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Association Between the Level of Homocysteine and Diabetic Retinopathy Among Type 2 Diabetic Patients: A Systemic Review and Meta-analysis

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Abstract: Aim: To examine the relationship between homocysteine and diabetic retinopathy in patients with type 2 diabetes mellitus. Methods: A search of PubMed, EMBASE, and the Cochrane Library was conducted for controlled clinical trials examining the association between homocysteine and diabetic retinopathy in type 2 diabetic patients. The retrieval of all available relevant studies as of January 15, 2022. The Newcastle-Ottawa scale was used to evaluate the quality of included studies. Using Review Manager 5.4, an analysis is conducted on the relevant data. Results: Hcy levels were higher in DR patients compared to NDR patients (total MD: 1.78, 95% CI: 1.02 to 2.54, $Z = 4.60$, $P < 0.01$). In addition, the meta-analysis of the studies revealed similar results in the PDR versus NPDR group (total MD: 1.85, 95%CI: 0.70 to 3.00, $P < 0.01$) and the NPDR vs NDR group (total MD: 0.59, 95% CI 0.33 to 0.85, $P = 0.21$). Still evident was heterogeneity in the majority of subgroup analyses ($I^2 \geq 50\%$, $P < 0.1$). Forest plots from various subgroups revealed a slight increase in Hcy between the DR and NDR, PDR and NPDR, and NPDR and NDR time periods. A funnel plot demonstrated that publication bias was significant. Conclusions: Our meta-analysis revealed that elevated Hcy is significantly associated with DR and likely plays an important role in its progression.

Keywords: Diabetic Retinopathy, Homocysteine, Type 2 Diabetes Mellitus, Meta-analysis

1. Introduction

The prevalence of diabetes mellitus is growing due to population increase, age, urbanization, and the rising rates of obesity and physical inactivity. According to estimates, 463 million people globally have diabetes in 2019; this number is expected to increase to 578 million by 2030 and 700 million by 2045 [1]. The most prevalent cause of diabetic retinopathy, which is responsible for the majority of vision loss in middle-aged and older people across the globe, is diabetes mellitus. By 2030, it is predicted that there will be 191 million DR, as the incidence of diabetes keeps rising [2]. The International Clinical Diabetic Retinopathy Disease Severity Scale, which was released in 2019 by the American Academy of Ophthalmology, is the most current clinical grading standard for DR. DR is subdivided into no apparent retinopathy, non-proliferative diabetic retinopathy, and proliferative diabetic diabetic retinopathy based on the findings seen during dilated ophthalmoscopy [3]. NPDR may develop into DR, which can result in vision loss or possibly blindness, if it is not properly treated. Within 5 years, 46.89 percent of those with Type 2 diabetes mellitus would acquire DR [4]. This is why it is so important to identify DR early and to treat it well. Homocysteine, a sulfur-containing amino acid that is a methionine intermediate metabolite [5], keeps the body's methylation and antioxidant systems functioning. Hyperhomocysteinemia, which is caused by an increase in homocysteine levels in the body due to a variety of factors, affects all organs since it lowers the body's methylation and antioxidant capabilities. As a result, it is connected to the

development of many illnesses, both directly and indirectly. Potential risk factors for cardiovascular disease, cerebrovascular illness, renal disease, immunological disorders, and inflammatory diseases include having high homocysteine levels [6-10]. Additionally, it has been related to psychiatric and neurodegenerative diseases such schizophrenia, Alzheimer's disease, and anxiety disorders [11, 12]. To treat hyperhomocysteinemia, pills including folic acid or vitamin B12 are now used [13, 14].

A greater Hcy was linked to NPDR by Tomi et al. [15] and may contribute to the emergence of NPDR in T2DM. According to Li et al. research 's [16] Hcy may be utilized as an early diagnostic tool to gauge the severity of DR and is an independent risk factor for type 2 diabetic retinopathy. However, He et al. [17] observed no statistically significant difference when comparing homocysteine levels in individuals with different stages of DR (P>0.05). Studies have shown inconsistent results regarding the association between Hcy and DR, and it is unclear how Hcy contributes to the development of DR. Hyperhomocysteinemia was shown to be a risk factor for DR, namely PDR, in a 2014 meta-analysis by Chong et al. [18] that included 31 trials and 6,394 people in total. Geographical differences affected the relationship between hyperhomocysteinemia and the risk of T1DM. Specifically in individuals with type 2 diabetes, Lei et al. [19] hypothesized that higher Hcy levels were linked to an increased risk of diabetic retinopathy. However, a lot more research have been published in recent years, and the stated outcomes of different investigations vary [15, 17, 20]. This research looked at the clinical importance of Hcy to offer an evidence-based basis for the prevention and management of DR in patients with T2DM in order to acquire a more thorough knowledge of the link between Hcy and DR in patients with T2DM.

2. Method and Materials

2.1. Study Selection and Identification

Without limiting the publishing language, two researchers (Lu X and Zhao XX) separately searched the PubMed, EMBASE, and Cochrane Library databases. obtaining every relevant study that is still accessible as of January 15, 2022. ("Diabetic Retinopathy" or "Diabetic Retinopathies" or "Diabetic Retinopathy"); and ("homocysteine" or "hyperhomocysteinemia"; "2-amino-4-mercaptobutyric acid"; "2-amino-4-mercaptobutyric acid"; "Homocysteine, L-Isomer"; or "L-Isome"); In order to find other relevant research, the reference lists of all retrieved papers are also used.

2.2. Integrity and Elimination Standards

Certain requirements have to be met by eligible studies: 2) Type 2 diabetes mellitus with or without diabetic retinopathy was the experiment's main focus. 3) Cases and controls' characteristics, such as their numbers, means, standard deviations, and homocysteine concentrations, were included. Duplicates, conference abstracts, animal/in vitro research, editorials, off-topic articles, correspondence, and samples other than blood were excluded. Studies with small sample numbers (less than 50) and poor quality (NOS, fewer than 6 points) were also disregarded.

