Associations of environmental characteristics and lifestyle behaviours with donor blood parameters

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2020

document version
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- CHAPTER TWO -

Urban-rural differences in the association between blood lipids and characteristics of the built environment: a systematic review and meta analysis

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BMJ Global Health. 2019; 4:e001017

Abstract

Introduction

The built environment defines opportunities for healthy eating and physical activity and may thus be related to blood lipids. The aim of this study is to systematically analyse the scientific evidence on associations between built-environment characteristics and blood lipid levels in adults.

Methods

PubMed, EMBASE and Web of Science were searched for peer-reviewed papers on population-based studies up to 9 October 2017. We included studies that reported on built-environment characteristics and blood lipid levels in adult populations (≥18 years). Two reviewers independently screened titles/abstracts and full-texts of papers and appraised the risk of bias of included studies using an adapted version of the Quality Assessment Tool for Quantitative Studies. We performed meta-analyses when five or more studies had sufficient homogeneity in determinant and outcome.

Results

After screening 6,903 titles/abstracts and 141 potentially relevant full-text articles, we included 50 studies. Forty-seven studies explored associations between urban versus rural areas with blood lipid levels. Meta-analyses on urban versus rural areas included 133,966 subjects from 36 studies in total. Total cholesterol levels were significantly and consistently higher in urban areas as compared to rural areas (mean difference 0.37 mmol/L, 95%CI 0.27 – 0.48). Urban/rural differences in HDL cholesterol were inconsistent across studies and the pooled estimate showed no difference (0.00 mmol/L 95%CI -0.03 – 0.04). LDL cholesterol and triglyceride levels were higher in urban than in rural areas (mean difference 0.28, 95%CI 0.17-0.39; and 0.09, 95%CI 0.03 – 0.14, respectively).

Conclusions

Total and LDL cholesterol levels and triglycerides were consistently higher in residents of urban areas than those of rural areas. These results indicate that residents of urban areas generally have less favourable lipid profiles as compared to residents of rural areas.

Systematic review registration: PROSPERO CRD42016043226.

Introduction

Elevated blood lipid levels are an established risk factor for cardiovascular diseases and contribute in a meaningful way to the global burden of disease. Globally, high total cholesterol levels are estimated to account for 4.5% of the total deaths[1-3]. Physical activity and low consumption of food high in saturated fat and dietary cholesterol, and high intake of food high in unsaturated fatty acids, especially omega-3 fatty acids, are associated with more favourable blood lipid profiles[4-6]. In particular the favourable effects of physical activity on high density lipoprotein (HDL) cholesterol and triglycerides is well documented[7]. Dietary- and physical activity behaviour is, in turn, influenced by built-environment characteristics that directly and indirectly facilitate or inhibit the maintenance of a healthy lifestyle[8,9]. For example, the availability, accessibility and affordability of food and fast-food outlets have been found to be associated with dietary behaviour[10], and the availability and proximity of opportunities to be physically active have been linked to leisure time physical activity[11,12]. Hence, in their capacity to affect lifestyle behaviour, built-environment characteristics may be 'upstream' determinants of blood lipid levels[13-20].

A common focus of the many studies that have investigated built-environment characteristics and blood lipid levels is the difference between residents of urban and rural areas. Urban-rural differences in blood lipid levels may be prevalent due to several aspects: urban areas may generally score higher on walkability as compared to rural areas, thereby facilitating light physical activity [21,22]. This could have beneficial effects in terms of reducing blood lipid levels for those living in more rural areas. Also, it may be that adults living in exposure to unhealthy food (outlets) may differ across urban and rural areas, which may influence blood lipid levels via dietary intake. Systematic reviews that examined urban-rural differences in relation to other health outcomes reported that rural residence is associated with higher bodyweight[18] and urban residence with higher risk/prevalence of type II diabetes[23], and, in India, with higher prevalence of hypertension[24]. A cross-country study with 17 countries reported the rate of major cardiovascular events (myocardial infarction, stroke and heart failure) was higher in rural compared to rural areas in low-and middle income countries (LMIC)[25]. Interestingly, urban communities had higher risk factor scores. For policy makers, gaining insight into the health effects of urbanisation is highly relevant, as the United Nations projects that by 2050, 70% of the global population will reside in urban areas[26,27]. In spite of it being a widely-studied topic, a comprehensive overview of the relationship between built-environment characteristics and blood lipids is lacking. Therefore, we aimed to systematically review and meta-analyse the scientific evidence on associations between built-environment characteristics

potentially related to physical activity, sedentary behaviour, dietary habits and blood lipid levels in adults.

