• Meta-Analysis •

Association between cystatin C and diabetic retinopathy among type 2 diabetic patients in China: a Meta-analysis

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Abstract

• **AIM:** To explore the correlation between cystatin C (Cys-C) and diabetic retinopathy (DR) in those patients with type 2 diabetes mellitus (DM) in China.

• METHODS: Articles were collected from China National Knowledge Infrastructure (CNKI), Wanfang, VIP, PubMed, EMBASE, Cochrane Library, Clinical Trials.gov, and Google Scholar. Quality and risk of bias within included studies was assessed using the Newcastle-Ottawa scale (NOS). Heterogeneity was determined by using Cochran's Q-test and Higgins l^2 statistics. Mean differences (MDs) and 95% confidence intervals (CIs) of Cys-C within the diabetes without retinopathy (DWR) and DR, DWR and non-proliferative diabetic retinopathy (NPDR), NPDR and proliferative diabetic retinopathy (PDR) were collected by using random-effects model because of high heterogeneity. Meta-analysis was conducted based on 23 articles of 2331 DR including NPDR and PDR patients and 2023 DWR patients through Review Manager 5.3. Subgroup analyses were also performed according to DM duration, body mass index (BMI), total cholesterol (TC), total triglycerides (TG), low-density lipoprotein C (LDL-C), and high-density lipoprotein C (HDL-C), sample origins and methods. Publication bias was assessed by the funnel plot.

• **RESULTS:** Cys-C level in DR patients was increased compared with that of DWR (total MD: 0.69, 95%Cl: 0.41 to 0.97, *Z*=4.79, *P*<0.01). Besides, the synthesized results of the studies showed the similar findings in the DWR vs NPDR group (total MD: 0.29, 95%Cl 0.20 to 0.39, *Z*=6.02, *P*<0.01) and the NPDR vs PDR group (total MD: 0.63, 95%Cl 0.43 to 0.82, *Z*=6.33, *P*<0.01). Heterogeneity of most of the

subgroup analyses was still obvious ($l^2 \ge 50\%$, P < 0.1). Forest plots of different subgroups indicated that there was a slight increase of Cys-C during the period between DWR and DR, DWR and NPDR, NPDR and PDR. Funnel plot showed that there was no significant publication bias.

- **CONCLUSION:** The elevated Cys-C is closely related with DR and probably plays a critical role in its progression.
- KEYWORDS: diabetic retinopathy; cystatin C; Meta-analysis DOI:10.18240/ijo.2021.09.21

Citation: Yang N, Lu YF, Yang X, Jiang K, Sang AM, Wu HQ. Association between cystatin C and diabetic retinopathy among type 2 diabetic patients in China: a Meta-analysis. *Int J Ophthalmol* 2021;14(9):1430-1440

INTRODUCTION

iabetes mellitus (DM) totally affected nearly 463 million people over the world in 2019 and this number is estimated to reach 578 million by 2030^[1]. Diabetic retinopathy (DR) is a serious microvascular complication deriving from DM^[2]. As the prevalence of DM continues to rise, incidences of DR which threatens the vision are projected to increase to 191 million by 2030. DR remains the major cause of blindness in adults worldwide^[3-4]. According to the clinical study, DR is divided into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is the earliest stage of DR and can develop into PDR without effective treatment^[5]. Various factors such as hypertension, obesity, hyperlipidemia and hyperglycemia cause DR exacerbation^[6]. Several mechanisms including altered endothelial cell junctions, inflammatory processes and central retinal venous congestion were proposed for its pathogenesis^[7]. Around 40% of patients with type 2 diabetes already have been diagnosed with retinopathy and another 20% will develop this disease in next 6y^[8]. Because of the high incidence, more diagnostic schemes are urgently needed.

Cystatin C (Cys-C) belongs to the type 2 cystatin gene family on chromosome 20^[9]. Almost every organ of the body can express Cys-C. Due to its high concentration in biologic fluids, Cys-C is an important extracellular inhibitor of cysteine proteases^[10-12]. It is a non-glycosylated protein that plays pleiotropic roles in human vascular patho-physiologv^[13]. Clinically, the index of Cys-C is used as a diagnostic parameter to record glomerular filtration rate (GFR) due to its easy detection and lower molecular weight. Previously, researchers have done Meta-analyses to prove that serum Cys-C is a predictor of diabetic nephropathy in diabetic patients^[14-15]. However, the fluctuation of Cys-C level may have more important clinical value than a mere parameter of kidney function^[16]. National Health and Nutrition Examination Survey (NHANES) found that Cys-C could be a better predictor for DR compared to creatinine, related to shared pathogenic pathways between retinopathy and Cys-C^[17-18]. One previous study demonstrated that higher serum Cys-C levels were positively associated with the frequency of DR, chronic heart disease and stroke in type 2 DM patients with normal renal function or mild renal impairment^[19]. Furthermore, such Meta-analysis on the correlation between Cys-C and DR has not been reported yet. Considering both nephropathy and retinopathy are microvascular complications of DM, we carried out the Meta-analysis to explore the clinical value of serum Cys-C for DR.

MATERIALS AND METHODS

Search Strategy and Selection Criteria We performed a computerized search of PubMed, EMBASE, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), VIP and Wanfang to identify potentially relevant articles published to August 2020. We also searched Google Scholar and Clinical Trials for unpublished studies. The search terms and strategies for PubMed were "diabetic retinopathy", "diabetic retinopathies", "retinopathies, diabetic", "retinopathy, diabetic", "Cystatin C", "Cys-C", "post-gamma-globulin", "post gamma globulin", "neuroendocrine basic polypeptide", "basic polypeptide, neuroendocrine", "Cystatin 3", "gammatrace" and "gamma trace". Two authors (Yang N and Lu YF) reviewed the list of articles. Two researchers (Yang N and Yang X) who read the full text of all studies determined the suitability for inclusion based on pre-specified inclusion criteria. The inclusion criteria included: case-control study; individuals with type 2 DM; the exact mean and standard deviation of Cys-C in serum and other sufficient data were provided. There was no limitation on age and no language or publishing date restrictions. If papers we collected are abstracts, letters, editorials, expert opinion, reviews, observational studies, or case reports, they would be excluded. In addition, overlapped or duplicate data, nonhuman research and insufficient data are also our exclusion criteria.

Data Extraction and Quality Assessment Two researchers (Yang N and Lu YF) participated in extracting data from the included studies. Disagreements about extracting data were solved through communication and discussion with a third

reviewer (Yang X). Information such as first author's name, year of publication, country, Cys-C detection method, sample, number of participants, sex, mean age, body mass index (BMI), HbA1c, Cys-C, total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) was extracted precisely. If included literature represented outliers such as very large or very small data, researchers would eliminate the unusual data. Quality assessment of each included study was performed according to the Newcastle-Ottawa Scale (NOS). Studies with a score less than 5 indicated a high risk of bias.

Statistical Analysis and Subgroup Analyses We performed statistical analyses by applying Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) provided by the Cochrane Collaboration by imputing the mean and standard deviation (SD) we recorded from included studies. The mean difference (MD) and 95% confidence interval (CI) were calculated, and P<0.05 was considered statistically significant. To adjust the possible heterogeneity among included studies, we divided samples into different subgroups as shown in Figure 1. We set the 10y as a cutting-off point for DM duration subgroup analysis. The subgroup of normal or abnormal TC, TG, HLD-C, and LDL-C according to Chinese Guidelines for Prevention and Treatment of Dyslipidemia in Adults (2016 Revision)^[20] were analyzed.

Assessment of Heterogeneity and Publication Bias Heterogeneity will be assessed by Cochran's *Q*-test and Higgins I^2 statistics. $I^2 \ge 50\%$ or P < 0.1 indicated that there was a statistical heterogeneity, random effect model (REM) was applied to analyze the data. Funnel plots were used to evaluate the publication bias by the RevMan. If the funnel plots were roughly symmetrical, no publication bias was present.

RESULTS

A workflow diagram of eliminating and including literatures was presented in Figure 2. A total of 195 articles were identified after removing duplicates and among them four were excluded due to comments and animal experiments. Next, 146 articles were further excluded after reading the abstract of the remaining articles for inconsistences in research contents or measures and 13 were excluded after reading the full text because proper outcomes did not occur. Finally, eight articles appearing inconsistent outcomes and one articles appearing the same outcomes were further excluded. The remaining 23 articles were selected for the Meta-analysis.

Characteristics of the Included Studies The main characteristics of the included studies were summarized in Table 1. The 23 included studies^[21-43] covered 2331 DR (NPDR or PDR) patients and 2023 diabetic without retinopathy (DWR) patients. DR patients were divided into NPDR and PDR in 12 studies. Among these 23 studies, 21 investigated serum Cys-C

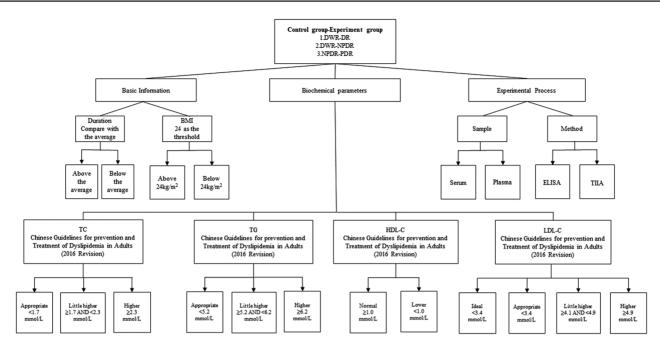


Figure 1 The diagram of criteria and classification for subgroup analyses.

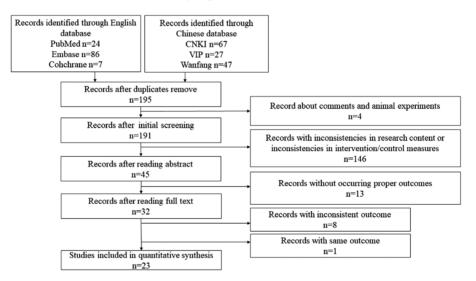


Figure 2 Flowchart of study selection.

levels and the other two investigated plasma Cys-C levels. The patients in 23 studies were all type 2 DM patients from China. Clinical characteristics like age, gender, DM duration, BMI, HbA1c, Cys-C, levels of TC, TG, HDL-C, LDL-C, and available renal function of DR patients were recorded. Eight research reported parameters related to renal function. Two articles provided data of GFR, five articles considered serum creatinine concentration (Scr) and one reported blood urea nitrogen (BUN) of samples. Among them, renal functions of patients in four studies^[19,26,30,38] were within normal range. Levels of other four groups or the DWR, DR subgroups were just a little away from standard. Blood sample origins including serum or plasma and experimental methods such as turbidimetric inhibition immune assay (TIIA) and enzyme linked immunosorbent assay (ELISA) were also recorded. Most patients were middle-aged or elderly and their age

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ranged from fifty to sixty. The overall duration of the disease varied from approximately 2 to 15y and most fluctuated within ten years. Most patients with DWR and DR (NPDR or PDR) showed BMI>24 kg/m². Blood lipid parameters such as TC, TG, and LDL-C saw a slight to moderate increase between control groups and experiment groups. Eight studies were rated as a total score of 6, thirteen studies as a score of 7 and two studies as a score of 8, none of them indicated a high risk of bias.

Meta-analysis of Overall Cys-C Levels in the DWR, NPDR, and PDR group The forest plot of included eleven studies with 1813 participants showed the difference of Cys-C levels between the overall DR and DWR group (Figure 3). The heterogeneity was high (P<0.1, I^2 >50%). The result revealed that there was an increasing level of Cys-C in patients with DR (total MD: 0.69, 95%CI: 0.41 to 0.97, Z=4.79, P<0.01). Among the 23 studies, another 12 articles classified DR into