2.3. Data Gathering and Quality Assessment

The first author's name, nation, publication year, blood components used for the test, method for detecting homocysteine, number of both cases and control groups, sex, mean age, duration, homocysteine concentration, and quality scores were all independently extracted by two reviewers (Lu X and Zhao XX) from the relevant studies. Discussions with a second reviewer on each item were used to settle any eligibility questions that arose throughout the extraction (Chen WJ). The Newcastle-Ottawa Scale was used to rate the research [21]. Studies getting 6 points on the NOS scale were considered to be of considerably better quality. The maximum NOS score that could be achieved was 9.

2.4. Data Analysis

The related data is analyzed using Review Manager [Rev Man (Computer application), Version 5.4.1, The Cochrane Collaboration, 2020]. The Cochrane's Q-test and I^2 statistics were used to assess the heterogeneity. The Q data were regarded as statistically significant if P<0.1, and I^2 values more than 50% denoted considerable heterogeneity. Based on the I^2 data, heterogeneity was classified as low (to 50%), moderate (50% to 75%), or high (>75%) [22]. Data with low heterogeneity ($I^2 \leq 50\%$), whereas random-effects models were used to study data with $I^2>50\%$ (REM). Calculating the mean difference and 95% confidence interval (CI) were calculated, and $P<0.05$ was regarded statistically significant. Funnel plots were utilized to assess the Rev Man's publishing bias. The funnel plots should be fairly symmetrical to rule out publication bias.

3. Results

3.1. Characteristics of the Studies Included

The procedure for including studies in this meta-analysis is shown in Figure 1. The first examination of the relevant literature included 9 Pubmed articles, 178 Embase articles, and 2 Cochrane Library papers. 154 articles that did not fit the inclusion criteria were discarded by reading the title and abstract, and 13 papers that did not satisfy the requirements by reading the full text were also excluded. As a consequence, 14 papers were included after using EndNote X9 to manage the literature. Table 1 provides a summary of the features of the included studies.

