studies, the TC/HDL has been categorized into several groups based on percentiles, with the association analysed by increases by 1 unit or 1 standard deviation. The different slopes of association between TC/HDL and CVD outcomes have been presented over categories of TC/HDL, which also actually indicated the association was non-linear (20,21). However, a threshold could not be identified by this strategy. Moreover, this strategy of categorized exposure is not recommended, as it leads to the loss of statistical power and the introduction of residual confounders. Therefore, in our study, TC/HDL was treated as a continuous variable and non-linear models were examined in an independent cohort study as the best fitted model. The TC/HDL threshold of 2.8 of was consistently identified in both cohorts for both genders, and for both CVD hospitalisation and re-hospitalisation.

Previous studies have not focussed on CVD as both a major cause and cost for hospital admission among patients with diabetes. To understand the potential risk of CVD hospitalisation in the next year, and the risk of a new episode (within 90 days) of a CVD event (re-hospitalisation) could be helpful for clinicians to facilitate tailored, more intensive management to those with high TC/HDL and to reduce hospitalisation inpatient costs.

Our study has several advantages. We examined associations between TC/HDL and CVD hospitalisation and re-hospitalisation in two independent prospective cohorts, which suggests the findings in this study are reliable. The variables used in this study are from routinely recorded demographic and clinical measurements in primary care settings, which suggesting that the findings in this study could increase the introduction of lipid lowering treatment for people with type 2 diabetes in clinical practice within countries that have routine recorded data accessible. We acknowledge that our study does not take into account diabetes duration, anti-diabetes treatments, prior history of CVD, other diabetes complications (e.g. renal failure), lifestyle risk factors (like smoking), and other comorbidities due to limitations in the original data due to limitations in the original data, but we feel that the clinical measurements included in our study could be proxies for missing predictors. A small minority of CVD events would have resulted in death, but data relating to mortality were not accessible due to linkage limitations. Based on the current study, the threshold is the same for the men and women. In this study, the event numbers are not enough for us to repeat the analyses by gender, which will be tested in the future studies.

As far as we are aware, our study is the first study to investigate the associations between TC/HDL and the 2-year risk of CVD hospitalisation and re-hospitalisation within 90 days of a previous hospitalisation in two independent prospective cohort studies. Our

study has two important implications for clinical practice. First, the relationship between TC/HDL and CVD outcomes are non-linear, which suggests that the risk of CVD outcomes might be substantially under-estimated by previous studies in which linear shapes were assumed. Secondly, our finding suggests that type 2 diabetes patients with a TC/HDL ratio at 2.8 have the lowest risk of CVD outcomes: much lower than the 4.0, accepted in previous clinical guidelines. This suggests that 33% (ECF cohort) - 44% (RAPSID cohort) of patients whose TC/HDL are between 2.8-4.0 (similar by gender: 32 (ECF) - 45% (RAPSID) in men; 34 (ECF) - 46% (RAPSID) in women) may need more intensive lipid lowering treatment, introduced at an earlier stage, to achieve this new optimal control target. Studies are required to assess the effectiveness and cost effectiveness of these strategies.

ACKNOWLEDGMENTS

We would like to thank Toby Prevost, Chris Bunn, Simon Cohn, Sarah Donald, Charlotte Paddison, Candice Ward, Peers for Progress, West Anglia CLRN, Cambridgeshire & Peterborough PCT, Primary Care Research Network – East of England, Eastern Diabetes Research Network, MRC Epidemiology Unit, participating general practices, Jackie Williams, Caroline Taylor, Kym Mercer, Kevin Baker, Ben Bowers, Kalsoom Akhter (CUH Wolfson Diabetes & Endocrinology Clinic), James Brimicombe (Cambridge University), Kim Birch of Trumpington St General Practice, CUH Wolfson Diabetes & Endocrinology Clinic Educators, The RAPSID Patient Committee (Phillip Jones, Liz Carvlin, Roger Smith) and the peers and peer support participants.

This work was supported by the National Institute for Health Research under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0808-17303) and National Institute for Health Research for Patient Benefit Programme (Ref PB-PG-0610-

22311). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interests.