| Setun 7 m=100, age 51.249.5y, duration 6.264-450; HbM, e.9.06%41.67%, Cys-C.08441.76 mmol/L. Blood 6 m=229 (WF 14089), age 55.124.7066 mmol/L, HDL-C.1254.041 mmol/L, LDL-C.2574.657 mmol/L. Blood 6 m=229 (WF 14089), age 55.124.706, Martion 6.42y, BMI 21.124.205, Cys-C. 0.724.018 mmol/L, TG 1402.6458 mmol/L. Setum 7 m=60 (MF 72023), age 55.124.7066, Martion 5.924.326, Cys-C. 0.724.018 mmol/L, TG 1249.04 mmol/L, TG 1249.058 mmol/L, HDL-C. 1484.058 mmol/L, LDL-C.2544.068 mmol/L, TG 1.1224.044 mmol/L, HDL-C. 1484.058 mmol/L, LDL-C.2544.068 mmol/L, TG 1.1224.044 mmol/L, HDL-C. 1244.058 mmol/L, LDL-C.2544.068 mmol/L, TG 1.1224.044 mmol/L, HDL-C. 1244.058 mmol/L, LDL-C.2544.058 mmol/L, TG 1.1224.054 mmol/L, TG 1.1244.058 mmol/L, TG 1.1244.058 mmol/L, TG 1.1244.058 mmol/L, TG 1.184.052 mmol/L, TG 1.184.052 mmol/L, TG 1.184.052 mmol/L, TG 2.124.073 mmol/L, TG 2.184.131 mmol/L, HDL-C 1.1244.058 mmol/L, LDL-C 2.346.051 mmol/L, TG 2.584.132 mmol/L, TG 2.1664.053 mmol/L, LDL-C 2.846.051 mmol/L, TG 2.584.132 mmol/L, HDL-C 1.014.058 mmol/L, LDL-C 2.846.051 mmol/L, TG 2.584.132 mmol/L, HDL-C 1.014.028 mmol/L, LDL-C 2.846.032 mmol/L, ST 4.464.84 mL/min Setum 6 7 796 (MF 8.432, M tration 6.6141.593, BMI 26.4494.612, HMML 6.7496.2193, LMML 6.7584.2394 mmol/L, LDL-C 2.846.032 mmol/L, LDL-C 2.846.032 mmol/L, LDL-C 2.846.032 mmol/L, ST 4.24.039 mmol/L, ST 4.24.039 mmol/L, ST 4.24.039 mmol/L, ST 4.84.039 mmol/L, ST 4.84.04 MMI 26. | Method | | Sample N | NOS | DWR | DR (NPDR/PDR) | |
|--|--------|---------|----------|-----|--|--|---|
| Blool 6 r=229 (MF 14089), age 55.12±7.965, duration 5.92±3.265, Cys-C 1.31±0.52 mmol/L. Plasma 7 r=60 (MF 2337), age 55.12±7.965, duration 6.424, BMI 21.12±2.05, Cys-C 0.72±0.18 mmol/L. Berun 7 r=20 (MF 2337), age 55.97±10.863, duration 6.47±1.613, BMI 24.95±297, HbA1 e. Serun 7 r=25.047 29.253, age 56.97±10.863, duration 6.47±1.613, BMI 24.95±297, HbA1 e. Serun 7 r=73. (MF 23122), age 57.12±6.35, duration 6.47±1.613, BMI 24.95±297, HbA1 e. Serun 7 r=73. (MF 23122), age 57.12±6.35, duration 6.47±1.057, MB1 24.72±3.29, HbA1 e. Serun 7 r=73. (MF 23122), age 57.13±6.33, duration 6.44±1.057, BMI 24.72±3.29, HbA1 e. Serun 6 r=73. (MF 23120), age 57.32±6.03 mmol/L. TC 5.12±0.55 mmol/L. FDLC 1.21±0.08 mmol/L. LDLC 2.76±0.63 mmol/L. FDLC 2.12±0.08 mmol/L. LDLC 2.35±0.91 mmol/L. Serun 6 r=r=23, age 56.4±10.57 mmol/L. TC 5.33±1.32 mmol/L. HDLC 1.12±0.05 2.8±1.03 mmol/L. Serun 6 r=r=23, age 56.4±10.57 mmol/L. Serun 6 r=r=37, age 56.4±10.57 mmol/L. Serun 6 r=r=38, rdt 21.22, duration 4.8±0.57 BMI 23.6±3.9, Cps-C Serun 6 r=r=38, rdt 21.22, duration 6.61±1.59, BMI 24.5±3.75 mmol/L. DLC 2.28±1.03 mmol/L. Serun 6 r=r=38, rdt 21.22, duration 6.61±1.59, BMI 24.5±6.55 mmol/L. DLC 2.28±1.03 mmol/L. Serun 6 r=r=38, rdt 21.22, duration 6.61±1.59, BMI 24.2±6.50 mmol/L. DLC 2.28±1.03 mmol/L. Serun 6 r=r=80 (MF 3.842), age 54.44±1.1257, duration 6.61±1.59, BMI 22.6±6.51 mmol/L. Berna 6 r=r=80 (MF 2.51/2), age 54.24±1.1257, duration 6.61±1.59, BMI 22.2±6.50 HMO1. Serun 6 r=r=80 (MF 2.51/2), age 57.2±1.0427, dmmol/L. Serun 6 r=r=80 (MF 2.50/12, dmation 5.6, BMI 23.2±6.50 HMO1. Serun 6 r=r=80 (MF 2.50/12, dmation 5.6, BMI 23.2±6.54 HMO1. Serun 6 r=r=80 (MF 2.51/2), age 57.2±1.0427, dmation 10. | TIIA | | | 2 | <i>n</i> =190, age 51.3±9.3y, duration 6.26±4.56y, HbA1c 9.06%±1.67%, Cys-C 0.84±0.76 mmol/L, TC 5.09±0.93 mmol/L, TG 2.42±0.66 mmol/L, HDL-C 1.25±0.41 mmol/L, LDL-C 2.57±0.57 mmol/L | <i>n</i> =170, age 57.3±9.2%, duration 9.72±6.29%, HbA1c 11.13%±1.29%, Cys-C 1.16±0.27 mmol/L, TC 5.12±0.78 mmol/L, TG 2.59±0.59 mmol/L, HDL-C 1.17±0.42 mmol/L, LDL-C 2.88±0.89 mmol/L | -C 1.16±0.27 mmol/L, TC 5.12±0.78 mmol/L, 9 mmol/L |
| Plasma 7 m60 (MF 23/37), age 523-35, duration 64-32, BMI 21.12#2.05, Cys-C 0.72#0.18 mmol/L. Sterm 7 r=52 (MF 23/37), age 557-310 S80, duration 64-74:101, BMI 24.05#.297, HbA1e 7.064-127%, Cys-C 0.604-019 mmol/L. 7.07 + 793-297, HbA1e 7.0111 7 r=53 (MF 31/22), age 571-134-683, duration 64-64:105, BMI 24.72#3.29, HbA1e 7.012194:15.6% r=70, Gys-C 0.610-019 mmol/L. 7.05 + 124-026 mmol/L. 8cmm 6 r=92 (MF 53.40), age 55.71-34.663 mmol/L. 7.01 + 24.72#3.29, HbA1e 9.11%:e2:20%, Cys-C 0.919-006 mmol/L. 7.05 + 124-026 mmol/L. 7.04 + 24.055 8cmm 6 r=92 (MF 53.40), age 55.73-86.074 mution 6.46±1.057, BMI 24.72=3.29, HbA1e 9.11%:e2:20%, Cys-C 0.919-067 mmol/L. 7.05 + 124-026 mmol/L. 8cmm 6 r=92 (MF 53.44) 05, duration 4.84.05, BMI 23.45.32, muol/L. 7.04 + 20.26 8cmm 6 r=92 (MF 53.04) age 56.41.05, duration 4.84.05, BMI 23.64.39, C98-0.03.04.01.1. 8cmm 6 r=93 (MF 21/22), age 64.1.1, duration 5.04.81.01.04.01.1. 2.02.82.0.23.04.00.01.1. 8cmm 6 r=93 (MF 51/22), age 54.1.05, duration 6.1.1.50, MBI 23.64.0.5, mmol/L. 7.02.96.4.1.94.00.01.04.01.04.00.00.00.00.1.1.02.00.00.00.01.1.02 | E | TIIA I | | 9 | <i>n</i> =229 (M/F 140/89), age 55.12±7.96y, duration 5.92±3.26y, Cys-C 1.31±0.52 mmol/L | n=86 (M/F 62/24), age 58.35±7.63y, duration 8.74±3.95y, Cys-C 3.15±0.34 mmol/L | ±0.34 mmol/L |
| 7 n=5 (MF 29/2), age 56.97±10.86, duration 6.47±1.61, BMI 24.95±2.97, HbA1e, T3808±1.27%, CS=C 000:01019 mmol/L. TG 7.7±0.94 mmol/L. HDL-C.1.47%, CS=C 000:01019 mmol/L. TG 7.15±0.75 mmol/L. TG 1.72±0.94 mmol/L. 8erum 7 r=753 (MF 21/22), age 57.13±6.83, duration 6.46±1.05y, BMI 24.72±3.29, HbA1e 0.02% dist.15%, CS=C 0.91±0.05 mmol/L. TG 5.13±0.75 mmol/L. HDL-C.1.21±0.08 mmol/L. LDL-C.276±0.63 mmol/L. 8erum 6 r=92 (MF 29/24), age 56.73 p5 (MI 1001, CF 5.12±0.75 mmol/L. HDL-C.1.13±0.60, mmol/L. LDL-C.376±0.63 mmol/L. 8erum 6 r=92 (MF 29/24), age 56.73 p5 (MI 1001, CF 8.39±1.32 mmol/L., HDL-C.1.18±0.65 mmol/L. 8erum 6 r=92 (MF 2012) age 56.410 (MI 27.62 38±1.32 mmol/L. 8erum 7 rC 5.88±0.42 mmol/L. 8erum 6 r=57.38±0.12 (MF 21/22), age 54.15 (mmol/L. 8erum 6 r=43 (MF 21/22), age 54.15 (mmol/L. 8erum 7 rC 2.88±0.42 mmol/L. 8erum 6 r=43 (MF 21/22), age 54.19 (mmtion 0.17.75, HbA1e 9.28%±1.02%, Cys-C 0.98±0.12 mmol/L. 8erum 7 r=40 (MF 21/22), age 54.19 (mmtion 11.75, HbA1e 9.28%±1.02%, Cys-C 0.98±0.12 mmol/L. 8erum 7 r=40 (MF 21/22), age 54.19 (mmtion 11.75, HbA1e 9.28%±1.02%, Cys-C 0.98±0.12 mmol/L. 8erum 6 r=43 (MF 21/22), age 54.19 (mmtion 11.75, HbA1e 7.4%±2.1%, Cys-C 0.98±0.12 mmol/L. 8erum 6 r=43 (MF 21/22), age 57.2±11.42, (mmtion 0.1±6.25, BMI 22.2±4.59, HbA1e 8.99%±1.35, mmol/L. 8erum 7 r=40 (MF 57/52), age 57.2±11.42, (mmtion 10.1±6.25, BMI 22.2±4.59, HbA1e 8.99%±1.94%, Cys-C 0.88±0.50, mmol/L, SeF 0.12±1.53, mmol/L, SeF 0.12±1.51, mmol/L, HDL-C.1.01±0.50, mmol/L, LDL-C 2.56±0.76 mmol/L, SeF 0.12±1.53, mmol/L, HDL-C.1.01±0.50, mmol/L, LDL-C 2.56±0.76 mmol/L, SeF 0.12±1.53, mmol/L, HDL-C.1.01±0.50, mg 55.21±1.42, (mmtion 0.5-5, Cys-C 0.88±0.67 mmol/L, HDL-C.1.01±0.50, age 55.21±1.42, (mmtion 0.5-5, Cys-C 0.88±0.67 mmol/L, HDL-C.1.35±0.24 mmol/L, LDL-C 2.81±0.55 (MF 12.1299) mmol/L, FO 1.75±0.79 mmol/L, HDL-C.1.35±0.24 m | E | | | ٢ | <i>n</i> =60 (<i>M</i> /F 23/37), age 52±3y, duration 6±2y, BMI 21.12±2.05, Cys-C 0.72±0.18 mmol/L, TG 4.02±0.85 mmol/L | n=60 (M/F 25/35), age 55±5y, duration 10±3y, BMI 21.52±2.26, Cys-C 0.97±0.32 mmol/L, TG 6.42±0.87 mmol/L | .C 0.97±0.32 mmol/L, TG 6.42±0.87 mmol/L |
| Ferun 7 n=35 (MF 31/22), age 57.13±6.83y, duration 6.46±1.05y, BMI 24.72±3.29, HbA1e 10.21%±1.56%, Cys-C 0.91±0.00 mmo/L, TG 5.12±0.75 mmo/L, TG 1.64±0.26 mmo/L, Berun 6 n=92 (MF 52/40), age 56.37±8.07y, duration 2.3±2.01y, BMI 24.3%±1.93, HbA1e 10.21%±1.57, pmo/L, EDL-C 2.356±0.91 mmo/L, TG 5.83±1.32 mmo/L, TG 2.68±1.37 mmo/L, TG 2.68±1.37 mmo/L, TG 2.28±1.32 mmo/L, TG 1.98±0.32 mmo/L, DL-C 3.36±0.91 mmo/L, TG 2.68±1.37 mmo/L, DL-C 3.36±0.91 mmo/L, GF 8.97±8.87 mL/min, Ser 57.34±11.57 pmo/L Berun 6 n=92 (MF 52/40), age 56.37±0.57 mmo/L, TG 5.38±1.32 mmo/L, TG 2.28±1.32 mmo/L, TG 1.98±0.32 mmo/L, HD-C 0.98±0.25 mmo/L, DL-C 2.88±0.25 mmo/L, DL-C 3.84±0.42 mmo/L, TG 1.98±0.32 mmo/L, DL-C 0.96±0.24 mmo/L, DL-C 2.88±0.42 mmo/L, TG 1.98±0.32 mmo/L, HD-C 0.96±0.24 mmo/L, DL-C 2.88±0.42 mmo/L, TG 1.98±0.32 mmo/L, HD-C 0.96±0.24 mmo/L, Cl 2.28±1.22 mmo/L, DL-C 2.88±0.42 mmo/L, TG 1.92%, Cys-C 0.85±0.12 mmo/L, TG 1.92%, Cys-C 0.85±0.12 mmo/L, TG 1.25%, DMI 26.49±0.12 mmo/L, DL-C 2.88±0.12 mmo/L, TG 1.75, HDA 16 9.28%±1.02%, Cys-C 0.85±0.12 mmo/L, DL-C 2.85±0.76 mmo/L, DL-C 2.85±0.76 mmo/L, TG 2.92%.24 mL/min Berum 6 n=80 (MF 8342), age 54.40±11.25y, duration 10.175, HDA 16 9.28%±1.02%, Cys-C 0.85±0.12 mmo/L, TG 1.75±0.99 mmo/L, TG 1.75±0.51 mmo/L, TG 1.75±0.79 mmo/L, HD-C 1.01±0.26 mmo/L, LD-C 2.56±0.62 mmo/L, TG 1.75±0.79 mmo/L, TG 1.75±0.79 mmo/L, HD-C 1.03±0.27 mmo/L, TD-C 2.56±0.62 mmo/L, TG 1.75±0.79 mmo/L, TG 1.75±0.79 mmo/L, HD-C 1.03±0.51 mmo/L, TG 4.12±0.99 mmo/L, TG 1.75±0.79 mmo/L, HD-C 1.03±0.51 mmo/L, TG 4.12±0.97 mmo/L, TG 4.12±0.99 mmo/L, TG 1.75±0.51 mmo/L, TG 4.12±0.99 mmo/L, TG 1.75±0.79 mmo/L, HD-C 1.03±0.51 mmo/L, TG 1.75±0.51 mmo/L, Errun 6 s4%±0.19%, Cys-C 1.85±0.53 mmo/L, TD-C 2.36±0.62 mmo/L, TG 4.12±0.93 mmo/L, TG 4.12±0.93 mmo/L, TG 4.02±0.79 mmo/L, HD-C 1.3±0.54 mmo/L, HD -C 1.3±0.54 mm | E | | | 7 | <i>m</i> =52 (<i>M/</i> F 29/23), age 56.97±10.86y, duration 6.47±1.61y, BMI 24.95±2.97, HbA1 c 7.80%c±1.27%, Cys-C 0.60±0.19 mmo/L, TC 4.79±0.96 mmo/L, TG 1.72±0.44 mmo//L, HDL-C 1.48±0.55 mmo/L, LDL-C 2.54±0.68 mmo//L | m=40 (M/F 24/16), age 57.83±9.51y, duration 8.35±1.96y, BMI 25.13±3.34, HbA1c 9.46%±1.84%, Cys-C 1.02±0.36 mmol/L, TC 4.90±1.03 mmol/L, TG 1.79±0.47 mmol/L, HDL-C 1.45±0.43 mmol/L, LDL-C 2.62±0.73 mmol/L | ±3.34, HbA1e 9.46%±1.84%, Cys-C DL-C 1.45±0.43 mmol/L, LDL-C |
| Serum 6 n=92 (MF 5240), age 56.37±8.07%, duration 2.38±2.01%, BMI 24.38±1.93, HbA1e 9.11%±2.90%, Cys-C 0.91±0.67 mmo/L, TC 5.83±1.32 mmo/L, HDL-C 1.18±0.65 mmo/L, LDL-C 3.36±0.91 mmo/L, GT 8.897±18.57 mL/min, Serum 6 n=57, age 56.4±10.6%, duration 48±0.6%, BMI 23.6±3.9, Cys-C 0.85±0.25 mmo/L, LDL-C 2.38±0.32 mmo/L, HDL-C 0.96±0.24 mmo/L, LDL-C 2.38±0.42 mmo/L, GT 824.03 mmo/L, GT 82.03 mmo/L, HDL-C 0.96±0.24 mmo/L, LDL-C 2.38±0.12 mmo/L, GT 82.03 mmo/L, HDL-C 0.96±0.24 mmo/L, LDL-C 2.38±0.12 mmo/L, GT 82.09%±1.02%, Cys-C 0.98±0.12 mmo/L, LDL-C 2.56±0.76 mmo/L, TC 4.72±1.09 mmo/L, HDL-C 1.01±0.26 mmo/L, LDL-C 2.56±0.76 mmo/L, GT 21.22.99 mmo/L, HDL-C 1.01±0.26 mmo/L, LDL-C 2.56±0.76 mmo/L, Ser 66.42±11.43 µmo/L, HDL-C 1.01±0.26 mmo/L, CH 21.22.94 duration 5.6%, BMI 23.2±0.7, HDA1e 3.59%±1.99%, Cys-C 0.88±0.13 mmo/L, TC 4.12±0.99 mmo/L, Ser 66.42±11.43 µmo/L, HDL-C 1.01±0.26 mmo/L, TC 4.12±0.99 mmo/L, Ser 64.2±11.43 µmo/L, HDL-C 1.01±0.27 mmo/L, DL-C 2.56±0.76 mmo/L, Ser 64.2±11.43 µmo/L, HDL-C 1.01±0.27 mmo/L, LDL-C 2.56±0.76 mmo/L, Ser 64.2±11.43 µmo/L, HDL-C 1.01±0.27 mmo/L, TC 4.12±0.99 mmo/L, Ser 64.2±1.96, PM 22.2±4.59, HDA1e 3.59%±1.95%, Cys-C 0.88±0.57 mmo/L, Ser 64.2±11.43 µmo/L, HDL-C 1.03±0.27 mmo/L, LDL-C 2.36±0.62 mmo/L, Ser 64.2±1.95, HDA1e 3.2±4.59, HDA1e 3.55±0.76 mmo/L, Ser 64.12±1.99 mmo/L, Ser 64.12±3.1 µmo/L, HDL-C 1.03±0.27 mmo/L, LDL-C 2.36±0.62 mmo/L, Ser 64.12±3.1 µmo/L, HDL-C 1.03±0.27 mmo/L, Ser 64.2±5.39, HDA1e Ser 64.5±0.37 mmo/L, Ser 64.12±3.1 µmo/L, Ser 64.12±3.1 µmo/L, Ser 64.12±3.1 µmo/L, Ser 64.12±3.1 µmo/L, Ser 64.12±5.31 µmo/L, HDL-C 1.03±0.27 mmo/L, Ser 64.12±5.31 µmo/L, HDL-C 1.03±0.27 mmo/L, Ser 64.12±5.31 µmo/L, Ser 64.12±3.1 µmo/L, Ser 64.12±3.1 µmo/L, Ser 64.12±5.31 µmo/L, Ser 64.12±3.1 µmo/L, Ser 64.12±3.2 µmo/L, Ser 64.2±4.123, NM 22.2±4.33±4.03, HDA1 | E | TIIA | | 7 | | m=53 (M/F 32/21), age 56.27±8.38y, duration 5.62±1.02y, BMI 25.36±4.17, HbA1e 8.89%±0.91%, Cys-C 1.19±0.17 mmo//L, TC 4.89±0.15 mmo//L, TG 1.62±0.13 mmo//L, HDL-C 1.18±0.08 mmo//L, LDL-C 2.69±0.42 mmo//L | ±4.17, HbA1e 8.89%±0.91%, Cys-C DL-C 1.18±0.08 mmo//L, LDL-C |
| Setun 6 n=57, age 56.4±10.65, duration 48±0.65, BMI 23.6±3.9, Cys-C 0.85±0.25 mmol/L, TC 5.28±1.32 mmol/L, GFR 74.6±8.4 mL/min EDL-C 2.88±0.42 mmol/L, GFR 74.6±8.4 mL/min Setum 6 n=43 (MF 21/22), age 64.13, duration 11.75, HbA1e 9.28%±1.02%, Cys-C 0.98±0.12 mmol/L, HDL-C 0.98±0.12 mmol/L, HDL-C 0.98±0.12 mmol/L, HDL-C 0.98±0.12 mmol/L, HDL-C 1.01±0.26 mmol/L, TC 4.72±1.09 mmol/L, TG 2.12±0.89 mmol/L, HDL-C 1.01±0.26 mmol/L, EDL-C 2.56±0.76 mmol/L, Ser 66.42±11.43 µmol/L Plasma 7 n=40 (MF 25/152), age 57.2±11.423, duration 6.61±1.50, BMI 26.49±6.12, HbA1e 7.4%±2.1%, Cys-C 1.35±0.54 mmol/L, EDL-C 2.56±0.76 mmol/L, Ser 66.42±11.43 µmol/L Setum 6 n=00 (MF 57/52), age 57.2±11.423, duration 10.1±6.29, BMI 22.2±4.59, HbA1e 6.4%±0.1%, Cys-C 1.03±0.27 mmol/L, LDL-C 2.36±0.76 mmol/L, TG 1.7±0.79 mmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.76 mmol/L, TG 1.7±0.79 mmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.62 mmol/L, TG 1.7±0.79 mmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.76 mmol/L, Ser 66.42±11.43 µmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.76 mmol/L, Ser 69.12±15.31 µmol/L, BDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.62 mmol/L, TG 1.7±0.79 mmol/L, TG 1.7±0.72 mmol/L, TG 4.12±0.99 mmol/L, TG 1.7±0.79 mmol/L, TG 4.03±0.21 µmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.76 mmol/L, Ser 9.12±15.31 µmol/L, TG 4.12±0.33 mmol/L, TG 4.03±0.31 µmol/L, TG 4.03±0.27 mmol/L, TG 4.03±0.23 mmol/L, TG 4.03±0.57 mmol/L, TG 4.03±0.57 mmol/L, TG 4.03±0.57 mmol/L, TG 4.03±0.53 mmol/L, TG 4.03±0.55 mmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, TC 4.01±1.33 mmol/L, TG 2.05±0.52 mmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±0.51 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±0.51 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±0.57 mmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±0.57 mmol/L, HDL-C 1.35±0.34 mmol/L, DC 2.81±0.57 mmol/L, Ser 71.89±0.57 mmol/L, HDL-C 1.35±0.59, | L | 711A | | 9 | <i>n</i> =92 (M/F 52/40), age 56.37±8.07y, duration 2.38±2.01y, BMI 24.38±1.93, HbA1c 9.11%±2.90%, Cys-C 0.91±0.67 mmo/L TC 5.83±1.32 mmo/L, TG 2.68±1.73 mmo/L, HDL-C 1.18±0.62 mmo/L, LDL-C 3.36±0.91 mmo/L, GFR 8.97±18.57 mL/min, Scr 57.84±11.57 µmo/L | n=98 (M/F 46/52), age 59.97±13.01y, duration 7.08±5.32y, BMI 24.98±2.93, HbA1c 9.52%±1.37%, Cys-C 1.71±0.52 mmo/L TC 4.89±1.32 mmo/L, TG 3.05±1.27 mmo/L, HDL-C 1.10±0.26 mmo/L, LDL-C 4.08±0.92 mmo/L, GFR 77.84±21.57 mL/min, Scr 65.24±13.27µmo/L | 8+2.93, HbAlc 9.52%+1.37%, Cys-C DL-C 1.10+0.26 mmo/L, LDL-C /L |
| Serum 6 n=43 (M/F 2/122), age 64.1y, duration 11.7y, HbA1e 9.28%=1.02%, Cys-C 0.98±0.12 mmol/L Serum 6 n=80 (M/F 38/42), age 54.40±11.25y, duration 6.61±1.50y, BMI 26.49±6.12, HbA1e 8.59%±1.04%, Cys-C 0.86±0.11 mmol/L, TC 4.72±1.09 mmol/L, TG 2.12±0.80 mmol/L, HDL-C 1.01±0.26 mmol/L, LDL-C 2.56±0.76 mmol/L, Ser 66.42±11.43 µmol/L, HDL-C 1.01±0.26 mmol/L, DL-C 2.56±0.76 mmol/L, Ser 66.42±11.43 µmol/L, HDL-C 1.01±0.26 mmol/L, DL-C 2.56±0.76 mmol/L, Ser 66.42±11.43 µmol/L, HDL-C 1.01±0.26 mmol/L, LDL-C 2.56±0.76 mmol/L, Ser 66.42±11.43 µmol/L, HDL-C 1.01±0.27 mmol/L, LDL-C 2.56±0.76 mmol/L, TG 4.72±6.79 µmol/L, TG 4.72±0.99 mmol/L, TG 4.72±0.99 mmol/L, TG 4.12±0.99 mmol/L, TG 4.12±0.79 mmol/L, TG 4.01±1.53 µmol/L, TG 4.01±1.53 µmol/L, TG 4.01±1.53 µmol/L, TG 4.01±1.53 µmol/L, TG 4.01±1.33 mmol/L, TG 4.01±1.33 mmol/L, TG 2.03±0.52 mmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±0.57 mmol/L, S | F | TIIA S | | 9 | <i>m</i> =57, age 56.4±10.6y, duration 4.8±0.6y, BMI 23.6±3.9, Cys-C 0.85±0.25 mmol/L, TC 5.28±1.32 mmol/L, TG 1.98±0.32 mmol/L, HDL-C 0.96±0.24 mmol/L, LDL-C 2.88±0.42 mmol/L, GFR 74.6±8.4 mL/min | n=43, age 60.1±12.9y, duration 7.8±1.2y, BMI 24.2±2.8, Cys-C 1.39±0.21 mmol/L, TC 5.41±1.09 mmol/L, TG 2.01±0.29 mmol/L, HDL-C 0.96±0.24 mmol/L, LDL-C 2.94±0.56 mmol/L, GFR 66.4±6.6 mL/min | 0.21 mmol/L, TC 5.41±1.09 mmol/L, TG nol/L, GFR 66.4±6.6 mL/min |
| Serum 6 <i>n=80</i> (M/F 38/42), age 5440±11.25y, duration 661±1.50y, BMI 26.49±6.12, HbA1c 8.59%±1.94%, Cys-C 0.86±0.11 mmol/L, TC 4.72±1.09 mmol/L, TG 2.12±0.89 mmol/L, HDL-C 1.01±0.26 mmol/L, LDL-C 2.56±0.76 mmol/L, Scr 66.42±11.43 µmol/L Plasma 7 <i>n=40</i> (M/F 26/14), age 52.8y, duration 5.6y, BMI 23.2±0.7, HbA1c 7.4%±2.1%, Cys-C 1.35±0.54 mmol/L Serum 6 <i>n=109</i> (M/F 57/52), age 57.2±11.42y, duration 10.1±6.2y, BMI 22.2±4.59, HbA1c 6.4%±0.1%, Cys-C 0.98±0.23 mmol/L, TC 4.12±0.99 mmol/L, TG 1.75±0.79 mmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.62 mmol/L, Scr 69.12±15.31 µmol/L Sample NOS DWR Sample NOS DWR Serum 7 <i>n=30</i> (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmol/L Serum 6 <i>n=30</i> (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmol/L, TG 1.75±0.79 mmol/L, HDL-C 1.03±0.27 mmol/L, Scr 69.12±15.31 µmol/L Serum 7 <i>n=30</i> (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmol/L, HDL-C 1.35±0.57 mmol/L, Scr 69.12±15.31 µmol/L Serum 6 <i>n=30</i> (M/F 19/17), age 52.01±5.44y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L Serum 7 <i>n=45</i> (M/F 22/23), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L, HDL-C 1.35±0.34 mmol/L, TG 2.05±0.52 mmol/L, RC 4.01±1.33 mmol/L, RC 2.05±0.52 mmol/L, HDL-C 1.35±0.34 mmol/L, RC 4.01±1.33 mmol/L, Scr 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, RC 4.01±1.33 mmol/L, Scr 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, RC 4.01±1.35 mmol/L, Scr 71.89±10.21 µmol/L, HDL-C 1.35±0.34 mmol/L, RC 4.05±6.59, duration 0.5-55, Cys-C 0.88±0.67 mmol/L, RC 4.05±0.55 mmol/L, RC 4.05±0.55 mmol/L, RC 4.05±0.55 mmol/L, HDL-C 1.35±0.34 mmol/L, RC 4.05±0.55 mmol/L, RC | Г | TIIA S | | 9 | <i>m</i> =43 (<i>M</i> /F 21/22), age 64.1 y, duration 11.7y, HbA1c 9.28%±1.02%, Cys-C 0.98±0.12 mmol/L | n =43 (M/F 23/20), age 63.9y, duration 11.9y, HbA1c 9.72% \pm 1.08%, Cys-C 1.51 \pm 0.36 mmol/L | Cys-C 1.51±0.36 mmol/L |
| Plasma 7 n=40 (M/F 26/14), age 52.8y, duration 5.6y, BMI 23.2±0.7, HbA1c 7.4%±2.1%, Cys-C 1.35±0.54 mmo/L Serum 6 n=109 (M/F 57/52), age 57.2±11.42y, duration 10.1±6.2y, BMI 22.2±4.59, HbA1c 6.4%±0.1%, Cys-C 0.88±0.23 mmo/L, TC 4.12±0.99 mmo/L, TG 1.75±0.79 mmo/L, HDL-C 1.03±0.27 mmo/L, LDL-C 2.36±0.62 mmo/L, Ser 69.12±15.31 µmo/L Sample NOS NOS DWR Serum 7 n=30 (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmo/L Serum 6 n=387 (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.88±0.67 mmo/L Serum 6 n=387 (M/F 192/195), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmo/L Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1c 8.94%±1.35%, Cys-C 1.42±0.33 mmo/L, TC 4.01±1.33 mmo/L, TG 2.05±0.52 mmo/L, HDL-C 1.35±0.34 mmo/L, TC 2.81±0.57 mmo/L, Ser 71.89±10.21 µmo/L | L | | | 9 | <i>m</i> =80 (<i>M</i> /F 38/42), age 54.40±11.25y, duration 6.61±1.50y, BMI 26.49±6.12, HbA1c 8.59%±1.94%, Cys-C 0.86±0.11 mmo/ <i>L</i> , TC 4.72±1.09 mmo/ <i>L</i> , TG 2.12±0.89 mmo/ <i>L</i> , HDL-C 1.01±0.26 mmo/ <i>L</i> , LDL-C 2.56±0.76 mmo/ <i>L</i> , Ser 66.42±11.43 µmo/ <i>L</i> | <i>m</i> =80 (M/F 42/38), age 53.41±10.91y, duration 7.12±1.81y, BMI 26.53±4.80, HbA1c 8.96%±2.14%, Cys-C 1.42±0.25 mmol/L, TC 4.89±1.12 mmol/L, TG 2.96±0.96 mmol/L, HDL-C 0.96±0.24 mmol/L, LDL-C 2.76±0.89 mmol/L, Ser 72.23±15.41 μmol/L | DL-C 0.96±0.24 mmol/L, LDL-C |
| Serum 6 n=109 (M/F 57/52), age 57.2±11.42y, duration 10.1±6.2y, BMI 22.2±4.59, HbA1e 6.4%:40.1%, Cys-C 0.98±0.23 mmol/L, TC 4.12±0.99 mmol/L, TG 1.75±0.79 mmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.62 mmol/L, Scr 69.12±15.31 µmol/L, Sample NOS Sample NOS DWR Serum 7 n=30 (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmol/L Serum 7 n=30 (M/F 13/17), age 52.01±5.44y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L Serum 6 n=387 (M/F 192/195), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L, HDL-C 1.35±0.34 mmol/L, TC 4.01±1.33 mmol/L, TG 2.05±0.52 mmol/L, HDL-C 1.35±0.34 mmol/L, TC 2.08±0.67 mmol/L, Ser 1.89±10.21 µmol/L, Ser 3.200/L, Ser | H | | | 7 | <i>m</i> =40 (<i>M</i> /F 26/14), age 52.8y, duration 5.6y, BMI 23.2±0.7, HbA1c 7.4%±2.1%, Cys-C 1.35±0.54 mmol/L | <i>n</i> =40 (M/F 19/21), age 53.1y, duration 8.7y, BMI 23.5±0.5, HbA1c 7.5%±1.9%, Cys-C 3.16±0.29 mmol/L | 5%±1.9%, Cys-C 3.16±0.29 mmol/L |
| Sample NOS DWR Serum 7 n=30 (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmol/L Serum 7 n=45 (M/F 22/23), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L Serum 6 n=387 (M/F 192/195), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1e Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1e Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1e Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1e Serum 7 n=100 (M/F 60/40), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L, | | | | 9 | <i>m</i> =109 (M/F 57/52), age 57.2±11.42y, duration 10.1±6.2y, BMI 22.2±4.59, HbA1c 6.4%±0.1%, Cys-C 0.98±0.23 mmol/L, TC 4.12±0.99 mmol/L, TG 1.75±0.79 mmol/L, HDL-C 1.03±0.27 mmol/L, LDL-C 2.36±0.62 mmol/L, Ser 69.12±15.31 µmol/L | n=95 (M/F 54/41), age 57.5±10.23y, duration 10.2±5.1y, BMI 24.61±4.24, HbA1c 7.5%±1.7%, Cys-C 1.26±0.41 mmol/L, TC 4.33±1.05 mmol/L, TG 1.91±0.66 mmol/L, HDL-C 1.01±0.51 mmol/L, LDL-C 2.48±0.43 mmol/L, Scr 70.23±12.11 µmol/L | 4.24, HbA1c 7.5%±1.7%, Cys-C DL-C 1.01±0.51 mmol/L, LDL-C |
| Serum 7 n=30 (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmol/L Serum 7 n=45 (M/F 22/23), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1e 8.94%±1.35%, Cys-C 1.42±0.33 mmol/L, TC 4.01±1.33 mmol/L, TG 2.05±0.52 mmol/L, HDL-C 1.35±0.54 mmol/L, LDL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, BHL-C 1.35±0.54 mmol/L, Ser 71.89±10.21 µmol/L, BHL-C 1.35±0.54 mmol/L, Not 71.89±10.21 µmol/L, BHL-C 1.35±0.54 mmol/L, BHL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, BHL-C 1.35±0.54 mmol/L, Ser 71.89±10.21 µmol/L, Ser 71.89±10.21 µmol/L, BHL-C 1.35±0.54 mmol/L, BHL-C 2.81±0.57 mmol/L, Ser 71.89±10.21 µmol/L, BHL-C 1.35±0.54 mmol/L, Ser 71.89±10.21 µmol/L, Ser 71.80±10.10, Ser 71.89±10.21 µmol/L, Ser 71.80±10.10, Ser 71.80±10.1 | Ae | | | SON | DWR | NPDR | PDR |
| Serum 7 n=45 (M/F 22/23), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1c 8.94%±1.35%, Cys-C 1.42±0.33 mmol/L, TC 4.01±1.33 mmol/L, TG 2.05±0.25 mmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Scr 71.89±10.21 µmol/L 8.100 (M/F 60/40), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L | | | | ٢ | <i>n</i> =30 (M/F 13/17), age 52.01±5.44y, duration 8.1±1.5y, Cys-C 0.84±0.23 mmol/L | .76±7.25y, duration 8.0±1.2y, | $n{=}30~({\rm M/F}~16/14),$ age 53.16±4.28y, duration 10.1±2.3y, Cys-C 2.42±0.40 mmol/L |
| Serum 6 n=387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1c 8.94%±1.35%, Cys-C 1.42±0.33 mmol/L, TC 4.01±1.33 mmol/L, TG 2.05±0.52 mmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Scr 71.89±10.21 µmol/L, Sr 71.85±10.21 µmol/L, Sr 71.89±10.21 µmol/L, Sr 71.85±10.21 µmol/L, Sr 71.25±10.21 µmol/L, Sr 71.25±10.21 µmol/L, Sr 71.25±10.21 µmol/L | E. | ELISA S | | ٢ | n=45 (M/F 22/23), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L | age 65.3±5.4y, duration 3-15y, Cys-C | $n=46 \text{ (M/F } 25/21\text{)}, \text{ age } 68.6\pm5.8\text{y}, \text{ duration } 5-20\text{y}, \text{ Cys-C}$ 3.31±1.86 mmol/L |
| 7 n=100 (M/F 60/40), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L | L | TIIA | | 9 | <i>n</i> =387 (M/F 192/195), age 55.21±12.01y, duration 6.38±4.03y, BMI 25.33±4.03, HbA1c 8.94%±1.35%, Cys-C 1.42±0.33 mmol/L, TC 4.01±1.33 mmol/L, TG 2.05±0.52 mmol/L, HDL-C 1.35±0.34 mmol/L, LDL-C 2.81±0.57 mmol/L, Scr 71.89±10.21 µmol/L | 56.33±12.55% duration 4.24, HbA1e 9.01%±1.44%, ., TG 2.24±0.71 mmol/L, /L, LDL-C 2.89±0.61 mmol/L, | <i>n</i> =108 (<i>M</i> /F 45/63), age 59.83±11.87y, duration 12.30±5.34y, BMI 26.89±5.73, HbA1e 10.22%±1.79%, Cys-C 1.85±0.45 mmol/L, TG 2.64±0.69 mmol/L, HDL-C 1.17±0.30 mmol/L, LDL-C 3.27±0.72 mmol/L, Ser 80.11±14.21 µmol/L |
| 1.30±0.86 mmo/L | E | | | ٢ | <i>n</i> =100 (M/F 60/40), age 64.5±6.9y, duration 0.5-5y, Cys-C 0.88±0.67 mmol/L | ı, age 65.3±5.4y, duration 3-15y, Cys-C | <i>m</i> =100 (M/F 45/55), age 68±4.8y, duration 5-20y, Cys-C 3.31±1.86 mmol/L |