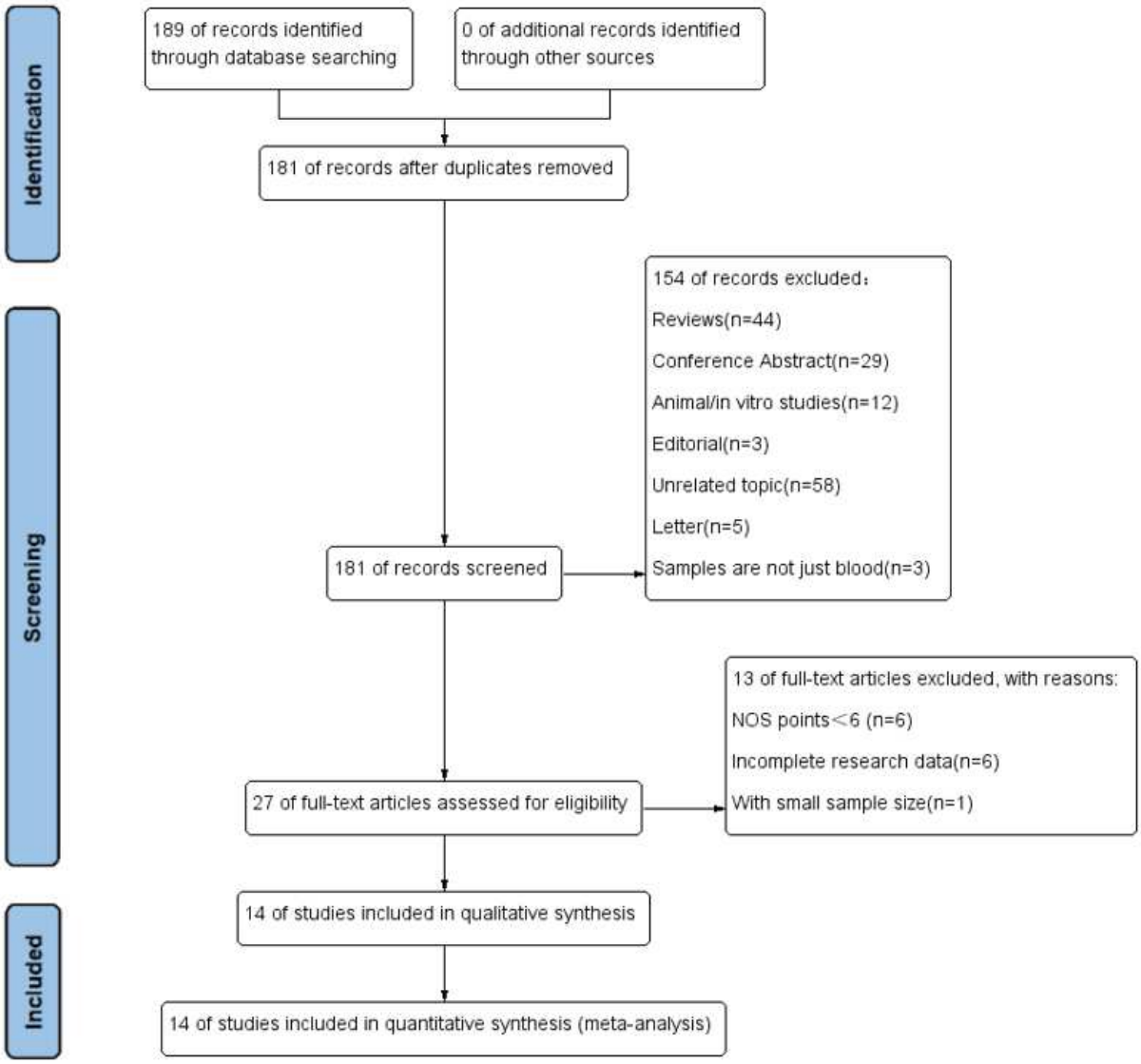

Figure 1. *Procedure for screening literature.*

Table 1. *Patients and trials with specific characteristics.*

Author publication year	Country	Sample	Method	NOS	Group	Number	Sex (M/F)	Mean age (y)	T2DM duration (y)	Hcy (μmol/L)
Brazionis [28] 2008	Australia	Plasma	FPIA	8	group 1:no DR	120	-	65.0 (59.0-69.0)	7.0 (4.8-12.0)	9.2 (7.5-11.5)
					group 2: DR	48	-	66.5 (60.3-69.0)	12.0 (7.3-21.5)	10.5 (9.0-13.8)
Chen [29] 2010	China	Serum	ELISA	6	group 1:no DR	45	22/23	64.5±6.9	0.5-5.0	8.35±6.02
					group 2: NPDR	42	22/20	65.3±5.4	3.0-15.0	9.23±5.12
					group 3: PDR	46	25/21	68.6±5.8	5.0-20.0	10.97±7.45
					group 4: controls	40	20/20	59.25±6.5	-	7.85±1.86
Goldstein [30] 2004	America	Plasma	HPLC	6	group 1:no DR	62	92/87	72.06±1.24	11.96±8.13	13.46±0.74
					group 2: NPDR	71		68.1±1.04	14.58±8.04	14.56±0.64
					group 3: PDR	46		69.2±1.36	17.62±9.29	15.86±1.34
					group 4: controls	156	80/76	69±0.4	-	11.75±0.24
Gupta [31] 2018	India	Serum	chemiluminescent technology	8	group 1: PDR	39	33/6	53.3±5.4	-	17.98±6.26
					group 2:no DR	39	33/6	54.8±6.1	-	17.71±8.17
Li [20] 2021	China	Serum	ELISA	7	group 1:no DR	40	21/19	49.28±1.60	3.14±1.07	11.76±2.53
					group 2: NPDR	39	24/15	49.21±1.63	6.03±1.21	13.35±2.78
					group 3: PDR	41	24/17	51.62±1.64	9.32±1.48	15.65±3.10

Author publication year	Country	Sample	Method	NOS	Group	Number	Sex (M/F)	Mean age (y)	T2DM duration (y)	Hcy (μmol/L)
Looker [32] 2003	America	Serum	HPLC	8	group 1:no DR	279	-	52.8 (45.9-60.9)	11.6 (5.1-17.6)	9.23 (8.84-9.65)
					group 2: NPDR	79				9.71 (8.94-10.59)
					group 3: PDR	23				9.89 (8.49-11.53)
Malaguarnera [33] 2014	Italy	Plasma	-	6	group 1:no DR	50	84/91	65.2±11.8	7.6±5.4	12.1±6.8
					group 2: NPDR	63				14.4±6.7
					group 3: PDR	62				18.2±5.6
					group 4: controls	80	42/38	44.6±10.5	-	7.8±6.4
Srivastav [34] 2016	India	Serum	ELISA	6	group 1:no DR	20	-	56.0±6.71	5.98±6.96	27.22±1.05
					group 2: NPDR with ME	20		54.3±6.91	11.7±6.84	28.9±8.3
					group 3: PDR with ME	20		51.02±7.21	11.7±6.35	30.8±2.1
					group 4: controls	20		53.26±9.81	-	17.12±7.0
Stabler [35] 1999	America	Serum	stable-isotope dilution gas chromatography/ mass spectrometry	6	group 1:no DR	223	-	58.3±8.0	9.3±7.1	9.5±4.3
					group 2: DR	218				10.0±3.3
Yang [36] 2002	China	Plasma	HPLC	7	group 1: controls	19	12/7	55.6±21.0		9.7±2.7
					group 2: T2DM without any complications	39	17/22	56.9±1.1	-	11.3±4.9
					group 3: DR	16	8/8	57.9±9.6		14.7±5.3
Fotiou [37] 2014	Greece	Serum	FPIA	6	group 1:no DR	75	69/71	61.0 (55.0-67.0)	6.0 (3.0-9.0)	11.1 (9.5-13.6)
					group 2: DR	65		68.0 (60.0-75.0)	15.0 (10.0-22.0)	16.3 (14.7-19.8)
He [17] 2020	China	Serum	automatic biochemical analyzer	6	group 1: T2DM	72	118/93	56.97±12.17	10.00 (3.25-15.75)	11.31±2.25
					group 2: DR	45		61.73±13.37	16.00 (8.50-20.00)	11.52±2.52
					group 3: DN	49		66.57±13.20	13.00 (8.50-20.00)	12.58±3.66
					group 4: DR+DN	45		60.47±11.91	19.00 (10.00-22.50)	11.91±2.42
					group 5: controls	76	43/33	61.46±9.65	-	10.44±2.09
Tomić [15] 2022	Croatia	Blood	chemiluminescent immunoassay	6	group 1:no DR	69	59.4%	58.0 (22.0-81.0)	8 (2-39)	14.1 (6.9-68)
					group 2: NPDR	25	70%	62.0 (33.0-76.0)	19.5 (5-40)	19.3 (13-57.5)
Nguyen [38] 2009	Australia	Plasma	-	7	group 1:no DR	643	51.9%	65.3±9.2	0 (5)	8.8 (3.7)
					group 2: DR	278	52.1%	65.0±9.2	7 (15)	8.9 (3.4)

NOS: The Newcastle-Ottawa Scale; DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NDR: No diabetic retinopathy; ME: Macular edema; DN: Diabetic nephropathy; M: Male; F: Female; T2DM: Type 2 diabetes mellitus; Hcy: Homocysteine; HHcy: Homocysteine>15μmol/L; FPIA: Fluorescence polarization immunoassay; ELISA: Enzyme-linked immunosorbent assay; HPLC: High performance liquid chromatography.