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FIGURE LEGENDS AND TABLES

Table-1. Baseline Characteristics of study populations in East Cambridge and Fenland (ECF) and RAPSID RAndomised controlled trial of Peer Support In type 2 Diabetes (RAPSID) cohorts

	ECF cohort	RAPSID cohort
	4,704	1,121
rdiovascular disease hospitalisation, n (%)	588 (12.5)	183 (16.3)
rdiovascular disease rehospitalisation, n (%)	316 (6.7)	78 (7.0)
male, n (%)	1,919 (40.8)	444 (39.6)
id Lowering treatment, n (%)	3,342 (71.4)	731 (65.2)
e, years	65.0 (56.0 to 77.0)	65.8 (60.0 to 72.1)
dy mass index, kg/m2	30.8 (26.2 to 34.3)	32.3 (28.0 to 35.4)
stolic blood pressure, mmHg	135.0 (125.0 to 143.0)	139.3 (128.3 to 151.0)
astolic blood pressure, mmHg	76.5 (70.0 to 82.0)	75.5 (69.0 to 82.3)
A1c, mmol/mol	61.6 (49.7 to 70.5)	56.5 (48.0 to 63.0)
tal cholesterol, mmol/L	4.3 (3.6 to 5.0)	4.2 (3.6 to 5.0)
gh density lipoprotein, mmol/L	1.3 (1.0 to 1.6)	1.2 (1.0 to 1.4)
w density lipoprotein, mmol/L	2.5 (1.7 to 3.3)	2.4 (1.5 to 2.7)
tal cholesterol to high density lipoprotein cholesterol ratio (TC/HDL)	3.1 (2.6 to 4.5)	3.7 (2.8 to 4.4)

Categorical variable is presented as n (%). Continuous variable is presented as median (interquartile rage).

Table-2. Adjusted incidence rates ratios for cardiovascular disease (CVD) hospitalisation and re-hospitalisation by 1 unit increase in TC/HDL ratio in groups classified by TC/HDL threshold (2.8) in East Cambridge and Fenland (ECF) and RAPSID RAndomised controlled trial of Peer Support In type 2 Diabetes (RAPSID) cohorts

*‡ Indicates age and gender were adjusted; * indicates Age, gender, systolic blood pressure, diastolic blood pressure, body mass index, HbA1c, low density lipoprotein cholesterol, and lipid lowering treatment were adjusted.*

	ECF Cohort				RAPSID Cohort			
	TC/HDL ratio ≤ 2.8 (n=2,211, (47.0%))	*P-value*	TC/HDL ratio > 2.8 (n=2,493, (53.0%))	*P-value*	TC/HDL ratio ≤ 2.8 (n=269, (24.0%))	*P-value*	TC/HDL ratio > 2.8 (n=852, (76.0%))	*P-value*
	CVD Hospitalisation							
pitalisation, n (%)	216 (9.8)	-	372 (14.9)	-	39 (14.5)		144 (16.9)	
usted incidence rates o‡	1.09 (1.00 to 1.19)	0.020	1.55 (1.53 to 1.57)	<0.0001	1.05 (0.86 to 1.27)	0.890	1.24 (1.20 to 1.27)	0.016
usted incidence rates o*	1.05 (0.97 to 1.14)	0.062	1.39 (1.37 to 1.41)	<0.0001	1.00 (0.85 to 1.19)	0.595	1.18 (1.15 to 1.22)	0.012
	CVD Re-hospitalisation							
hospitalisation, n (%)	91 (4.1)	-	225 (9.0)	-	18 (6.6)		60 (7.2)	
usted incidence rates o‡	1.08 (0.95 to 1.22)	0.390	1.46 (1.43 to 1.49)	<0.0001	1.07 (0.98 to 1.18)	0.932	1.30 (1.24 to 1.36)	0.001
usted incidence rates o*	1.04 (0.94 to 1.17)	0.272	1.20 (1.17 to 1.23)	<0.0001	0.90 (0.72 to 1.12)	0.385	1.17 (1.13 to 1.21)	0.043

Figure-1. Adjusted dose-response associations between total cholesterol to high density lipoprotein cholesterol ratio and adjusted odds ratios for cardiovascular disease (CVD) hospitalisation and rehospitalisation in East Cambridge and Fenland (ECF) and RAPSID RAndomised controlled trial of Peer Support In type 2 Diabetes (RAPSID) cohorts

Age, gender, systolic blood pressure, diastolic blood pressure, body mass index, HbA1c, low density lipoprotein cholesterol, and lipid lowering treatment were adjusted.