| Cui 2019 ELISA | Serum | ~ | n=42 (M/F 23/19), age 57.98±8.62y, duration 7.17±2.76y, BMI 25.98±5.92, HbA1c 8.1196±1.54%, Cys-C 0.72±0.31 mmo//L, TC 5.32±0.80 mmo//L, TG 1.92±0.99 mmo//L, LDL-C 2.97±0.80 mmo//L | n=38 (M/F 20/18), age 58.31±9.10y, duration 7.99±3.05y, BMI 26.76±5.78, HbA1e 9.77%±1.89%, Cys-C 0.99±0.38 mmol/L, TC 5.42±0.96 mmol/L, TG 2.15±0.78 mmol/L, LDL-C 3.09±0.80 mmol/L | n=34 (M/F 18/16), age 56.82±8.69y, duration 8.32±2.98y, BMI 25.81±6.44, HbA1e 10.66%±2.03%, Cys-C 1.59±0.42 mmol/L, TC 5.88±1.35 mmol/L, TG 1.99±0.82 mmol/L, LDL-C 3.43±1.01 mmol/L |
|----------------------------------|-------|---|---|---|--|
| Han 2019 — | Serum | | n=52 (M/F 30/22), age 56.42±8.90y, duration 6.04±2.61y, BMI 23.42±3.41, HbA1c 6.25%±0.70%, Cys-C 1.34±1.17 mmol/L, TC 4.66±0.73 mmol/L, TG 1.92±0.37 mmol/L, HDL-C 1.55±0.94 mmol/L, LDL-C 2.24±0.90 mmol/L, Scr 69.90±13.71 µmol/L | n=56 (M/F 32/24), age 57.84±7.36y, duration 10.14±3.94y, BMI 23.17±2.32, HbA1 e 6.71%±0.69%, Cys-C 1.64±0.17 mmo/L, TC 5.36±0.67 mmo/L, TG 2.15±0.38 mmo/L, HDL-C 1.28±0.64 mmo/L, LDL-C 3.63±0.83 mmo/L, Scr 78.74±13.09 µmo/L | m=42 (<i>MF</i> 22/20), age 59.24±11.10y, duration 14.16±3.61y, BMI 22.33±3.10, HbA1e 7.33%±0.66%, Cys-C 1.89±0.17 mmo/L, TC 5.94±0.84 mmo/L, TG 2.67±0.54 mmo/L, HDL-C 1.48±0.87 mmo/L, LDL-C 4.11±0.67 mmo/L, Ser 99.19±19.80 µmo/L |
| Jin 2019 TIIA | Serum | Г | n=82 (M/F 39/43), age 57.62±8.50y, Cys-C 0.61±0.44 mmol/L, Scr 68.61±4.74 µmol/L | n=54 (M/F 26/28), age 57.61±8.00y, HbA16, Cys-C 0.64±0.05 mmol/L, Scr 68.63±4.74 µmol/L | n=46 (MF 22/24), age 58.02±9.63 , Cys-C 0.66±0.08 mmo/L, Scr 71.00±6.14 µmo/L |
| Li 2015 TIIA | Serum | Г | n=49 (M/F 24/25), age 70.03±8.2y, duration 5.3±3.2y, HbA1c 6.7%±0.8%, Cys-C 0.95±0.38 mmol/L | n=41 (M/F 20/21), age 69.69±8.78y, duration 7.5±4.7y, HbA1e 7.6%±0.8%, Cys-C 1.75±0.31 mmol/L | n=35 (M/F 19/16), age 73.14±7.25y, duration 10.3±5.1y, HbA1c 8.9%±0.7%, Cys-C 2.24±0.67 mmo/L |
| Wang Latex 2018 Agglutination | Serum | L | n=50 (M/F 23/27), age 61.9±5.4y, duration 5.9±1.7y, BMI 26.4±3.0, HbA.1c 7.2%±0.9%, Cys-C 1.08±0.68 mmo/L, TC 4.80±0.82 mmo/L, TG 2.18±0.92 mmo/L, HDL-C 1.34±0.42 mmo/L, LDL-C 3.48±0.74 mmo/L | <i>m</i> =50 (M/F 24/26), age 61.7±5.2y, duration 8.0±1.8y, BMI 26.5±3.2, HbA1e 8.0%±1.2%, Cys-C 1.34±0.50 mmo/L, TC 5.41±0.95 mmo/L, TG 2.93±2.29 mmo/L, HDL-C 1.19±0.33 mmo/L, LDL-C 3.72±0.76 mmo/L | n=50 (M/F 23/27), age 61 5:46.3y, duration 9.4±2.2y, BMI 25.7±2.6, HbA1.e 10.1%±2.3%, Cys-C 1.60±0.71 mmo/L, TC 5.85±0.94 mmo/L, TG 2.96±1.81 mmo/L, HDL-C 1.18±0.25 mmo/L, LDL-C 3.81±0.84 mmo/L |
| Wang TIIA 2019 | Serum | ~ | <i>m</i> =125 (<i>M</i> /F 64/61), age 56.8±5.4y, duration 2.9±1.1y, BMI 25.1±2.4, HbA1c 7.2%±1.8%, Cys-C 0.9±40.13 mmol/L, TC 4.92±1.03 mmol/L, TG 1.81±0.76 mmol/L, HDL-C 1.46±0.65 mmol/L, LDL-C 2.53±1.02 mmol/L | <i>m</i> =118 (M/F 61/57), age 57.3±6.2y, duration 7.1±1.7y, BMI 246±1.9, HbA1e 8.6%±2.1%, Cys-C 1.15±0.14 mmol/L, TC 4.99±1.08 mmol/L, TG 1.75±0.72 mmol/L, HDL-C 1.38±0.57 mmol/L, LDL-C 2.65±1.01 mmol/L | n=97 (<i>M/F</i> 50/47), age 57.8±5.8y, duration 9.2±2.4y, BMI 25.5±2.1, HbA1e 10.4%±2.5%, Cysc T.35±0.19 mmo/L, TC 5.13±1.14 mmo/L, TG 1.88±0.84 mmo/L, HDL-C 1.33±0.61 mmo/L, LDL-C 2.58±1.04 mmo/L |
| Wei 2017 ELISA | Serum | × | n=28 (M/F 14/14), age 53.22±9.39y, duration 6.16±5.44y, BMI 25.52±4.00, HbA1c 7.59%±1.59%, Cys-C 0.84±0.20 mmol/L, BUN 5.81±2.88 mmol/L | n=54 (M/F 22/32), age 55.85±7.85%, duration 10.77±5.75%, BMI 24.68±3.33, HbA1e 8.51%d=1.70%, Cys-C 1.10±0.48 mmol/L, BUN 5.97±2.70 mmol/L | n=35 (M/F 18/17), age 56.59±10.80y, duration 13.76±8.62y, BMI 24.54±4.14, HbA1e 9.95%±2.18%, Cys-C 1.31±0.69 mmol/L, BUN 6.00±1.88 mmol/L |
| Yang TIIA 2016 | Serum | 9 | <i>n</i> =28, age 45.4±5.9y, duration 6.54±5.86y, Cys-C 1.35±0.18 mmol/L | <i>n</i> =45, age 53.4±8.7y, duration 12.54±3.97y, Cys-C 1.64±0.21 mmol/L | <i>n</i> =97, age 65.4±7.4y, duration 15.54±6.43y, Cys-C 2.47±0.49 mmo/L |