3.2. Analysis of the Overall Hcy Levels in the NDR, NPDR, and PDR Groups

A difference in Hcy levels between the DR and NDR groups overall was seen in the forest plot of fourteen trials with 3062 participants (Figure 2). All research that was labeled in the study as DR, NPDR, or PDR was considered DR. Significant heterogeneity was high ($P<0.1$, $I^2>50\%$). According to the results, individuals with DR had higher levels of Hcy than healthy controls (total MD: 1.78, 95%CI: 1.02 to 2.54, $Z=4.60$, $P<0.01$). There are nine articles with the DR classification of NPDR or PDR. The variation in mean Hcy values between NPDR and PDR is seen in Figure 3. The forest plot showed that the PDR had a substantially greater Hcy content than the NPDR (total MD: 1.85, 95%CI: 0.70 to 3.00, $P<0.01$). The Hcy level in the NPDR vs. NDR group is shown in Figure 4 (total MD: 0.59, 95%CI 0.33 to 0.85, $P=0.21$). The Hcy levels of the DR and Control groups are shown in Figure 5. (total MD: 5.19, 95%CI 2.46 to 7.93, $P<0.01$).

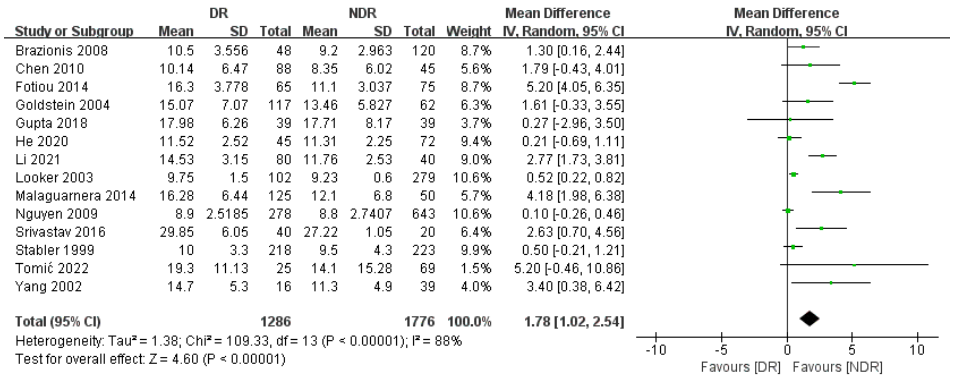

Figure 2. *The woodland parcel of Hcy situated between the DR and NDR groups.*

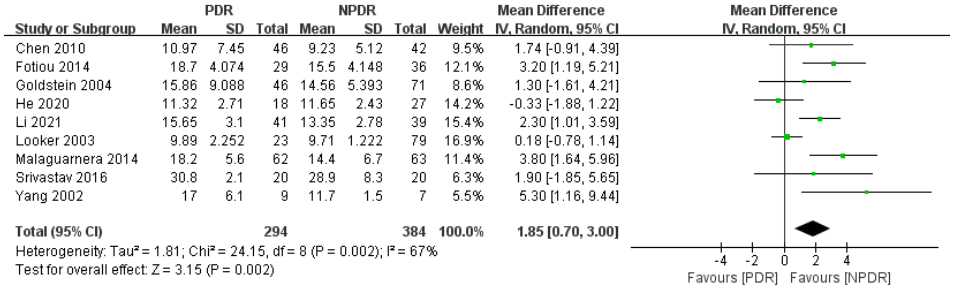

Figure 3. *The woodland tract of Hcy between the groups of PDR and NPDR.*

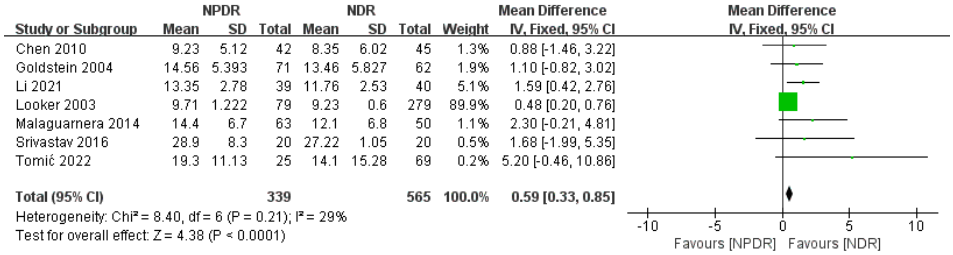

Figure 4. *The Hcy woodland parcel between the NPDR and NDR groups.*

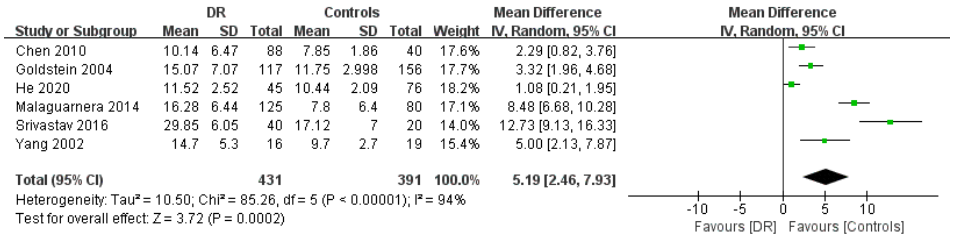

Figure 5. *The Hcy woodland plot between the DR and Controls groups.*