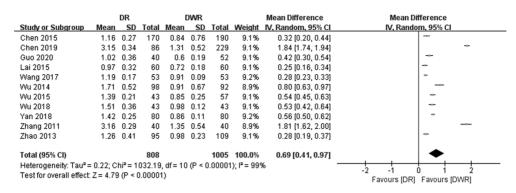


Figure 3 The forest plot of Cys-C between the DR and DWR group.

| | N | IPDR | | 1 | OWR | | | Mean Difference | Mean Difference |
|-----------------------------------|------------|----------|---------|-----------|---------|--------|----------|--------------------|------------------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% Cl | IV, Random, 95% Cl |
| Bao 2018 | 1.12 | 0.28 | 50 | 0.84 | 0.23 | 30 | 9.5% | 0.28 [0.17, 0.39] | |
| Chen 2010 | 1.3 | 0.86 | 42 | 0.88 | 0.67 | 45 | 4.8% | 0.42 [0.09, 0.75] | |
| ChenJ 2017 | 1.54 | 0.42 | 155 | 1.42 | 0.33 | 387 | 10.3% | 0.12 [0.05, 0.19] | |
| ChenYS 2017 | 1.3 | 0.86 | 100 | 0.88 | 0.67 | 100 | 7.1% | 0.42 [0.21, 0.63] | |
| Cui 2019 | 0.99 | 0.38 | 38 | 0.72 | 0.31 | 42 | 8.6% | 0.27 [0.12, 0.42] | |
| Han 2019 | 1.64 | 0.17 | 56 | 1.34 | 1.17 | 52 | 4.9% | 0.30 [-0.02, 0.62] | |
| Jin 2019 | 0.64 | 0.05 | 54 | 0.61 | 0.44 | 82 | 9.9% | 0.03 [-0.07, 0.13] | |
| Li 2015 | 1.75 | 0.31 | 41 | 0.95 | 0.38 | 49 | 8.8% | 0.80 [0.66, 0.94] | |
| Wang 2018 | 1.34 | 0.5 | 50 | 1.08 | 0.68 | 50 | 6.6% | 0.26 [0.03, 0.49] | |
| Wang 2019 | 1.15 | 0.14 | 118 | 0.94 | 0.13 | 125 | 10.8% | 0.21 [0.18, 0.24] | - |
| Wei 2017 | 1.1 | 0.48 | 54 | 0.84 | 0.2 | 28 | 8.7% | 0.26 [0.11, 0.41] | |
| Yang 2016 | 1.64 | 0.21 | 45 | 1.35 | 0.18 | 28 | 10.0% | 0.29 [0.20, 0.38] | |
| Total (95% CI) | | | 803 | | | 1018 | 100.0% | 0.29 [0.20, 0.39] | • |
| Heterogeneity: Tau ² : | = 0.02; C | hi² = 9 | 5.10, ď | f = 11 (F | , < 0.0 | 0001); | l² = 88% | | |
| Test for overall effect | : Z = 6.02 | 2 (P < (| 0.0000 | D) Ì | | | | | -1 -0.5 0 0.5 |
| | | | | | | | | | Favours (NPDR) Favours (DWR) |

Figure 4 The forest plot of Cys-C between the NPDR and DWR group.

| 1 | PDR | | N | IPDR | | | Mean Difference | Mean Difference |
|----------|--|---|--|---|---|---|--|--|
| Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% Cl | IV, Random, 95% Cl |
| 2.42 | 0.4 | 30 | 1.12 | 0.28 | 50 | 8.8% | 1.30 [1.14, 1.46] | |
| 3.31 | 1.86 | 46 | 1.3 | 0.86 | 42 | 5.0% | 2.01 [1.41, 2.61] | |
| 1.85 | 0.47 | 108 | 1.54 | 0.42 | 155 | 9.1% | 0.31 [0.20, 0.42] | - |
| 3.31 | 1.86 | 100 | 1.3 | 0.86 | 100 | 6.7% | 2.01 [1.61, 2.41] | |
| 1.59 | 0.42 | 34 | 0.99 | 0.38 | 38 | 8.7% | 0.60 [0.41, 0.79] | |
| 1.89 | 0.17 | 42 | 1.64 | 0.17 | 56 | 9.3% | 0.25 [0.18, 0.32] | - |
| 0.66 | 0.08 | 46 | 0.64 | 0.05 | 54 | 9.4% | 0.02 [-0.01, 0.05] | |
| 2.24 | 0.67 | 35 | 1.75 | 0.31 | 41 | 8.2% | 0.49 [0.25, 0.73] | |
| 1.6 | 0.71 | 50 | 1.34 | 0.5 | 50 | 8.2% | 0.26 [0.02, 0.50] | |
| 1.35 | 0.19 | 97 | 1.15 | 0.14 | 118 | 9.4% | 0.20 [0.15, 0.25] | |
| 1.31 | 0.69 | 35 | 1.1 | 0.48 | 54 | 8.0% | 0.21 [-0.05, 0.47] | + |
| 2.47 | 0.49 | 97 | 1.64 | 0.21 | 45 | 9.1% | 0.83 [0.71, 0.95] | - |
| | | 720 | | | 803 | 100.0% | 0.63 [0.43, 0.82] | • |
| 0.10; CI | hi² = 5 | 88.26, | df = 11 (| (P < 0. | 00001) | ; I² = 98% | _ | -2 -1 0 1 2 |
| Z = 6.33 | (P < 0 | 0.00001 |) | | | | | Favours (PDR) Favours (NPDR) |
| | Mean 2.42 3.31 1.85 3.31 1.59 1.89 0.66 2.24 1.6 1.35 1.31 2.47 0.10; C | 2.42 0.4 3.31 1.86 1.85 0.47 3.31 1.86 1.59 0.42 1.89 0.17 0.66 0.08 2.24 0.67 1.6 0.71 1.35 0.19 2.47 0.49 0.10; Chi ² = 5 | Mean SD Total 2.42 0.4 30 3.31 1.86 00 1.85 0.47 108 3.31 1.86 100 1.59 0.42 34 1.89 0.17 42 0.66 0.08 46 2.24 0.67 35 1.6 0.71 50 1.35 0.19 97 1.31 0.69 35 2.47 0.49 97 720 0.10; Chi² = 588.26, | Mean SD Total Mean 2.42 0.4 30 1.12 3.31 1.86 46 1.3 1.85 0.47 108 1.54 3.31 1.86 100 1.3 1.59 0.42 34 0.99 1.89 0.17 42 1.64 0.66 0.08 46 0.64 0.61 0.08 46 0.64 1.89 0.17 42 1.64 0.66 0.08 46 0.64 1.89 0.17 5 1.75 1.6 0.71 50 1.34 1.35 0.19 97 1.64 1.31 0.69 35 1.11 2.47 0.49 97 1.64 | Mean SD Total Mean SD 2.42 0.4 30 1.12 0.28 3.31 1.86 46 1.3 0.86 1.85 0.47 108 1.54 0.42 3.31 1.86 100 1.3 0.86 1.69 0.42 34 0.99 0.38 1.89 0.17 42 1.64 0.17 0.66 0.08 46 0.64 0.65 2.24 0.67 35 1.75 0.31 1.66 0.71 50 1.34 0.5 1.35 0.19 97 1.15 0.14 1.31 0.69 35 1.1 0.48 2.47 0.49 97 1.64 0.21 720 0.10; Chi ² = 588.26, df = 11 (P < 0. | Mean SD Total Mean SD Total 2.42 0.4 30 1.12 0.28 50 3.31 1.86 46 1.3 0.86 42 1.85 0.47 108 1.54 0.42 155 3.31 1.86 100 1.3 0.86 100 1.59 0.42 34 0.99 0.38 38 1.89 0.17 42 1.64 0.17 56 0.66 0.08 46 0.64 0.05 54 2.24 0.67 35 1.75 0.31 41 1.6 0.71 50 1.34 0.5 50 1.35 0.19 97 1.64 0.21 45 T20 803 0.10; Chi ^p = 588.26, df = 11 (P < 0.00001) | Mean SD Total Mean SD Total Weight 2.42 0.4 30 1.12 0.28 50 8.8% 3.31 1.86 46 1.3 0.86 42 5.0% 1.85 0.47 108 1.54 0.42 155 9.1% 3.31 1.86 100 1.3 0.86 100 6.7% 1.89 0.47 108 1.04 0.17 56 9.3% 1.89 0.17 42 1.64 0.16 9.3% 38 8.7% 1.89 0.17 50 1.34 0.5 50 9.3% 0.66 0.08 46 0.64 0.05 54 9.4% 2.24 0.67 35 1.75 0.31 41 8.2% 1.35 0.19 97 1.56 0.14 118 9.4% 2.47 0.49 97 1.64 0.21 45 9.1% <td>Mean SD Total Mean SD Total Weight V, Random, 95% Cl 2.42 0.4 30 1.12 0.28 50 8.8% 1.30 [1.14, 1.46] 3.31 1.86 46 1.3 0.86 42 50.% 2.01 [1.41, 1.46] 3.31 1.86 047 108 1.54 0.42 155 9.1% 0.31 [0.20, 0.42] 3.31 1.86 100 1.3 0.86 100 6.7% 2.01 [1.61, 2.41] 1.59 0.42 3.4 0.99 0.38 38 8.7% 0.60 [0.41, 0.79] 1.89 0.17 42 1.64 0.17 56 9.3% 0.25 [0.18, 0.32] 0.66 0.08 46 0.5 54 9.4% 0.02 [-0.01, 0.05] 2.24 0.67 35 1.75 0.31 41 8.2% 0.49 [0.25, 0.73] 1.6 0.71 50 1.34 0.5 50 8.2% 0.20 [0.15, 0.25]</td> | Mean SD Total Mean SD Total Weight V, Random, 95% Cl 2.42 0.4 30 1.12 0.28 50 8.8% 1.30 [1.14, 1.46] 3.31 1.86 46 1.3 0.86 42 50.% 2.01 [1.41, 1.46] 3.31 1.86 047 108 1.54 0.42 155 9.1% 0.31 [0.20, 0.42] 3.31 1.86 100 1.3 0.86 100 6.7% 2.01 [1.61, 2.41] 1.59 0.42 3.4 0.99 0.38 38 8.7% 0.60 [0.41, 0.79] 1.89 0.17 42 1.64 0.17 56 9.3% 0.25 [0.18, 0.32] 0.66 0.08 46 0.5 54 9.4% 0.02 [-0.01, 0.05] 2.24 0.67 35 1.75 0.31 41 8.2% 0.49 [0.25, 0.73] 1.6 0.71 50 1.34 0.5 50 8.2% 0.20 [0.15, 0.25] |

Figure 5 The forest plot of Cys-C between the NPDR and PDR group.

NPDR and PDR. Mean difference of Cys-C between DWR and NPDR was presented in Figure 4. The forest plot indicated higher Cys-C level in the NPDR than that of the DWR (total MD: 0.29, 95%CI: 0.20 to 0.39, P<0.01). Meanwhile, the similar effect was observed in the PDR *vs* NPDR group (total MD: 0.63, 95%CI 0.43 to 0.82, P<0.01; Figure 5).

Subgroup Analysis Results The results comparison between DWR and DR was presented in Figure 6. The heterogeneity of most of the subgroup analyses was still obvious ($l^2 \ge 50\%$, P < 0.1). The Cys-C level of the DR group was noticeably higher than that of the DWR group except BMI ≤ 24 kg/m² subgroup (subtotal MD: 1.03, 95%CI -0.50 to 2.56, Z=1.32, P=0.19) and plasma subgroup (subtotal MD: 1.03, 95%CI -0.50 to 2.56, Z=1.32, P=0.19). Two exceptions showed the same result because both included the same articles. In

subgroup analyses between DWR and NPDR, NPDR and PDR, the difference of the level of Cys-C between control group and experiment group presented the same trend as the comparison between DWR and DR. As Figure 7 showed, different subgroups in DWR and NPDR attained huge decrease in heterogeneity to some extent such as BMI>24 kg/m² (P=0.16, I^2 =39%). Particularly, ELISA (P=0.54, I^2 =0) displayed no heterogeneity. Forest plots of different subgroups indicated that there was a slight increase of Cys-C during the period between DWR and NPDR. In another subgroup analyses of NPDR and PDR in Figure 8, heterogeneity of the majority remained the similarly high level as DWR and DR ($I^2 \ge 50\%$, P < 0.1). One obvious decline was only observed in the subgroup of LDL-C<3.4 mmol/L (P=0.07, I^2 =69%). Likewise, a small increase could be seen in the process from NPDR to PDR.

Cystatin C and diabetic retinopathy

| 1.2.1 Duration ≤ 10(ye Chen 2015 | Mean | SD | Total | Mean | SD | Total | Weight | Mean Difference IV, Random, 95% Cl | I IV, Rar | <u>1dom, 95% Cl</u> |
|---|--|--|--|---|---|--|--|--|-----------|---------------------------------------|
| | | 0.27 | 170 | 0.84 | 0.76 | 190 | 1.9% | 0.32 [0.20, 0.44] | 1 | |
| Chen 2019 | 3.15 | 0.34 | 86 | 1.31 | 0.52 | 229 | 1.9% | 1.84 [1.74, 1.94] |] | |
| Guo 2020 | 1.02 | 0.36 | 40 | 0.6 | 0.19 | 52 | 1.9% | 0.42 [0.30, 0.54] |] | |
| Lai 2015 Wang 2017 | 0.97 1.19 | 0.32 0.17 | 60 53 | 0.72 0.91 | 0.18 | 60 53 | 1.9% 2.0% | 0.25 [0.16, 0.34] 0.28 [0.23, 0.33] | | - |
| Wu 2014 | 1.71 | 0.52 | 98 | 0.91 | 0.67 | 92 | 1.8% | 0.80 [0.63, 0.97] | | |
| Wu 2015 | 1.39 | 0.21 | 43 | 0.85 | 0.25 | 57 | 1.9% | 0.54 [0.45, 0.63] | j | |
| ran 2018 | 1.51 | 0.36 | 43 | 0.98 | 0.12 | 43 | 1.9% | 0.53 [0.42, 0.64] |] | |
| Zhang 2011 | 3.16 | 0.29 | 40 | 1.35 | 0.54 | 40 | 1.8% | 1.81 [1.62, 2.00] | | |
| Subtotal (95% CI) Heterogeneity: Tau ² = | 0.32; CI | hi² = 99 | 633 99.87, d | f= 8 (P | < 0.00 | 816 0001); P | 17.2% = 99% | 0.75 [0.38, 1.13] | 1 | |
| Test for overall effect: 2 | Z = 3.94 | (P < 0 | .0001) | | | | | | | |
| 1.2.2 Duration>10(yea Nu 2018 | | 0.36 | 43 | 0.98 | 012 | 43 | 1,9% | 0.53 [0.42, 0.64] | 1 | |
| Zhao 2013 | 1.26 | 0.41 | 95 | 0.98 | 0.23 | 109 | 1.9% | 0.28 [0.19, 0.37] |] | |
| Subtotal (95% CI) Heterogeneity: Tau² = | 0.03; CI | hi² = 11 | 138 1.15, df | = 1 (P = | : 0.000 | 152 (18); ² = 1 | 3.9% 91% | 0.40 [0.16, 0.65] | 1 | - |
| Test for overall effect: 2 | | | | | | | | | | |
| 1.2.3 BMI ≤ 24(kg/m2) Lai 2015 | 0.97 | 0.32 | 60 | 0.72 | 0 1 8 | 60 | 1.9% | 0.25 [0.16, 0.34] | 1 | |
| Zhang 2011 | 3.16 | 0.29 | 40 | 1.35 | | 40 | 1.8% | 1.81 [1.62, 2.00] | 1 | |
| Subtotal (95% CI) | | | 100 | | | 100 | 3.8% | 1.03 [-0.50, 2.56] | | |
| Heterogeneity: Tauª = Fest for overall effect: 2 | 1.21; CI Z = 1.32 | hiª = 20 ! (P = 0 |)9.09, d .19) | f=1 (P | < 0.00 | 0001); I* | = 100% | | | |
| 1.2.4 BMI>24(kg/m2) | | | | | | | | | | |
| 3uo 2020 | 1.02 | | 40 | | 0.19 | 52 | 1.9% | 0.42 [0.30, 0.54] | | |
| Nang 2017 | 1.19 | 0.17 | 53 | 0.91 | 0.09 | 53 | 2.0% | 0.28 [0.23, 0.33] | | ~ |
| Nu 2014 | | 0.52 | 98 80 | 0.91 | 0.67 | 92 80 | 1.8% | 0.80 [0.63, 0.97] | | |
| ran 2018 Subtotal (95% CI) | 1.42 | 0.25 | 271 | 0.86 | 0.11 | 277 | 2.0% 7.7% | 0.56 (0.50, 0.62) 0.51 (0.31, 0.70) | 1 | • |
| Heterogeneity: Tau ² = | 0.04; CI | hi² = 68 | 3.00, df | = 3 (P < | 0.000 | | | 0.01 [0.01, 0.10] | 1 | |
| Fest for overall effect: 2 | Z = 5.04 | (P < 0 | .00001) |) | | | | | | |
| 1.2.5 TC<5.2(mmol/L) Chen 2015 | 1.16 | 0.27 | 170 | 0.84 | 0.76 | 190 | 1.9% | 0.32 [0.20, 0.44] | 1 | |
| 3uo 2020 | 1.02 | 0.36 | 40 | 0.6 | 0.19 | 52 | 1.9% | 0.42 [0.30, 0.54] | 1 | |
| Wang 2017 | 1.19 | 0.17 | 53 | 0.91 | 0.09 | 53 | 2.0% | 0.28 [0.23, 0.33] | 1 | - |
| Nu 2014 | 1.71 | 0.52 | 98 | 0.91 | 0.67 | 92 | 1.8% | 0.80 [0.63, 0.97] |] | |
| r'an 2018 Zhao 2013 | 1.42 1.26 | 0.25 | 80 95 | 0.86 | 0.11 | 80 109 | 2.0% | 0.56 [0.50, 0.62] 0.28 [0.19, 0.37] | | |
| Subtotal (95% CI) | | | 536 | | | 576 | 11.6% | 0.43 [0.29, 0.57] | | • |
| Heterogeneity: Tau ² = Test for overall effect: 2 | 0.03; CI 7 = 6 10 | hi² = 77 I/P < 0 | 26, df | = 5 (P < | < 0.000 | 001); l²= | 94% | | | |
| 1.2.6 5.2≤TC<6.2(mn | | | | | | | | | | |
| Wu 2015 | 1.39 | 0.21 | 43 | 0.85 | 0.25 | 57 | 1.9% | 0.54 [0.45, 0.63] | 1 | - |
| Subtotal (95% CI) | | | 43 | | | 57 | 1.9% | 0.54 [0.45, 0.63] | 1 | • |
| Heterogeneity: Not app Test for overall effect: 2 | | | 0.0000 | 1) | | | | | | |
| I.2.7 TG<1.70(mmol/L | .) | | | | | | | | | |
| Nang 2017 | 1.19 | 0.17 | 53 | 0.91 | 0.09 | 53 | 2.0% | 0.28 [0.23, 0.33] | | |
| Subtotal (95% CI) | | | 53 | | | 53 | 2.0% | 0.28 [0.23, 0.33] | 1 | • |
| Heterogeneity: Not app Fest for overall effect: 2 | plicable Z = 10.6 | i0 (P < | 0.0000 | 1) | | | | | | |
| 1.2.8 1.7≤TG<2.3(mn | | | | | | | | | | |
| Chen 2015 | 1.16 | 0.27 | 170 | 0.84 | | 190 | 1.9% | 0.32 [0.20, 0.44] | | |
| Lai 2015 | | 0.32 | 60 | 0.72 | | 60 | 1.9% | 0.25 [0.16, 0.34] | 1 | |
| Wu 2014 | | 0.52 | | | | | | | | |
| | 1.71 | 0.02 | 98 328 | 0.91 | 0.67 | 92 342 | 1.8% | 0.80 [0.63, 0.97] |] | • |
| Subtotal (95% CI) Heterogeneity: Tau² = | 0.06; CI | hi² = 31 | 328 .18, df | | | 342 | 5.7% | |] | • |
| Subtotal (95% Cl) Heterogeneity: Tau² = Test for overall effect: 2 | 0.06; CI Z = 3.15 | hi² = 31 | 328 .18, df | | | 342 | 5.7% | 0.80 [0.63, 0.97] |] | • |
| Subtotal (95% CI) Heterogeneity: Tau² = | 0.06; CI Z = 3.15 | hi² = 31 i (P = 0 | 328 .18, df | = 2 (P < | 0.000 | 342 | 5.7% | 0.80 (0.63, 0.97) 0.45 (0.17, 0.73) |]] | • |
| Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: J 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% CI) | 0.06; CI Z = 3.15 I/L) 1.39 | hi² = 31 i (P = 0 0.21 | 328 1.18, df 1.002) | | 0.000 | 342 001); I² = | 5.7% 94% | 0.80 [0.63, 0.97] |]] | • • |
| Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: J 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% CI) Heterogeneity: Not app | 0.06; Cl Z = 3.15 I IL) 1.39 plicable | hi² = 31 i (P = 0 0.21 | 328 1.18, df 1.002) 43 43 43 | = 2 (P < 0.85 | 0.000 | 342 001); I ² = 57 | 5.7% 94% 1.9% | 0.80 [0.63, 0.97] 0.45 [0.17, 0.73] 0.54 [0.45, 0.63] |]] | • |
| Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: J 1.2.9 HDL-C<1.0(mmo Mu 2015 Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect: J | 0.06; Cl Z = 3.15 ML) 1.39 plicable Z = 11.7 | hi² = 31 i (P = 0 0.21 | 328 1.18, df 1.002) 43 43 43 | = 2 (P < 0.85 | 0.000 | 342 001); I ² = 57 | 5.7% 94% 1.9% | 0.80 [0.63, 0.97] 0.45 [0.17, 0.73] 0.54 [0.45, 0.63] |]] | • |
| Subtotal (95% CI) Heterogeneity: Tau ^a = Test for overall effect: 3 1.2.9 HDL-C<1.0(mm Wu 2015 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 3 1.2.10 HDL-C ≥ 1.0(mr Chen 2015 | 0.06; Cl Z = 3.15 1/L) 1.39 plicable Z = 11.7 nol/L) 1.16 | hi [#] = 31 i (P = 0 0.21 '2 (P < 0.27 | 328 1.18, df .002) 43 43 0.0000 170 | = 2 (P < 0.85 1) 0.84 | 0.000 | 342 001); I² = 57 57 190 | 5.7% : 94% 1.9% 1.9% | 0.80 (0.83, 0.97) 0.45 (0.17, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) | 1 | • |
| Subtotal (95% CI) Heterogeneily: Tau ² = Test for overall effect : 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% CI) Heterogeneily: Not app Test for overall effect : 1.2.10 HDL-C≥1.0(mr Chen 2015 Guo 2020 | 0.06; Cl Z = 3.15 I/L) 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 | hi [#] = 31 (P = 0 0.21 2 (P < 0.27 0.36 | 328 1.18, df: .002) 43 43 0.0000 170 40 | = 2 (P < 0.85 1) 0.84 0.6 | 0.000 0.25 0.76 0.19 | 342 001); I [≠] = 57 57 190 52 | 5.7% : 94% 1.9% 1.9% 1.9% | 0.80 (0.63, 0.97) 0.45 (0.17, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) | | • |
| Subtotal (95% C), Heterogeneity: Tau ² = Test for overall effect: <i>j</i> 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% C)) Heterogeneity: Not app Test for overall effect: <i>j</i> 1.2.10 HDL-C ≥ 1.0(mm Chen 2015 Guo 2020 Wang 2017 | 0.06; Cl Z = 3.15 I/L) 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 | hi [#] = 31 (P = 0 0.21 '2 (P < 0.27 0.36 0.17 | 328 1.18, df: .002) 43 43 0.0000 170 40 53 | = 2 (P < 0.85 1) 0.84 0.6 0.91 | 0.25 0.76 0.19 0.09 | 342 001); I² = 57 57 57 190 52 53 | 5.7% : 94% 1.9% 1.9% 1.9% 1.9% 2.0% | 0.80 (0.63, 0.97) 0.45 [0.17, 0.73] 0.54 [0.45, 0.63] 0.54 [0.45, 0.63] 0.52 [0.20, 0.44] 0.42 [0.30, 0.54] 0.28 [0.20, 0.34] | | • • |
| Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect. <i>i</i> 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect. <i>i</i> 1.2.10 HDL-C ≥ 1.0(mr Chen 2015 Guo 2020 Wang 2017 Wu 2014 | 0.06; Cl Z = 3.15 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 1.71 | hi [#] = 31 (P = 0 0.21 '2 (P < 0.27 0.36 0.17 0.52 | 328 1.18, df: .002) 43 43 0.0000 170 40 53 98 | = 2 (P < 0.85 1) 0.84 0.6 0.91 0.91 | 0.25 0.76 0.19 0.09 0.67 | 342 001); I² = 57 57 57 190 52 53 92 | 5.7% : 94% 1.9% 1.9% 1.9% 1.9% 2.0% 1.8% | 0.80 (0.83, 0.87) 0.45 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) 0.28 (0.23, 0.33) 0.80 (0.63, 0.87) | | • • • |
| Subtotal (95% CI) -teterogeneity. Tau [∞] = Fest for overall effect : 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% CI) -teterogeneity. Not ap.) Fest for overall effect : 1.2.10 HDL-C≥1.0(mm Chen 2015 Suo 2020 Wang 2017 Wu 2014 Yan 2018 | 0.06; Cl Z = 3.15 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 1.71 1.42 | hi [#] = 31 (P = 0 0.21 '2 (P < 0.27 0.36 0.17 | 328 1.18, df: .002) 43 43 0.0000 170 40 53 | = 2 (P < 0.85 1) 0.84 0.6 0.91 | 0.25 0.76 0.19 0.09 | 342 001); I² = 57 57 57 190 52 53 | 5.7% : 94% 1.9% 1.9% 1.9% 1.9% 2.0% | 0.80 (0.63, 0.97) 0.45 [0.17, 0.73] 0.54 [0.45, 0.63] 0.54 [0.45, 0.63] 0.52 [0.20, 0.44] 0.42 [0.30, 0.54] 0.28 [0.20, 0.34] | | • • • |
| Subtotal (95% CI) reletrogeneity, Tau ² = Fest for overall effect : 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% CI) Heterogeneity, Not app Fest for overall effect : 2.2.10 HDL-C≥1.0(mm Chen 2015 ≥ 1.0(mm Chen 2015 ≥ 1.0(mm Chen 2015 ≥ 1.0(mm Chen 2015 ≥ 1.0(mm Chen 2015 ≥ 1.0(mm) Chen 201 | 0.06; CI Z = 3.15 1.39 plicable Z = 11.7 noI/L) 1.16 1.02 1.19 1.71 1.42 1.26 | hi [#] = 31 i (P = 0 0.21 2 (P < 0.36 0.17 0.52 0.25 0.41 | 328 (.18, df: .002) 43 43 0.0000 170 40 53 98 80 95 536 | = 2 (P < 0.85 1) 0.84 0.6 0.91 0.91 0.86 0.98 | 0.25 0.76 0.19 0.67 0.11 0.23 | 342 001); * = 57 57 190 52 53 92 80 109 576 | 5.7% 94% 1.9% 1.9% 1.9% 1.9% 2.0% 1.9% 2.0% 1.9% 1.9% | 0.80 (0.83, 0.87) 0.45 (0.17, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.42 (0.30, 0.54) 0.42 (0.30, 0.54) 0.28 (0.23, 0.33) 0.80 (0.63, 0.67) 0.56 (0.50, 0.62) | | |
| Subtotal (95% CI) - elerogeneiky: Tau* = Test for overall effect 2 12.29 HDL-C<1.0(mmo wu 2015 Subtotal (95% CI) - elerogeneiky: Not app reat for overall effect 2 12.0 HDL-C ≥ 1.0(mr Chen 2015 Suo 2020 Wang 2017 Wang 2017 Wang 2017 Kang 2018 Chao 2013 Subtotal (95% CI) - elerogeneiky: Tau* = | 0.06; Cl Z = 3.15 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 1.71 1.42 1.26 0.03; Cl | hi [#] = 31 i (P = 0 0.21 2 (P < 0.27 0.36 0.17 0.52 0.41 hi [#] = 77 | 328 1.18, df: .002) 43 43 0.0000 170 40 53 98 80 95 536 .26, df: | = 2 (P < 0.85 1) 0.84 0.91 0.91 0.86 0.98 = 5 (P < | 0.25 0.76 0.19 0.67 0.11 0.23 | 342 001); * = 57 57 190 52 53 92 80 109 576 | 5.7% 94% 1.9% 1.9% 1.9% 1.9% 2.0% 1.9% 2.0% 1.9% 1.9% | 0.80 (0.83, 0.87) 0.45 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) 0.80 (0.63, 0.87) 0.80 (0.63, 0.87) 0.56 (0.50, 0.62) 0.28 (0.19, 0.37) | | |
| Subtotal (95% C) Helerogeneiky: Tau* = Test for overall effect 2 12.29 HDL-C<1.0(mmo Wu 2015 Subtotal (95% C) Helerogeneiky: Not app test for overall effect 2 12.10 HDL-C ≥ 1.0(mr Chen 2015 Suo 2020 Wang 2017 Wu 2014 Chao 2013 Subtotal (95% C) Helerogeneiky: Tau* = Test for overall effect 2 | 0.06; Cl Z = 3.15 I/L) 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 1.71 1.42 1.26 0.03; Cl Z = 6.10 | hi [#] = 31 i (P = 0 0.21 2 (P < 0.27 0.36 0.17 0.52 0.41 hi [#] = 77 | 328 1.18, df: .002) 43 43 0.0000 170 40 53 98 80 95 536 .26, df: | = 2 (P < 0.85 1) 0.84 0.91 0.91 0.86 0.98 = 5 (P < | 0.25 0.76 0.19 0.67 0.11 0.23 | 342 001); * = 57 57 190 52 53 92 80 109 576 | 5.7% 94% 1.9% 1.9% 1.9% 1.9% 2.0% 1.9% 2.0% 1.9% 1.9% | 0.80 (0.83, 0.87) 0.45 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) 0.80 (0.63, 0.87) 0.80 (0.63, 0.87) 0.56 (0.50, 0.62) 0.28 (0.19, 0.37) | | |
| Subtotal (95% C) deterogeneiky: Tau ² = Test for overall effect 2 1.2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% C) 1.eterogeneiky: Not app Test for overall effect 2 1.2.10 HDL-C≥1.0(mr Not app Subtotal (95% C) 1.eterogeneiky: Tau ² = Test for overall effect 2 1.2.11 HDL-C≥2.0(mm Tuan 2016) Subtotal (95% C) 1.2.11 HDL-C>2.0(mm Tuan 2016) Tuan 2016) | 0.06; Cl Z = 3.15 I/L) 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 1.71 1.42 1.26 0.03; Cl Z = 6.10 | hi ² = 31 ; (P = 0 0.21 ; 2 (P < 0.27 0.27 0.26 0.36 0.17 0.52 0.41 hi ² = 77 (P < 0 | 328 (.18, df: .002) 43 43 0.00000 170 40 53 98 80 95 536 (.26, df: .00001) | = 2 (P < 0.85 1) 0.84 0.91 0.91 0.86 0.98 = 5 (P < | 0.000 0.25 0.76 0.19 0.09 0.67 0.11 0.23 <0.000 | 342 001); * = 57 57 57 190 52 53 92 80 109 576 001); * = | 5.7% 94% 1.9% 1.9% 1.9% 2.0% 1.8% 2.0% 1.8% 94% | 0.80 (0.83, 0.97) 0.45 (0.17, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) 0.28 (0.23, 0.33, 0.97) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.43 (0.29, 0.57) | | · · · · · · · · · · · · · · · · · · · |
| Subtotal (95% C) eletrogeneiky: Tau ² = fest for overall effect 2 eletrogeneiky: Tau ² = fest for overall effect 2 subtotal (95% C) teterogeneiky: Not app fest for overall effect 2 tau (195% C) beno 2015 beno 2015 ben | 0.06; CI Z = 3.15 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 1.71 1.26 0.03; CI Z = 6.10 1.26 0.01L) 1.26 | hi [#] = 31 (P = 0 0.21 2 (P ≤ 0.27 0.36 0.17 0.52 0.52 0.41 hi [#] = 77 (P ≤ 0 0.41 | 328 .18, df: .002) 43 43 0.0000 170 40 53 98 95 536 536 536 536 536 536 536 53 | = 2 (P * 0.85 1) 0.84 0.91 0.91 0.91 0.98 = 5 (P * 0.98 | 0.000 0.25 0.76 0.19 0.09 0.67 0.11 0.23 <0.000 | 342 001); ² = 57 57 57 190 52 53 92 80 109 576 001); ² = | 5.7% 94% 1.9% 1.9% 1.9% 2.0% 1.8% 2.0% 1.8% 1.9% 1.9% | 0.80 (0.83, 0.87) 0.45 (0.47, 0.73) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.56 (0.50, 0.52) 0.56 (0.50, 0.57) 0.43 (0.29, 0.57) | | |
| Subtotal (95% C) - detrogeneik/: Tau ² = Test for overall effect 2 - test (95% C) - telerogeneik/: Not app | 0.06; CI Z = 3.15 1.39 plicable Z = 11.7 nol/L) 1.16 1.02 1.19 1.71 1.26 0.03; CI Z = 6.10 1.26 0.01L) 1.26 | hi [#] = 31 (P = 0 0.21 2 (P ≤ 0.27 0.36 0.17 0.52 0.52 0.41 hi [#] = 77 (P ≤ 0 0.41 | 328 .18, df: .002) 43 43 0.0000 170 40 53 98 95 536 536 536 536 536 536 536 53 | = 2 (P * 0.85 1) 0.84 0.91 0.91 0.91 0.98 = 5 (P * 0.98 | 0.000 0.25 0.76 0.19 0.09 0.67 0.11 0.23 <0.000 | 342 001); * = 57 57 57 190 52 53 92 80 109 576 001); * = | 5.7% 94% 1.9% 1.9% 1.9% 2.0% 1.8% 2.0% 1.8% 94% | 0.80 (0.83, 0.97) 0.45 (0.17, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) 0.28 (0.23, 0.33, 0.97) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.43 (0.29, 0.57) | | |
| Subtotal (95% C) +derogeneik/: Tau ² = Test for overall effect 2 test for overall effect 2 Subtotal (95% C) +derogeneik/: Not app Test for overall effect 2 t.2.10 HDL-C≥1.0(mr Subtotal (95% C) +derogeneik/: Tau ² = Test for overall effect 2 Subtotal (95% C) +derogeneik/: Tau ² = Test for overall effect 2 t.2.11 LDL-C2-2(mm Tau 2010) Subtotal (95% C) +derogeneik/: Not app Test for overall effect 2 Test for overall effect 2 Tes | 0.06; CI Z = 3.15 1.39 plicable Z = 11.7 nol(L) 1.16 1.02 1.19 1.71 1.42 1.26 0.03; CI Z = 6.10 0(L) 1.26 0.03; CI Z = 5.90 | hi [#] = 31 (P = 0 0.21 2 (P ≤ 0.27 0.36 0.17 0.52 0.52 0.41 hi [#] = 77 (P ≤ 0 0.41 | 328 .18, df: .002) 43 43 0.0000 170 40 53 98 95 536 536 536 536 536 536 536 53 | = 2 (P * 0.85 1) 0.84 0.91 0.91 0.91 0.98 = 5 (P * 0.98 | 0.000 0.25 0.76 0.19 0.09 0.67 0.11 0.23 <0.000 | 342 001); * = 57 57 57 190 52 53 92 80 109 576 001); * = | 5.7% 94% 1.9% 1.9% 1.9% 2.0% 1.8% 2.0% 1.8% 94% | 0.80 (0.83, 0.97) 0.45 (0.17, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) 0.28 (0.23, 0.33, 0.97) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.43 (0.29, 0.57) | | |
| Subtotal (95% C) eletrogenetiky Tau ² = Test for overall effect. 2 L2.9 HDL-C<1.0(mmo Wu 2015 Subtotal (95% C) eletrogenetiky. Not app Test for overall effect. 2 L2.10 HDL-C≥1.0(mr Chen 2015 Sub 2020 Vang 2017 Vu 2014 Vang 2017 Vu 2014 Vang 2018 Subtotal (95% C) +eletrogenetiky. Tau ² = Test for overall effect. 2 L2.11 LDL-C<2.6(mm Chen 2013 Subtotal (95% C) +eletrogenetiky. R04 Heterogenetiky. R04 | 0.06; CI Z = 3.15 1.39 plicable Z = 11.7 nol(L) 1.16 1.02 1.19 1.71 1.42 1.26 0.03; CI Z = 6.10 0(L) 1.26 0.03; CI Z = 5.90 | $hi^{P} = 31$ (P = 0 0.21 2 (P < 0 0.27 0.36 0.17 0.25 0.41 $hi^{P} = 77$ (P < 0 0.41 | 328 .18, df: .002) 43 43 0.0000 170 40 53 98 95 536 536 536 536 536 536 536 53 | = 2 (P * 0.85 1) 0.84 0.91 0.91 0.91 0.98 = 5 (P * 0.98 | 0.000 0.25 0.76 0.19 0.67 0.11 0.23 <0.000 0.23 | 342 001); * = 57 57 57 190 52 53 92 80 109 576 001); * = | 5.7% 94% 1.9% 1.9% 1.9% 2.0% 1.8% 2.0% 1.8% 94% | 0.80 (0.83, 0.97) 0.45 (0.17, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.32 (0.20, 0.44) 0.42 (0.30, 0.54) 0.28 (0.23, 0.33, 0.97) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.43 (0.29, 0.57) | | |