3.3. Findings from Subgroup Analysis

The effects of DR and NDR are contrasted in Figure 6. Most subgroup analyses still showed evidence of heterogeneity (P<0.1, I^2>50%). The DR group exhibited substantially higher Hcy levels than the NDR group, with the exception of the Oceania subgroup (subtotal MD: 0.57, 95%CI -0.58 to 1.72, Z=0.98, P=0.33) and FPIA subgroup (subtotal MD: 3.25, 95%CI -0.57 to 7.07, Z=1.67, P=0.10). The outcome of two exceptions was the same since both included one same article. The difference in Hcy levels between the control and experimental groups followed the same trend as the comparison between DR and NDR in subgroup comparisons between PDR and NPDR. Figure 7 illustrates how the heterogeneity of numerous subgroups in PDR and NPDR considerably reduced, including plasma (P=0.23, I^2 = 39%). Particularly, there was no heterogeneity in America (P=0.47, I^2 = 0%), Europe (P=0.69, I^2 =0%), or ELISA (P=0.92, I^2 =0%) displayed no heterogeneity. Various subgroups' forest plots showed a little increase in Hcy levels between the PDR and NPDR eras. The level of heterogeneity was equivalent to that of DR and NDR in a different subgroup analysis of NPDR and NDR in Figure 8 (P<

0.1, I^2> 50%). Comparable results are shown for the DR and Control groups in Figure 9 (P<0.1, I^2>50%).

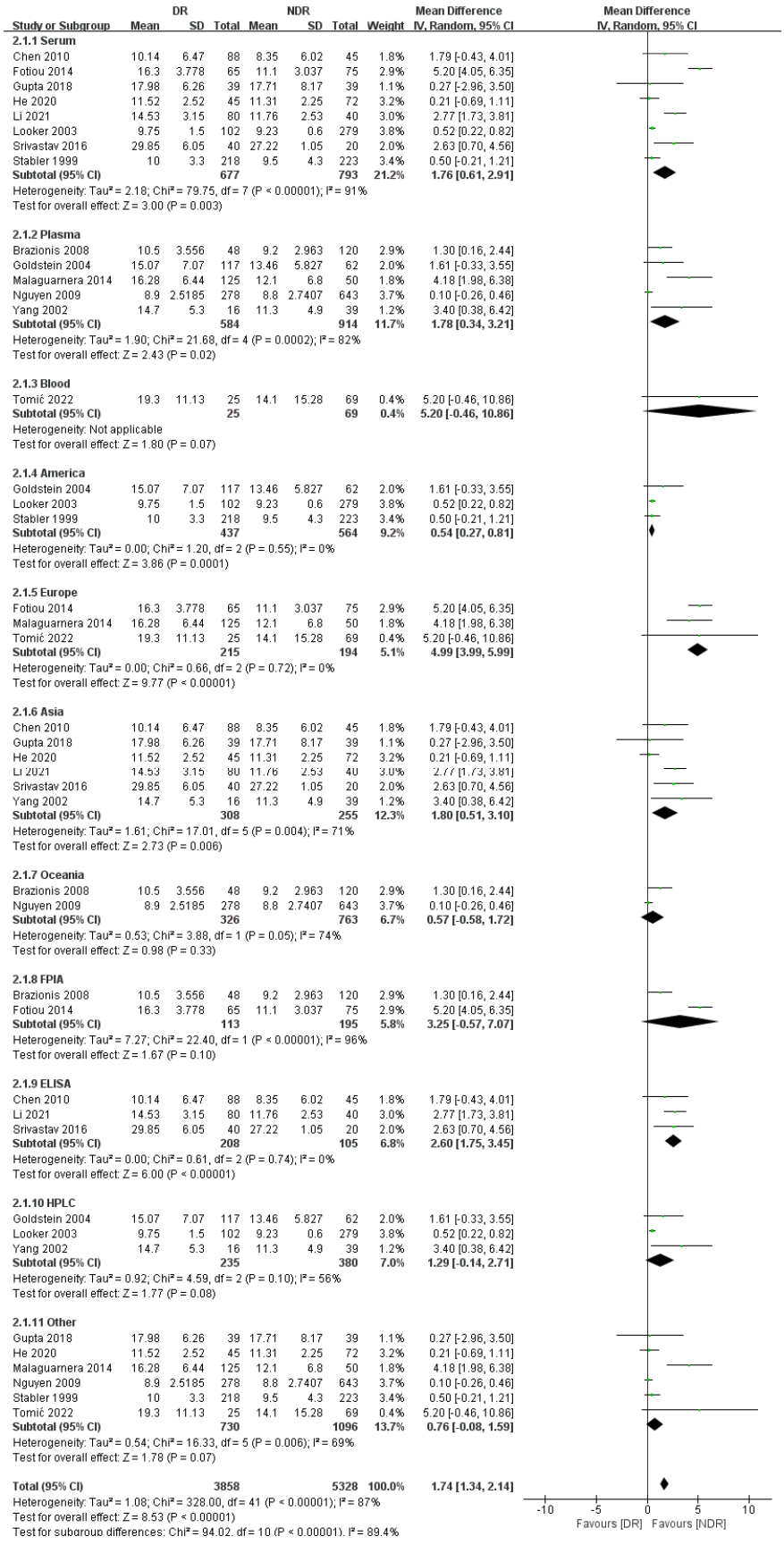

Figure 6. *The forest plot of Hcy between various sample, location, and detection technique subgroups of DR and NDR.*