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| Subtotal (95% C) + detrogeneik/: Tau ² = Test for overall effect 2 test for overall effect 2 Subtotal (95% C) + detrogeneik/: Not app Test for overall effect 2 t.2.10 HDL-C≥1.0(mr Subtotal (95% C) + detrogeneik/: SC) Subtotal (95% C) + detrogeneik/: Tau ² = Test for overall effect 2 t.2.11 LDL-C2-26(mm Thea 2013 Subtotal (95% C) + detrogeneik/: Not app Test for overall effect 2 t.2.12 LDL-C2-3(mm Thea 2015 Nang 2017 | 0.06; CI Z = 3.15 1.39 1.39 pilcable Z = 11.7 nolAJ 1.16 1.02 1.19 1.26 0.03; CI Z = 6.10 0.03; CI Z = 6.10 0.03; CI Z = 5.90 0.01 L) 1.16 0.03; CI Z = 5.90 0.01 L) 1.19 1.19 | $hi^{\mu} = 31$ i (P = 0 0.21 i (2 (P < 0.27) 0.36 0.36 0.37 0.52 0.41 $hi^{\mu} = 77$ i (P < 0 0.41 i (P < 0.27) 0.25 0.41 0.27 0.21 0.21 0.25 0.41 0.21 0.21 0.21 0.22 0.25 0.41 0.21 0.21 0.21 0.25 0.41 0.21 0.21 0.21 0.22 0.25 0.41 0.21 0.21 0.21 0.25 0.41 0.22 0.25 0.41 0.27 0.25 0.41 0.27 0.22 0.25 0.41 0.27 0.22 0.25 0.41 0.27 0.22 0.22 0.25 0.41 0.27 0.32 0.32 0.32 0.37 0.32 0.37 0.32 0.37 0.32 0.37 0.3 | 328 1.18, df: .002) 43 43 43 0.0000 1700 40 53 98 80 95 536 .26, df: .00001) 95 95 .00001) 1700 65 536 .26, df: .00001) | = 2 (P + 0.85 1) 0.84 0.6 0.91 0.91 0.98 0.98 0.98 0.98 | 0.000 0.25 0.76 0.19 0.09 0.11 0.23 0.000 0.23 0.23 0.23 0.76 0.18 0.09 | 342 001); F = 57 57 57 190 52 53 92 80 109 109 109 109 109 109 53 | 5.7% 9.94% 1.9% 1.9% 1.9% 2.0% 1.8% 2.0% 1.9% 1.9% 1.9% 1.9% 1.9% | 0.80 (D.83, 0.87) 0.45 (0.47, 0.73) 0.54 (0.45, 0.83) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.52 (0.20, 0.44) 0.42 (0.30, 0.54) 0.58 (0.50, 0.62) 0.28 (0.19, 0.37) 0.43 (0.29, 0.57) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) | | |
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| Subtotal (95% C) +elerogeneiky: Tau ² = Test for overall effect ; 2.29 HDL-C<1.0(mmo Wu 2015 Subtotal (95% C) +elerogeneiky: Not app Test for overall effect ; 2.210 HDL-C≥1.0(mr how 2017 Wu 2014 Wu 2015 Wu 2014 Wu 2015 Wu 2014 Wu 2014 Wu 2015 Wu 2014 Wu 2014 Wu 2015 Wu 2014 Wu | 0.06; Ci (2 = 3.15 IL) 1.39 plicable Z = 11.7 nolL) 1.16 1.02 1.17 1.26 0.03; Ci (2 = 6.10 0.04) 1.26 plicable Z = 6.90 00L) 1.26 plicable Z = 6.90 00L) 1.26 0.97 1.39 1.39 1.39 1.32 1.42 0.02; Ci (2 = 5.44 1.42 1.42 1.42 1.42 1.26 0.03 1.42 1.26 0.03 1.26 0.03 0.04 1.26 0.07 1.26 0.97 1.39 1.42 1.42 1.42 1.42 1.42 1.26 0.97 1.39 1.42 1.42 1.42 1.42 1.42 1.42 1.42 1.42 1.26 0.97 1.39 1.42 | hi ⁷ = 31 (P = 0 0.21 2 (P < 0 0.36 0.36 0.25 0.25 0.25 0.41 hi ⁷ = 77 0 (P < 0 0.41 (P < 0 0.32 0.32 0.17 0.32 0.25 hi ⁷ = 66 (P < 0 0.27 0.32 0.25 0.32 0.32 0.25 0.32 0.34 0.25 0.25 0.34 0.25 0.25 0.34 0.25 0.25 0.34 | 328 1.18, df1 43 43 43 0.0000 170 40 53 98 80 05 536 536 536 536 536 536 536 53 | = 2 (P + 0.85 1) 0.84 0.6 0.98 = 5 (P + 0.98 0.88 0.98 0.88 0 | 0.000 0.25 0.76 0.19 0.67 0.67 0.63 0.64 0.67 | 342 001); F = 57 57 57 190 52 53 92 80 001); F = 109 109 576 60 53 57 80 001); F = 190 109 109 109 109 109 109 109 | 5.7% 94% 1.9% | 0.80 (0.83, 0.87) 0.45 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.28 (0.19, 0.37) 0.28 (0.29, 0.54) 0.32 (0.20, 0.44) 0.35 (0.50, 0.62) 0.39 (0.25, 0.53) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) | | |
| Subtotal (95% C) detrogenetik, Tau ² = Test for overall effect 2 Test for overall effect 2 Subtotal (95% C) Test for overall effect 2 t.2.9 HDL C≥1.0(mr hm 2015 Subtotal (95% C) Tear 2019 Subtotal (95% C) Tear 2019 Subtotal (95% C) Tear 2019 Subtotal (95% C) Tear 2013 Subtotal (95% C) Tear 2014 Wu 2015 Subtotal (95% C) Tear 2014 Subtotal (95% C) Tear 2014 Subto | 0.06; C12 = 3.15 1.39 1.39 pilcable Z = 11.7 nolL) 1.16 1.22 1.17 1.26 0.03; C12 1.26 0.03; C12 1.26 0.03; C12 1.26 0.97 1.19 1.26 0.03; C12 2.5.90 0L) 1.42 0.02; C12 5.44 1.16 1.42 1.42 1.42 1.26 0.97 1.39 1.42 1 | $hi^{2} = 31$ (P = 0 0.21 2 (P < 0 0.27 0.36 0.17 0.52 0.52 0.52 0.25 0.41 $hi^{2} = 77$ (P < 0 0.21 0.25 0.41 $hi^{2} = 77$ 0.22 0.21 0.22 0.21 0.22 0.32 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.36 0.36 0.21 0.21 0.22 0.22 0.22 0.22 0.36 0.21 0.22 0.21 0.22 | 328 1.18, df 43 43 43 0.0000 170 40 43 98 98 99 536 536 536 506 170 95 95 95 95 95 95 95 95 95 95 | = 2 (P + 0.85 1) 0.84 0.91 0.91 0.98 0.98 0.98 0.98 0.98 0.98 0.98 0.98 | < 0.000 0.25 0.76 0.001 0.23 0.001 0.23 0.23 0.76 0.11 0.09 0.25 0.11 0.000 0.25 | 342 0001); = 57 57 57 190 52 30 576 5001); = 109 109 109 109 109 109 109 109 | 5.7% 5.7% 1.9% 1.9% 1.9% 2.0% 2.0% 2.0% 1.9% 2.0% 1.9% 2.0% 1.9% 2.0% 1.9% 2.0% 1.9% 1.9% 2.0% 1.9% | 0.80 (0.83, 0.87) 0.45 (0.47, 0.73) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.55 (0.50, 0.82) 0.28 (0.19, 0.37) 0.55 (0.50, 0.82) 0.28 (0.19, 0.37) 0.55 (0.50, 0.82) 0.28 (0.19, 0.37) 0.55 (0.50, 0.82) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) 0.25 (0.13, 0.33) 0.54 (0.45, 0.83) 0.80 (0.83, 0.37) 0.39 (0.22, 0.34) | | |
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| Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.29 HDL-C<1.0(mmo W. 2015 Subtotal (95% C) deterogeneity: Not app Test for overall effect ; 2.10 HDL-C ² 1.0(mr Chen 2015 2.10 HDL-C ² 1.0(mr Chen 2015 Chen 2018 Chen 2018 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.11 LDL-C<2.6(mm Chen 2018 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 HDL-CC2.0 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.12 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.14 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.14 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.14 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.14 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.14 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Test for overall effect ; 2.14 HDL-CC3 Subtotal (95% C) deterogeneity: Tau ² = Subtotal (95% C) deterogeneity: Tau ² = Subtotal (95% C) deterogeneity: Tau ² = Subtotal (9 | 0.06; C123, 315 Z = 3,15 1,39 DELCADE Z = 11.7 noIL) 1.10 Z = 6,10 1.10 Z = 6,10 0.03; C1 Z = 6,90 0.04 L) 1.26 0.097 1.19 1.26 0.097 1.19 1.26 0.097 1.19 1.26 0.097 1.19 1.26 0.097 1.19 1.26 0.097 1.19 1.26 0.097 1.19 1.26 0.097 1.27 0.097 1.28 0.097 | $hi^{\mu} = 31$ $i^{\mu} (P = 0$ 0.21 $i^{\mu} (P < 0$ 0.36 0.17 0.52 0.41 $hi^{\mu} = 77$ 0.27 0.41 1 (P < 0 0.41 1 (P < 0 0.27 0.32 $i^{\mu} = 66$ $i^{\mu} = 82$ 0.27 0.34 0.35 0.41 0.34 0.34 0.34 0.34 0.35 0.41 0.34 0.34 0.35 0.41 0.34 0.34 0.35 0.34 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0.34 0.35 0. | 328 328 30 30 30 30 30 30 30 30 30 30 30 30 30 | $= 2 (P^{-1} + Q^{-1}) + Q^{-1} + Q^{-$ | 0.000 0.25 0.76 0.09 0.67 0.23 0.000 0.23 0.23 0.000 0.23 0.000 0.23 0.000 0.23 0.000 0.25 0.11 0.23 0.000 0.76 0.25 0.12 0.000 0.76 0.25 0.12 0.123 <0.000 0.76 0.25 0.11 0.23 <0.000 0.76 0.23 <0.000 0.18 | 342 0001); = 57 57 57 1900 52 53 90 576 576 576 109 109 109 109 109 109 109 109 | 5.7% 5.7% 1.9% 1.9% 1.9% 2.0% 1.9% 2.0% 1.9% 2.0% 1.9% | 0.80 (0.83, 0.87) 0.45 (0.47, 0.73) 0.45 (0.47, 0.73) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.28 (0.19, 0.37) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) 1.55 (0.16, 0.34) 0.32 (0.20, 0.44) 1.64 (0.03) 0.54 (0.45, 0.63) 0.56 (0.50, 0.52) 0.38 (0.20, 0.44) 1.84 (0.43, 0.33) 0.56 (0.50, 0.52) 0.38 (0.20, 0.44) 1.84 (0.43, 0.33) 0.55 (0.42, 0.54) 0.32 (0.20, 0.44) 1.84 (0.43, 0.33) 0.55 (0.42, 0.54) 0.32 (0.20, 0.44) 1.84 (0.43, 0.33) 0.55 (0.42, 0.54) 0.55 (0.50, 0.52) 0.28 (0.19, 0.37) 0.52 (0.32, 0.52) 0.28 (0.19, 0.37) 0.52 (0.32, 0.52) 0.28 (0.19, 0.37) 0.52 (0.32, 0.52) 0.28 (0.19, 0.37) 0.52 (0.32, 0.52) 0.25 (0.16, 0.34) | | |
| Subtotal (95% C) deterogeneiky: Tau ² = Test for overall effect ; 2 ta2 9 t0L-C<1.0(mmo W 2015 Subtotal (95% C) 1 deterogeneiky: Not app Test for overall effect ; 2 10 t0L-C≥1.0(mr Chan 2016 Chan 2017 W 2014 V 2018 Chan 2018 C | 0.06; cl 2 Z = 3.15 1.39 0.06; cl 2 Z = 11.7 nolL) 1.16 1.02 Z = 11.7 1.26 0.03; cl 2 0.03; cl 2 0.04L) 1.26 0.03; cl 2 0.04L) 1.26 0.04L) 1.26 0.03; cl 2 0.04L) 1.26 0.02; cl 2 0.02; cl 2 0.02; cl 2 0.02; cl 2 0.02; cl 2 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.0 | $hr^2 = 31$ (P = 0 0.21 (2 (P < 0.27) 0.36 0.17 0.52 0.52 0.52 0.25 0.41 $hr^2 = 77$ 0.21 (P < 0 0.41 (P < 0 0.27 0.27 0.21 (P < 0 0.41 $hr^2 = (P < 0)$ 0.27 0.22 (P < 0) 0.27 0.22 (P < 0) 0.27 0.22 (P < 0) 0.27 0.22 (P < 0) 0.32 0.34 0.32 0.25 (P < 0) 0.34 0.32 0.25 0.25 (P < 0) 0.34 0.34 0.32 0.25 0.25 (P < 0) 0.32 0.21 0.34 0.34 0.36 0.25 0.25 0.21 0.32 0.22 0.34 0.32 0.22 0.22 0.34 0.32 0.22 0.22 0.34 0.32 0.22 0.22 0.34 0.32 0.25 0. | 328 3 328 4 300000 170 40 43 43 43 0.0000 170 40 53 80 95 536 536 50001; 95 95 0.00001; 170 60 53 43 40 53 80 0.00001; 170 40 95 95 536 43 80 0.00001; 170 40 95 95 536 43 80 0.00001; 170 40 95 95 536 43 80 0.00001; 170 40 95 95 536 43 80 0.00001; 170 40 95 536 43 80 0.00001; 170 40 95 536 43 80 0.00001; 170 40 95 536 43 80 0.00001; 170 40 80 80 80 80 80 80 80 80 80 8 | = 2 (P + 0.85 1) 0.84 0.6 0.91 0.98 = 5 (P + 0.98 0.98 = 5 (P + 0.98 0.98 0.98 = 5 (P + 0.98 | 0.000 0.25 0.76 0.09 0.67 0.23 0.000 0.23 0.23 0.000 0.23 0.11 0.23 0.000 0.23 0.11 0.25 0.11 0.26 0.12 0.18 0.54 | 342 0001); = 57 57 1900 57 57 109 109 109 109 109 109 109 109 | 5.7% 9.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9 | 0.80 (0.83, 0.87) 0.45 (0.47, 0.73) 0.45 (0.47, 0.73) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.28 (0.23, 0.33) 0.80 (0.33, 0.37) 0.28 (0.19, 0.37) 0.56 (0.50, 0.22) 0.39 (0.25, 0.53) 0.42 (0.45, 0.65) 0.42 (0.45, 0.65) 0.44 (0.45, | | |
| Subtotal (95% C) deterogeneik, Tau ² = Test for overall effect 2 test for overall effect 3 test for overall effect 3 test for overall effect 3 that 2018 that 2018 thath | 0.06; cl 2 Z = 3.15 1.39 0.06; cl 2 1.39 0.139 0.139 0.139 0.139 0.139 1.16 1.16 1.02 2 = 6.10 0.03; cl 2 2 = 6.10 0.03; cl 2 2 = 6.10 0.03; cl 2 2 = 6.10 0.03; cl 2 2 = 6.00 0.01 1.16 0.03; cl 2 2 = 6.00 0.07 1.19 1.39 1.42 1.26 0.97 1.39 1.42 1.26 0.27; cl 2 2 = 4.02 0.27; cl 2 2 = 4.02 0.27; cl 2 1.16 0.27; cl 2 2 = 4.02 0.27; cl 2 0.27; cl | $hi^{2} = 31$ $i^{2} (P = 0$ 0.21 $i^{2} (P < 0$ 0.36 0.75 0.75 0.41 $i^{2} (P < 0$ 0.41 $i^{2} (P < 0$ 0.27 0.25 0.41 0.27 0.21 0.25 0.41 0.27 0.21 0.22 0.32 0.32 0.21 0.22 0.32 0.21 0.22 0.32 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.21 0.22 0.36 0.25 0.41 0.22 0.21 0.22 0.36 0.22 0.36 0.26 0.32 0.29 0.29 0.29 0.32 0.29 0.29 0.29 0.32 0.29 0.29 0.21 0.25 0.41 0.52 0.36 0.25 0.41 0.52 0.36 0.29 | 328 328 43 43 0.0000 170 40 40 40 53 98 95 536 536 536 536 536 50001; 95 95 536 00001; 170 80 053 43 002, dri 80 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 95 53 80 90 90 90 90 90 90 90 90 90 90 90 90 90 | = 2 (P + 0.85 1) 0.84 0.6 0.91 0.98 = 5 (P + 0.98 0.98 = 5 (P + 0.98 0.98 0.98 = 5 (P + 0.98 | 0.000 0.25 0.76 0.09 0.67 0.23 0.000 0.23 0.23 0.000 0.23 0.11 0.23 0.000 0.23 0.11 0.25 0.11 0.26 0.12 0.18 0.54 | 342 0001); = 57 57 1900 57 57 109 109 109 109 109 109 109 109 | 5.7% 9.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9 | 0.80 (0.83, 0.87) 0.45 (0.47, 0.73) 0.45 (0.47, 0.73) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.28 (0.23, 0.33) 0.80 (0.33, 0.37) 0.28 (0.19, 0.37) 0.56 (0.50, 0.22) 0.39 (0.25, 0.53) 0.56 (0.50, 0.22) 0.28 (0.19, 0.37) 0.56 (0.50, 0.22) 0.29 (0.19, 0.37) 0.56 (0.50, 0.22) 0.29 (0.19, 0.37) 0.56 (0.50, 0.22) 0.39 (0.25, 0.53) 0.56 (0.50, 0.22) 0.56 (0.50, 0.22) 0.57 (0.50, 0.22) 0.57 (0.50, 0.22) 0.57 (0.50, 0.22) 0.57 (0.50, 0.22) 0.57 (0.50, | | |
| Subtotal (95% C) deterogeneik, Tau*= Test for overall effect 2 L2.9 HDL-C<1.0(mm Vu 2015 Subtotal (95% C) telerogeneik (95% C) telerogeneik, Not ap Test for overall effect 2 L2.10 HDL-C≥1.0(mr Than 2018 Than 2013 Subtotal (95% C) telerogeneik, Tau*= test for overall effect 2 L2.11 LDL-C2.6(mm Than 2018 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 LDL-C3.0(mm Than 2018 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 LDL-C3.0(mm Than 2018 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 LDL-C3.0(mm Than 2018 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 LDL-C3.0(mm Than 2018 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 L12 L12 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 L12 L12 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 L12 L12 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 L12 L12 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 L12 L12 Subtotal (95% C) telerogeneik, Tau*= Test for overall effect 2 L2.12 L12 L2.12 L12 | 0.06; cl 2 Z = 3.15 1.39 0.06; cl 2 1.39 0.139 0.139 0.139 0.139 0.139 0.139 0.111 1.16 1.16 1.12 1.16 1.12 1.16 1.12 1.16 1.12 1.16 1.12 2.5.40 0.97 1.19 1.39 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.97 1.19 1.42 1.26 0.21; cl 19 1.42 1.26 0.21; cl 19 1.42 1.26 0.21; cl 19 1.42 1. | $hr^2 = 31$ (P = 0 0.21 (P < 0 0.27 0.36 0.17 0.52 0.25 0.27 0.32 0.25 0.27 0.36 0.27 0.36 0.27 0.36 0.27 0.36 0.221 0.36 0.221 0.36 0.221 0.36 0.221 0.32 0.25 0.41 $hr^2 = 822$ (P < 0 0.29 (P < 0 0.22 (P < 0 0.29 (P = 0 (P = 0) (P = 0 | 328 328 328 343 0.0000 170 40 53 95 536 536 536 536 536 536 536 53 | = 2 (P + 0.85 1) 0.84 0.6 0.91 0.98 = 5 (P + 0.98 0.98 = 5 (P + 0.98 0.98 0.98 = 5 (P + 0.98 | 0.000 0.25 0.76 0.09 0.67 0.23 0.000 0.23 0.23 0.000 0.23 0.11 0.23 0.000 0.23 0.11 0.25 0.11 0.26 0.12 0.18 0.54 | 342 0001); F = 57 57 57 190 52 92 90 57 57 190 57 60 001); F = 190 60 001; F = 190 109 109 109 109 109 109 53 57 57 109 109 53 57 57 57 57 57 57 57 57 57 57 | 5.7% 9.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9 | 0.80 (0.83, 0.87) 0.45 (0.47, 0.73) 0.45 (0.47, 0.73) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.54 (0.45, 0.83) 0.22 (0.20, 0.44) 0.42 (0.30, 0.33) 0.80 (0.83, 0.87) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.56 (0.50, 0.52) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.56 (0.50, 0.52) 0.39 (0.25, 0.53) 0.53 (0.42, 0.64) 0.53 (0.42, 0.64) 0.55 (0.50, 0.52) 0.28 (0.19, 0.37) 0.54 (0.42, 0.64) 0.55 (0.50, 0.52) 0.28 (0.19, 0.37) 0.52 (0.10, 0.24) 0.35 (0.10, 0.27) 0.52 (0.10, 0.34) 0.55 (0.50, 0.52) 0.25 (0.16, 0.34) 0.25 (0.16, | | |
| Subtotal (95% C) deterogeneiky: Tau ² = Test for overall effect 2 Test for overall effect 2 Subtotal (95% C) tetrogeneiky: Not app Test for overall effect 2 t.2.10 HDL-C≥1.0(mr Subtotal (95% C) t.2.10 HDL-C≥1.0(mr Subtotal (95% C) tetrogeneiky: Tau ² = Test for overall effect 2 t.2.10 HDL-C≥2.0(mr Theorement): Tau ² = Test for overall effect 2 t.2.11 HDL-C>2.0(mr Theorement): Tau ² = Test for overall effect 2 t.2.12 HDL-C>2.0(mr Theorement): Tau ² = Test for overall effect 2 t.2.12 HDL-C>2.0(mr Theorement): Tau ² = Test for overall effect 2 t.2.13 Subtotal (95% C) teterogeneiky: Tau ² = Test for overall effect 2 t.2.13 Subtotal (95% C) teterogeneiky: Tau ² = Test for app 13 Subtotal (95% C) teterogeneiky: Tau ² = Test for app 13 Sub | 0.06; cl 2 Z = 3.15 1.39 plicable Z = 11.7 molL) 1.16 1.22 1.17 1.16 1.12 1.16 0.03; cl 2 = 6.10 olL) 1.26 plicable 2 = 6.10 olL) 1.26 0.097 1.39 1.39 1.25 5.44 1.39 1.25 5.44 1.25 0.97 1.51 1.26 0.97 3.16 3.15 1.22 0.21; cl 2 = 4.05 0.97 3.16 1.21; cl 1.26 0.97 3.16 1.21; cl 1.26 0.97 1.19 1.26 0.97 1.39 1.25 0.97 1.39 1.25 0.97 1.39 1.25 0.97 1.19 1.26 0.97 1.19 1.26 0.97 1.19 1.26 0.97 1.19 1.26 0.97 1.19 1.26 0.97 1.19 1.26 0.97 1.19 1.25 0.97 1.19 1.25 0.97 1.19 1.25 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.12 1.26 0.97 1.27 1.27 1. | $hr^2 = 31$ $ir^2 = 0.21$ $ir^2 (P < 0.27)$ 0.27 0.32 0.27 0.32 0.41 $hr^2 = 77, 0.32$ 0.41 $hr^2 = 77, 0.34$ $hr^2 = 0.27$ 0.32 0.34 $hr^2 = 86, 0.32$ 0.29 $hr^2 = 22, 0.32$ 0.32 0.34 $hr^2 = 82, 0.32$ 0.32 0.34 $hr^2 = 82, 0.32$ 0.32 0.32 0.32 0.32 0.32 0.32 0.33 0.32 0.32 0.32 0.34 $hr^2 = 82, 0.32$ 0.32 0.32 0.32 0.32 0.32 0.32 0.34 $hr^2 = 82, 0.32$ 0.32 0.33 0.33 0.33 0.34 0.32 0.34 0.35 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.32 0.33 0.33 0.33 0.34 0.34 0.35 | 328 328 328 343 0.0000 170 43 43 0.0000 170 53 536 536 536 536 536 536 536 | = 2 (P * 0.85 1) 0.84 0.91 0.98 0.91 0.98 | 0.000 0.25 0.76 0.001 0.23 0.000 0.23 0.24 0.000 0.25 0.11 0.25 0.12 0.11 0.26 0.12 0.11 0.23 0.24 0.000 | 342 0001); " = 57 57 57 190 52 28 80 109 109 109 109 109 109 109 10 | 5.7% 9.94% 1.9% 1.9% 2.0% 2.0% 2.0% 1.9% 2.0% 1.9% 2.0% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9 | 0.80 (0.83, 0.87) 0.45 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.54 (0.45, 0.63) 0.28 (0.19, 0.37) 0.28 (0.19, 0.37) 0.32 (0.20, 0.44) 0.32 (0.20, 0.44) 0.35 (0.50, 0.52) 0.39 (0.25, 0.53) 0.56 (0.50, 0.52) 0.39 (0.25, 0.53) 0.56 (0.50, 0.52) 0.56 (0.48, 0.55) | | |

Figure 6 The forest plot of Cys-C between different DM duration, BMI, TC, TG, HDL-C, LDL-C, sampling subgroups of the DR and DWR group.

Publication Bias Analysis We performed a funnel plot analysis to investigate the potential publication bias among included articles. In addition to data of DR-DWR from

| Study or Subgroup | N Mean | IPDR SD | Total | l Mean | DWR SD | Total | Weight | Mean Difference IV, Random, 95% Cl | Mean Difference IV, Random, 95% Cl |
|--|--|--|--|---|--------------------------------|---|--|--|--|
| 1.2.1 BMI≤24(kg/m2 | | 30 | rotal | meall | 30 | rotal | - reignt | 19, random, 35% Cl | IV, Randolli, 35% Ci |
| Han 2019 | | 0.17 | 56 | 1 34 | 1.17 | 52 | 1.4% | 0.30 [-0.02, 0.62] | |
| Subtotal (95% CI) | 1.01 | • | 56 | 1.01 | | 52 | 1.4% | 0.30 [-0.02, 0.62] | |
| Heterogeneity: Not ap | plicable | | | | | | | ,, | |
| Test for overall effect: | | |).07) | | | | | | |
| 1.2.2 BMI>24(kg/m2) | | | | | | | | | |
| ChenJ 2017 | 1.54 | 0.42 | 155 | 1.42 | 0.33 | 387 | 6.5% | 0.12 [0.05, 0.19] | |
| Cui 2019 | 0.99 | 0.38 | 38 | 0.72 | 0.31 | 42 | 3.9% | 0.27 [0.12, 0.42] | |
| Wang 2018 | 1.34 | 0.5 | 50 | 1.08 | 0.68 | 50 | 2.3% | 0.26 [0.03, 0.49] | |
| Wang 2019 | 1.15 | 0.14 | 118 | 0.94 | 0.13 | 125 | 7.7% | 0.21 [0.18, 0.24] | - |
| Wei 2017 | 1.1 | 0.48 | 54 | 0.84 | 0.2 | 28 | 4.1% | 0.26 [0.11, 0.41] | |
| Subtotal (95% CI) | | | 415 | | | 632 | 24.5% | 0.20 [0.14, 0.25] | ◆ |
| Heterogeneity: Tau² = Test for overall effect: | | | | | 0.16); | l² = 399 | 16 | | |
| | | | | ·/ | | | | | |
| 1.2.3 TC<5.2(mmol/L) Wang 2019 | | 0.14 | 118 | | 0.13 | 125 | 7.7% | 0.21 (0.18, 0.24) | - |
| Vvang 2019 Subtotal (95% CI) | 1.15 | 0.14 | 118 118 | U.94 | 0.13 | 125 | 7.7% | 0.21 [0.18, 0.24] 0.21 [0.18, 0.24] | ▲ |
| Heterogeneity: Not ap | nlicable | | 118 | | | 125 | 1.1% | 0.21[0.10, 0.24] | · · |
| Test for overall effect: | | | 0.000 | 01) | | | | | |
| 1.2.4 5.2≤TC<6.2(mr | nol/L) | | | | | | | | |
| Cui 2019 | | 0.38 | 38 | 0.72 | 0.31 | 42 | 3.9% | 0.27 [0.12, 0.42] | |
| Subtotal (95% CI) | | | 38 | | | 42 | 3.9% | 0.27 [0.12, 0.42] | - |
| Heterogeneity: Not ap | plicable | | | | | | | | |
| Test for overall effect: | | |).0005) | | | | | | |
| 1.2.5 LDL-C<3.4(mmd | | | | | | | | | |
| ChenJ 2017 | | 0.42 | 155 | | 0.33 | 387 | 6.5% | 0.12 [0.05, 0.19] | |
| Cui 2019 | | 0.38 | 38 | 0.72 | | 42 | 3.9% | 0.27 [0.12, 0.42] | |
| Wang 2019 | 1.15 | 0.14 | 118 | 0.94 | 0.13 | 125 | 7.7% | 0.21 [0.18, 0.24] | - |
| Subtotal (95% CI) | | | 311 | | | 554 | 18.1% | 0.19 [0.12, 0.26] | |
| Heterogeneity: Tau ² = Test for overall effect: | | | | | 0.06); | I ² = 649 | 16 | | |
| 1.2.6 3.4≤LDL<4.1(n | mol/L) | | | | | | | | |
| Wang 2018 | 1.34 | 0.5 | 50 | 1.09 | 0.68 | 50 | 2.3% | 0.26 (0.03, 0.49) | |
| Subtotal (95% CI) | 1.54 | 0.5 | 50 | 1.00 | 0.00 | 50 | 2.3% | 0.26 [0.03, 0.49] | |
| Heterogeneity: Not ap | nlicable | | | | | | 21070 | 0120 [0100, 0140] | |
| Test for overall effect: | | |).03) | | | | | | |
| 1.2.7 ELISA | | | | | | | | | |
| Chen 2010 | 1.3 | 0.86 | 42 | 0.88 | 0.67 | 45 | 1.4% | 0.42 [0.09, 0.75] | |
| ChenYS 2017 | 1.3 | 0.86 | 100 | 0.88 | 0.67 | 100 | 2.7% | 0.42 [0.21, 0.63] | |
| Cui 2019 | 0.99 | 0.38 | 38 | 0.72 | 0.31 | 42 | 3.9% | 0.27 [0.12, 0.42] | |
| Wei 2017 | 1.1 | 0.48 | 54 | 0.84 | 0.2 | 28 | 4.1% | 0.26 [0.11, 0.41] | |
| Subtotal (95% CI) | | | 234 | | | 215 | 12.1% | 0.31 [0.21, 0.40] | • |
| Heterogeneity: Tau ² = | | | | | 0.54); | l² = 0% | | | |
| l est for overall effect. | | | | | | | | | |
| | | | | 1.42 | 0.33 | 387 | 6.5% | 0.12 [0.05, 0.19] | |
| 1.2.8 TIIA | 1.54 | 0.42 | | 1.74 | | 82 | 5.7% | 0.03 [-0.07, 0.13] | +- |
| 1.2.8 TIIA ChenJ 2017 | | 0.42 | 155 54 | 0.61 | | | | 0.80 [0.66, 0.94] | |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 | 0.64 | 0.05 | 54 | 0.61 | | 49 | | | |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 Li 2015 | 0.64 1.75 | 0.05 | 54 41 | 0.95 | 0.38 | 49 125 | 4.2% 7.7% | | |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 Li 2015 Wang 2019 | 0.64 1.75 1.15 | 0.05 0.31 0.14 | 54 41 118 | 0.95 0.94 | 0.38 0.13 | 125 | 7.7% | 0.21 [0.18, 0.24] | |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 Li 2015 Wang 2019 Yang 2016 | 0.64 1.75 | 0.05 0.31 0.14 | 54 41 | 0.95 | 0.38 | | | 0.21 [0.18, 0.24] 0.29 [0.20, 0.38] | - |
| Test for overall effect: 1.2.8 TIIA ChenJ 2017 Jin 2019 Li 2015 Wang 2019 Yang 2016 Subtotal (95% Cl) Heterogeneity: Tau ² = | 0.64 1.75 1.15 1.64 0.03; C | 0.05 0.31 0.14 0.21 hi ² = 8 | 54 41 118 45 413 7.93, d | 0.95 0.94 1.35 f = 4 (P | 0.38 0.13 0.18 | 125 28 671 | 7.7% 5.9% 30.0 % | 0.21 [0.18, 0.24] | - |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 Li 2015 Wang 2019 Yang 2016 Subtotal (95% CI) Heterogeneiky: Tau [*] = Test for overall effect: | 0.64 1.75 1.15 1.64 0.03; C | 0.05 0.31 0.14 0.21 hi ² = 8 | 54 41 118 45 413 7.93, d | 0.95 0.94 1.35 f = 4 (P | 0.38 0.13 0.18 | 125 28 671 001); F | 7.7% 5.9% 30.0% = 95% | 0.21 [0.18, 0.24] 0.29 [0.20, 0.38] 0.28 [0.12, 0.44] | |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 Li 2015 Wang 2019 Yang 2018 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Total (95% CI) | 0.64 1.75 1.15 1.64 0.03; C Z = 3.46 | 0.05 0.31 0.14 0.21 hi ² = 8 i (P = 0 | 54 41 118 45 413 7.93, d 0.0005) 1635 | 0.95 0.94 1.35 f = 4 (P | 0.38 0.13 0.18 < 0.00 | 125 28 671 001); I ² 2341 | 7.7% 5.9% 30.0% = 95% 100.0% | 0.21 [0.18, 0.24] 0.29 [0.20, 0.38] 0.28 [0.12, 0.44] 0.24 [0.20, 0.28] | - |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 Li 2015 Wang 2019 Yang 2016 Subtotal (95% Cl) Heterogeneiky: Tau ² = Test for overall effect: Total (95% Cl) | 0.64 1.75 1.15 1.64 0.03; C Z = 3.46 | 0.05 0.31 0.14 0.21 hi ² = 8 6 (P = 0 hi ² = 1 | 54 41 118 45 413 7.93, d 0.0005) 1635 08.54, | 0.95 0.94 1.35 f = 4 (P | 0.38 0.13 0.18 < 0.00 | 125 28 671 001); I ² 2341 | 7.7% 5.9% 30.0% = 95% 100.0% | 0.21 [0.18, 0.24] 0.29 [0.20, 0.38] 0.28 [0.12, 0.44] 0.24 [0.20, 0.28] | |
| 1.2.8 TIIA ChenJ 2017 Jin 2019 J 2015 Vang 2016 Subtotal (95% CI) Heterogeneity: Tau ²² = Fest for overall effect: Total (95% CI) | 0.64 1.75 1.15 1.64 0.03; C Z = 3.46 0.01; C Z = 10.9 | 0.05 0.31 0.14 0.21 hi ² = 8 i (P = 0 hi ² = 1) l6 (P < | 54 41 118 45 413 7.93, d 0.0005) 1635 08.54, 0.0000 | 0.95 0.94 1.35 f = 4 (P df = 20 (| 0.38 0.13 0.18 < 0.00 | 125 28 671 001); I ² 2341 00001); | 7.7% 5.9% 30.0% = 95% 100.0% ; ² = 82% | 0.21 [0.18, 0.24] 0.29 [0.20, 0.38] 0.28 [0.12, 0.44] 0.24 [0.20, 0.28] | 0.5 -0.25 0 0.25 0.5 Favours [NPDR] Favours [DWR] |