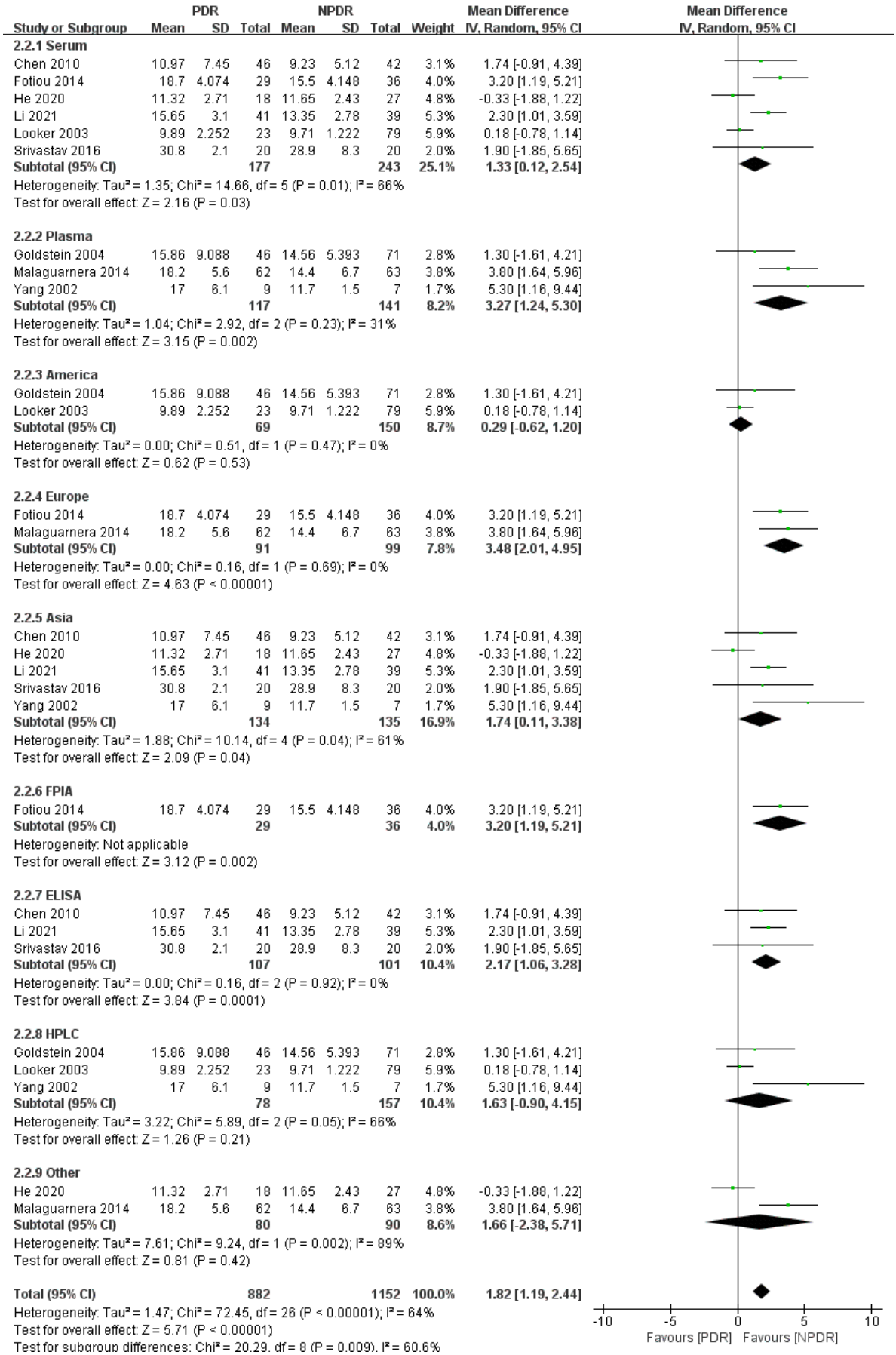

Figure 7. *The forest plot of Hcy between various PDR and NPDR sample, location, and detection technique subgroups.*

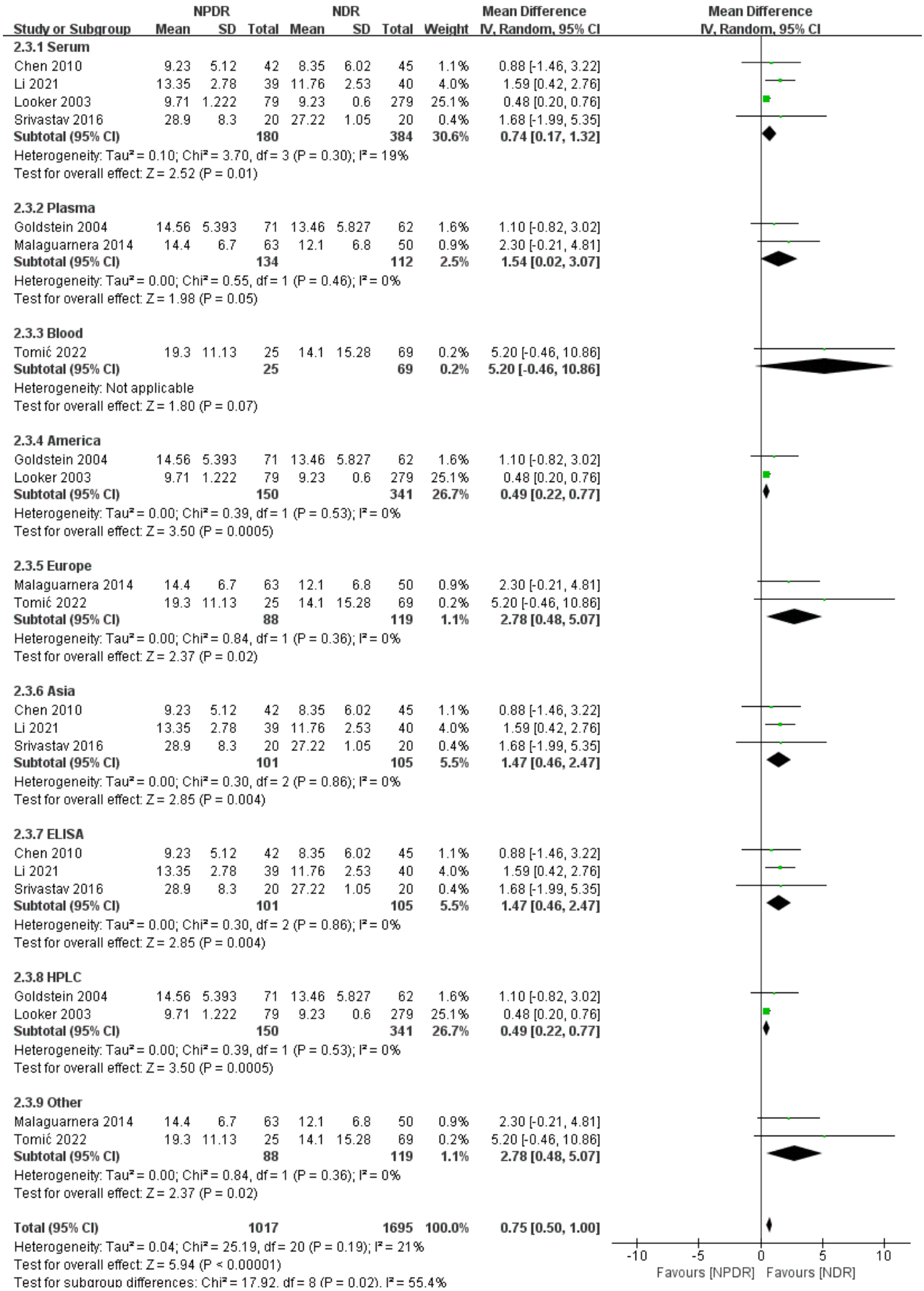

Figure 8. *The forest plot of Hcy between various sample, location, and detection technique subgroups of NPDR and NDR.*

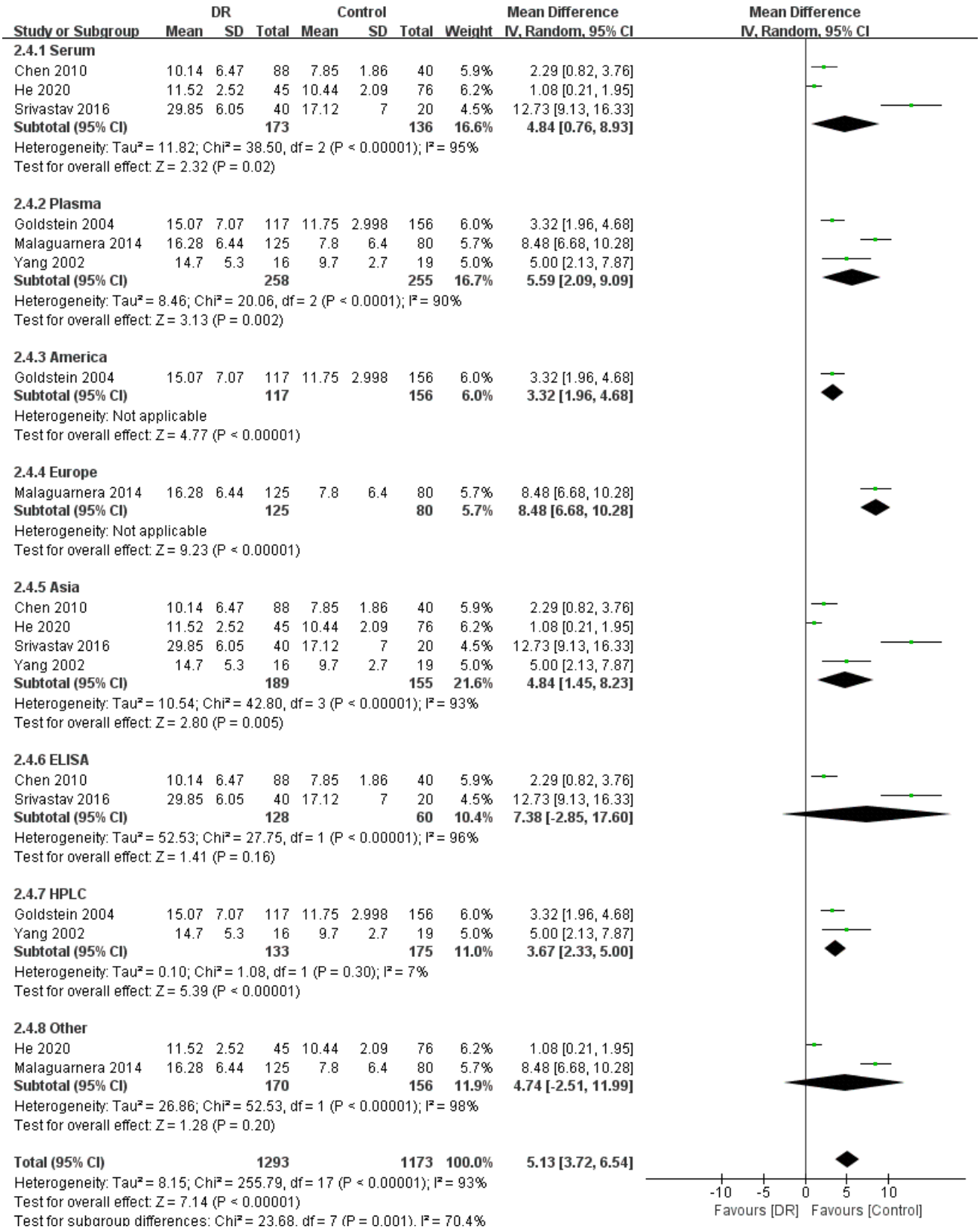

Figure 9. *The forest plot of Hcy between various sample, location, and detection technique subgroups of the DR and Control groups.*

3.4. Publication Bias Evaluation

We conducted a funnel plot analysis to determine the publication bias among the included papers. In addition to the data of DR-NDR from the 14 included publications, we included in the analysis data of PDR-NPDR and NPDR-NDR from the studies that were categorized as DR, NPDR, or PDR. The outcome demonstrated that the distribution of research

was manifestly asymmetric, therefore considerable publication bias was identified (Figure 10).