Figure 7 The forest plot of Cys-C between different BMI, TC, LDL-C, detection methods subgroups of the NPDR and DWR group.

included 11 articles without classifying DR into NPDR and PDR, we input data of NPDR-DWR and PDR-DWR from the other 12 research into DR-DWR. The result showed that the distribution of studies was almost symmetrical, therefore no significant publication bias was found (Figure 9).

DISCUSSION

Cys-C is widely used as a biomarker of kidney function for its relatively easy detection and lower molecular weight to measure GFR. Cys-C is removed from the blood by glomerular filtration, whose concentration will increase in serum due to failed kidney function. Previous Meta-analysis compared the diagnostic accuracy of Cys-C with creatinine^[14]. Based on this physical property, another Meta analysis proved the predicting value of Cys-C in diabetic nephropathy^[15]. In our study, we analyzed the role of Cys-C in DR. To prove its relationship with DR, we firstly analyzed 11 articles dealing with the comparison between DWR and DR. After data from these articles was input in Revman, forest plot showed that there was an increase in the level of Cys-C in DR in contrast with DWR. Further results showed that there was an obvious increase in levels of Cys-C from DWR to NPDR and NPDR to PDR. That is, as the DR disease progresses, the amount of Cys-C shows an upward trend, suggesting the Cys-C is strongly associated to DR severity. We carried out the subgroup analysis, the Cys-C

| | PDR | | NPDR | | | Mean Difference | Mean Difference |
|---|---------------------------------|------------------|-----------------------------|---------------|---------------|---|------------------------------|
| Study or Subgroup | Mean SD | Total | Mean SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% Cl |
| 2.2.1 Duration ≤ 10(y | | | | | | | |
| Bao 2018 Chen 2010 | 2.42 0.4 3.31 1.86 | 30 46 | 1.12 0.28 | 50 42 | 3.3% 1.4% | 1.30 [1.14, 1.46] 2.01 [1.41, 2.61] | |
| ChenJ 2017 | 1.85 0.47 | 108 | 1.54 0.42 | 155 | 3.5% | 0.31 [0.20, 0.42] | - |
| ChenYS 2017 | 3.31 1.86 | 100 | 1.3 0.86 | 100 | 2.2% | 2.01 [1.61, 2.41] | |
| Cui 2019 | 1.59 0.42 | 34 | 0.99 0.38 | 38 | 3.2% | 0.60 [0.41, 0.79] | |
| Li 2015 Wang 2018 | 2.24 0.67 1.6 0.71 | 35 50 | 1.75 0.31 1.34 0.5 | 41 50 | 2.9% 3.0% | 0.49 [0.25, 0.73] 0.26 [0.02, 0.50] | |
| Wang 2019 | 1.35 0.19 | 97 | 1.15 0.14 | 118 | 3.7% | 0.20 [0.02, 0.30] | - |
| Subtotal (95% CI) | | 500 | | 594 | 23.2% | 0.84 [0.50, 1.18] | • |
| Heterogeneity: Tau ² = | 0.22; Chi ² = 2 | 75.54, | df = 7 (P < 0.0 | 0001); I | ²= 97% | | |
| Test for overall effect: | Z = 4.82 (P <) | 0.0000 | 1) | | | | |
| 2.2.2 Duration>10(ye | ars) | | | | | | |
| Han 2019 | 1.89 0.17 | | 1.64 0.17 | 56 | 3.6% | 0.25 [0.18, 0.32] | - |
| Wei 2017 | 1.31 0.69 | 35 97 | 1.1 0.48 | 54 | 2.8% | 0.21 [-0.05, 0.47] | T |
| Yang 2016 Subtotal (95% CI) | 2.47 0.49 | 174 | 1.64 0.21 | 45 155 | 3.5% 10.0% | 0.83 [0.71, 0.95] 0.44 [0.00, 0.87] | |
| Heterogeneity: Tau ² = | 0.14: Chi ² = 7 | | f= 2 (P < 0.00 | | | 0.44 [0.00, 0.07] | - |
| Test for overall effect: | | | | | | | |
| 2.2.3 BMI ≤24(ka/m2 | | | | | | | |
| Z.Z.3 BMI ≈ Z4(Kg/mZ Han 2019 |) 1.89 0.17 | 42 | 1.64 0.17 | 56 | 3.6% | 0.25 [0.18, 0.32] | - |
| Subtotal (95% CI) | 1.00 0.11 | 42 | 1.04 0.11 | 56 | 3.6% | 0.25 [0.18, 0.32] | • |
| Heterogeneity: Not ap | plicable | | | | | | |
| Test for overall effect: | Z = 7.20 (P < | 0.00001 | 1) | | | | |
| 2.2.4 BMI>24(kg/m2) | | | | | | | |
| Chen.I 2017 | 1.85 0.47 | 108 | 1.54 0.42 | 155 | 3.5% | 0.31 [0.20, 0.42] | - |
| Cui 2019 | 1.59 0.42 | 34 | 0.99 0.38 | 38 | 3.2% | 0.60 [0.41, 0.79] | |
| Wang 2018 | 1.6 0.71 | 50 | 1.34 0.5 | 50 | 3.0% | 0.26 [0.02, 0.50] | |
| Wang 2019 | 1.35 0.19 | 97 | 1.15 0.14 | 118 | 3.7% | 0.20 [0.15, 0.25] | - |
| Wei 2017 Subtotal (95% CI) | 1.31 0.69 | 35 324 | 1.1 0.48 | 54 415 | 2.8% 16.2% | 0.21 [-0.05, 0.47] 0.31 [0.18, 0.45] | • |
| Heterogeneity: Tau ² = | 0.02: Chi ² = 1 | | f = 4 (P = 0.00 | | | 0.01[0.10, 0.40] | |
| Test for overall effect: | | | | ,, | | | |
| 2.2.5 1.7≤TG<2.3(mr | | | | | | | |
| Cui 2019 | 1.59 0.42 | 34 | 0.99 0.38 | 38 | 3.2% | 0.60 [0.41, 0.79] | |
| Wang 2019 | 1.35 0.42 | | 1.15 0.14 | 118 | 3.7% | 0.20 [0.15, 0.25] | - |
| Subtotal (95% CI) | | 131 | | 156 | 6.9% | 0.39 [-0.00, 0.78] | ◆ |
| Heterogeneity: Tau ² = | 0.08; Chi ² = 1 | 6.80, d | f=1 (P < 0.00 | 01); l² = | 94% | | |
| Test for overall effect: | Z = 1.95 (P = 1 | 0.05) | | | | | |
| 2.2.6 TG ≥2.3(mmol/ | .) | | | | | | |
| Wang 2018 | 1.6 0.71 | 50 | 1.34 0.5 | 50 | 3.0% | 0.26 [0.02, 0.50] | - |
| Subtotal (95% CI) | | 50 | | 50 | 3.0% | 0.26 [0.02, 0.50] | • |
| Heterogeneity: Not ap Test for overall effect: | | 0.02) | | | | | |
| Testion overall ellect. | 2 = 2.12 (F = 1 | 0.03) | | | | | |
| 2.2.7 LDL-C<3.4(mmd | | | | | | | |
| ChenJ 2017 | 1.85 0.47 | | 1.54 0.42 | 155 | 3.5% | 0.31 [0.20, 0.42] | - |
| Wang 2019 Subtotal (95% CI) | 1.35 0.19 | 97 205 | 1.15 0.14 | 118 273 | 3.7% 7.2% | 0.20 [0.15, 0.25] 0.24 [0.14, 0.35] | l ∎ |
| Heterogeneity: Tau ² = | 0.00: Chi ² = 3 | | = 1 (P = 0.07); | | | 0.24 [0.14, 0.35] | • |
| Test for overall effect: | | | | | | | |
| | | | | | | | |
| 2.2.8 3.4 ≤LDL<4.1(π Wang 2018 | 1.6 0.71 | 50 | 1.34 0.5 | 50 | 3.0% | 0.26 [0.02, 0.50] | |
| Subtotal (95% CI) | 1.6 0.71 | 50 | 1.34 0.5 | 50 | 3.0% | 0.26 [0.02, 0.50] | • |
| Heterogeneity: Not ap | | | | | | | - |
| Test for overall effect: | | 0.03) | | | | | |
| 2.2.9 FLISA | | | | | | | |
| 2.2.9 ELISA Chen 2010 | 3.31 1.86 | 46 | 1.3 0.86 | 42 | 1.4% | 2.01 [1.41, 2.61] | |
| ChenYS 2017 | 3.31 1.86 | 100 | 1.3 0.86 | 100 | 2.2% | 2.01 [1.61, 2.41] | |
| Cui 2019 | 1.59 0.42 | 34 | 0.99 0.38 | 38 | 3.2% | 0.60 [0.41, 0.79] | - |
| Wei 2017 Subtotal (05% CI) | 1.31 0.69 | 35 | 1.1 0.48 | 54 | 2.8% | 0.21 [-0.05, 0.47] | |
| Subtotal (95% CI) Heterogeneity: Tau ² = | 0 58 Chi² - 7 | 215 13 68 d | f=3 (P < 0.00 | 234 001\:P | 9.7% = 96% | 1.17 [0.40, 1.95] | |
| Test for overall effect: | | | - 50 - 5.00 | 5517,1 | - 30 /0 | | |
| | | | | | | | |
| 2.2.10 TIIA | 1 05 0 17 | 108 | 1 54 0 40 | 155 | 2.50 | 0.21 /0.20 0.40 | - |
| ChenJ 2017 Jin 2019 | 1.85 0.47 | 108 | 1.54 0.42 0.64 0.05 | 155 54 | 3.5% 3.7% | 0.31 [0.20, 0.42] 0.02 [-0.01, 0.05] | + · |
| Li 2015 | 2.24 0.67 | 35 | 1.75 0.31 | 41 | 2.9% | 0.49 [0.25, 0.73] | |
| Wang 2019 | 1.35 0.19 | | 1.15 0.14 | 118 | 3.7% | 0.20 [0.15, 0.25] | - |
| Yang 2016 | 2.47 0.49 | 97 383 | 1.35 0.18 | 28 396 | 3.5% 17.3% | 1.12 [1.00, 1.24] | ▲ ⁻ |
| Subtotal (95% Cl) Heterogeneity: Tau ² = | 0.00 Chil- 3 | | df = 1 /P < 0.0 | | | 0.42 [0.15, 0.70] | - |
| Test for overall effect: | | | ui – 4 (r. × 0.0 | 5501);1 | - 33 % | | |
| | | | | | | | |
| Total (95% CI) | 0.00.018 | 2074 | - 04 /F | | 100.0% | 0.51 [0.42, 0.60] | • |
| Heterogeneity: Tau ² = Test for overall effect: | 0.00; Chi*= 1 Z = 10.92 /P < | 025.03 0.0000 | ,ur= 31 (P <i 01)</i | 0.00001 | 7,1-= 979 | | -2 -1 0 1 2 |
| Test for subaroup diff | erences: Chi ² | = 18.78 | 3. df = 9 (P = 0 | .03). I² = | 52.1% | | Favours (PDR) Favours (NPDR) |
| | | | | | | | |

Figure 8 The forest plot of Cys-C between different DM duration, BMI, TG, LDL-C, detection methods subgroups of the PDR and NPDR group.

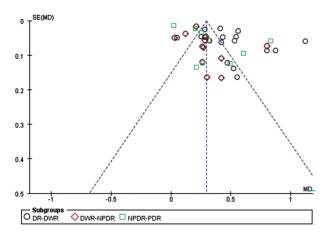


Figure 9 Funnel plot of included articles.

level of the DR group was significantly higher than that of the DWR group. Forest plots of different subgroups indicated that there was a slight increase during the period between DWR and NPDR.

Heterogeneity of subgroup BMI>24 kg/m² (P=0.16, $I^2=39\%$) and subgroup ELISA (P=0.54, $I^2=0$) becomes depleted. Increase could be apparent in the process from NPDR to PDR. DR is a serious microvascular complication deriving from DM. Some biochemical mechanisms have been proposed to explain the pathogenesis of retinopathy through effects on cellular metabolism, signal pathways. Implicated pathways such as oxidative stress, protein kinase C activation, inflammation, and vascular endothelial growth factor (VEGF) have been proved to relate with the process of DR^[44-45]. VEGF is a principal mediator of DR, capable of inducing changes in NPDR and PDR^[4]. Elucidation of VEGF-induced cellular and molecular mechanisms involved in DR has provided the foundation of developing novel therapeutic approaches to preventing ocular complications^[46]. As an extracellular inhibitor of cysteine protease, Cys-C involves in this biochemical mechanism. Previous study covering the neurovascular units (NVUs) in Parkinson's disease demonstrates that Cys-C induced angiogenesis via regulating the level of secreted VEGF protein in the NVUs. Cys-C induced VEGF attenuated 6-OHDA-lesioned PC12 cell degeneration by regulating p-PKC-a/p-ERK1/2-Nurr1 signaling and inducing enhanced autophagy. In the NVUs, VEGF in the conditioned media of 6-OHDA-lesioned PC12 cells over-expressing Cys-C markedly increased angiogenesis. Besides, blockage of autophagy by 3-methyladenine (3-MA) in the Cys-Cover-expressing PC12 cells significantly decreased VEGF expression and VEGF-mediated angiogenesis. It's proved that over-expression of Cys-C increased VEGF expression^[47]. In addition, one research about systemic lupus erythematosus (SLE) demonstrated that the increasing degrees of Cys-C are positively correlated with the level of VEGF in vivo^[48]. From the view of neuron, several studies of animals and humans have confirmed that retinal cells are damaged by diabetes dysfunction of Müller cells^[49]. Müller glia plays an important role in neovascularization, vascular leakage, and vascular lesion in diabetic retinas. VEGF signaling is closely related with Müller glia viability and neuroprotection in diabetic/ hypoxic retinas^[50]. As the conclusion that the level of Cys-C is positively correlated with the degree of VEGF talked before, we infer that Cys-C plays a vital role in the viability of Müller glia. Inflammation also plays an important role in DR development^[51]. Inflammatory cytokines, such as C-reactive protein and tumor necrosis factor alpha have been suggested to contribute to the progression of DR^[52]. Cys-C level was found to be correlated significantly to biomarkers reflecting inflammation, independent of renal function. It demonstrated that a partial correlation between Cys-C and multiple biomarkers of inflammation including CRP, interleukin-6, tumor necrosis factor- α soluble receptor land factor VIII^[53-54]. These researches help prove the effect of Cys-C on inflammation.

Despite the findings we achieved, the present Meta-analysis had several limitations. First, heterogeneity in our Metaanalysis may limit the generalization of the pooled result and the source of heterogeneity could not be discerned by a subgroup analysis. Subgroup analysis was also conducted to explore the heterogeneity. The heterogeneity of most of the subgroup analyses was still obvious in the comparison between DWR and DR, NPDR and PDR. It is worth mentioning that BMI>24 kg/m² and ELISA displayed lower heterogeneity in subgroup analysis between DWR and NPDR. Second, the number of studies in this Meta-analysis is relativelysmall. Third, some included studies had missed description such as method of detecting the level of Cys-C. Finally, all samples included in our analysis were all from China, lack of coherence from other countries.

In conclusion, this Meta-analysis verifies correlation between increased Cys-C levels and DR in Chinese type 2 DM patients. Large sample size prospective study is in need to confirm the findings in the future.

ACKNOWLEDGEMENTS

Foundations: Supported by the National Key R&D Program of China (No.2018YFC1314900; No.2018YFC1314902); National Natural Science Foundation of China (No.81971708); Science and Technology Project of Nantong City (No. MS12020037); Excellent Key Teachers in the "Qing Lan Project" of Jiangsu Colleges and Universities and "226 Project" of Nantong; Postgraduate Research & Practice Innovation Program of Jiangsu Province (No.KYCX20_2836); Jiangsu Students' Platform for Innovation and Entrepreneurship Training Program (No.2020103040185E).

Conflicts of Interest: Yang N, None; Lu YF, None; Yang X, None; Jiang K, None; Sang AM, None; Wu HQ, None. REFERENCES

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