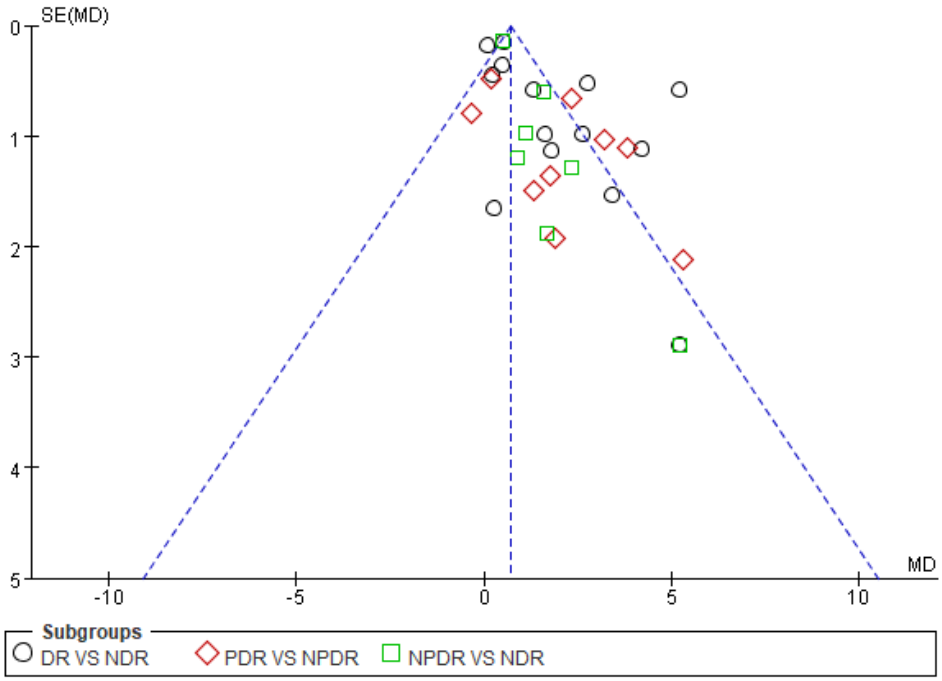

Figure 10. *The funnel plot of the articles covered.*

4. Discussion

Numerous research have examined the link between Hcy and DR, but their findings are conflicting. This Meta-analysis examined the relationships between Hcy and DR in order to reach a conclusion of high relevance. To demonstrate its association with DR, we first reviewed fourteen studies comparing DR and NDR. After the data from these papers were entered into Revman, forest plots revealed an increase in Hcy levels in DR relative to DWR. From PDR to NPDR and NPDR to NDR, the levels of Hcy were shown to have increased significantly. In other words, as the illness advances, the quantity of Hcy increases, indicating that a high Hcy level is a risk factor for the development of DR. The subgroup analysis revealed that the DR group had considerably higher Hcy levels than the NDR group. And the PDR against NPDR and NPDR versus NDR groups had identical outcomes. DR is one of the chronic microvascular consequences of DM in the eye, resulting in an increasing frequency of impaired vision and even blindness among diabetes patients. DR is the leading cause of blindness in adults of working age. Development and progression of DR is a complex process involving several molecular and biochemical pathways, whose interactions alter the internal environmental stability of retinal vasculature and cells. According to the pathophysiological mechanisms of DR development and progression, vascular endothelial growth factor (VEGF) is thought to be an important factor mediating the pathophysiological changes in DR, both in the proliferative phase of neovascularization and in the non-proliferative phase of diabetic macular edema, resulting in the development of anti-VEGF therapies, which have been rapidly promoted in the field of DR treatment [23]. Homocysteine is toxic to the vascular endothelium and promotes thrombosis; consequently, it may have a role in exacerbating the hypoxic condition found in diabetic retinopathy via increasing capillary bed closure [24]. Therefore, we believe that Hcy may induce vascular endothelial injury, resulting in increased VEGF secretion. Notably, dyslipidemia (primarily hypertriglyceridemia and low high-density lipoprotein cholesterol levels) is favorably linked with blood homocysteine levels [25]. Endoplasmic reticulum stress caused by Hcy leads deregulation of the cholesterol and triglyceride biosynthesis pathways, resulting in abnormal lipid metabolism [26, 27]. According to the Chinese clinical recommendations for the treatment of DR, dyslipidemia is a risk factor for the onset of DR. This provides more evidence that increased Hcy plays a crucial role in the development of the DR.

Despite the results obtained, this Meta-analysis has a number of drawbacks. First, there was substantial variability since the studies used a variety of techniques; consequently, care should be exercised when drawing generalizations. Second, the number of studies included in this Meta-analysis is modest. Thirdly, several included studies lacked essential information, such as the technique for determining the concentration of Hcy. And the funnel plot was asymmetrical, suggesting that the papers supporting insignificance may not have been published or were unavailable for the meta-analysis. In addition, conference proceedings were omitted, thus we may have overlooked some small unpublished findings. In addition, the assessment of Hcy levels in plasma or serum is not consistent among the included studies, and a variety of assays have been utilized in

earlier research. Consequently, a detection bias cannot be ruled out entirely in our analyses.

5. Conclusion

In conclusion, according to the paper's Meta-analysis, there is an association between increasing Hcy levels and DR in T2DM patients, despite the contradictory perspectives of several research. For this reason, a future investigation with a large sample size is required to corroborate the results.

Conflicts of Interest

All the authors do not have any possible conflicts of interest.

Acknowledgements

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