Methods

We conducted a systematic review and meta-analysis of studies seeking to assess the association between the built environment and total, HDL and low density lipoprotein (LDL) cholesterol; HDL/LDL cholesterol ratio; and/or triglyceride levels. The structure of this review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement. The protocol of this systematic review was published and registered in PROSPERO in advance (www.crd.york.ac.uk/prospero, ID:CRD42016043226).

Literature search strategy

To identify all relevant publications, we performed systematic searches in the bibliographic databases PubMed, EMBASE.com and the Web of Science Core Collection up to 9 October 2017 (LS, RdG). Search terms included indexed terms from MeSH in PubMed, EMtree in EMBASE, as well as free texts in titles and abstracts. Search terms related to 'cholesterol' or 'triglycerides' were used in combination with search terms including 'built environment'. Full-text, peer-reviewed articles in English, French and Dutch were included. Duplicate articles were excluded. The full search strategy for all databases can be found in Appendix A. In addition, reference lists of the full-text articles included were searched for potentially eligible articles (i.e. backward screening) and a citation search (i.e. forward screening (RdG)).

Screening and eligibility criteria

Study designs that sought to assess associations between the built environment and total cholesterol (TC), HDL and/or LDL cholesterol, and/or triglycerides were considered eligible for systematic review. Two authors (RdG and JL) independently screened all potentially relevant titles and abstracts. Subsequently, full-texts were screened for eligibility using pre-specified inclusion and exclusion criteria. Studies were included if they: (i) reported on adults (aged >18 years or mixed age groups, thus drawing separate conclusions/results for adults); (ii) were population-based; (iii) were peer-reviewed, published, full-texts; (iv) reported on the association between built and/or physical-environment characteristics and total, HDL and LDL cholesterol; HDL/LDL cholesterol ratio; and/or triglyceride levels; (v) included objectively or subjectively measured built-environment characteristics; (vi) and were written in Dutch, French or English. Studies were excluded if they: (i) reported on the same population as another study that was included (of these, only the most relevant article was included). There were no restrictions

with regard to ethnicity or nationality of study populations. Studies were eligible for meta-analyses if descriptive statistics (mean, standard deviation or standard error, and number of participants) were available as these are necessary to construct mean differences. Differences in judgment were resolved by reaching consensus (RdG and JL) and by consultation with a third author (KvdH) if disagreements were not resolved. Meta-analyses were performed in the event that more than five studies on the same environmental characteristic were identified with sufficient similarity in determinant and outcome.

Data extraction and study outcomes

A data extraction form was developed and pilot-tested on five randomly selected included studies and refined accordingly. Data were extracted by one author (RdG) and five percent were randomly checked (JL). The extraction form included author(s), country of study, year of publication, journal reference, participant characteristics (age, sex, number of participants, and inclusion criteria pertaining to age), study design, data collection methods, environment characteristics and definition of the exposure. Only two comparators were extracted: if multiple urbanisation levels – i.e. urban, rural, semi-rural – were reported, these were pooled into two categories where possible, otherwise only urban and rural were extracted. For this study data on urban and rural areas was extracted based on the categorisation as provided by the authors of the included studies. Hence, no uniform definition was used. As part of the quality assessment an item regarding the reporting on the used definition was included (see Q16 of Appendix B). Furthermore, we extracted the unit of measurement of blood lipids, whether lipid measurements were taken while fasting or non-fasting, summary measures of the outcome(s) including type of analysis, and, if applicable, regression coefficient, confidence intervals, mean, standard deviation and whether or not a statistical difference was found.

In the event that more clarification or additional information was required, the authors of the original studies were contacted up to five times. First, three attempts to contact the first author were made and, if unsuccessful, the second author and, subsequently, the last author were contacted. When contact details of any of these authors could not be found, attempts were made to contact any of the other authors until five attempts were made. We requested information from authors of 47 of the studies included and successfully contacted authors of 33 studies.

Quality assessment

To assess the quality of the studies included, we used an adapted version of the Quality Assessment Tool for Quantitative Studies (QATQS, Appendix B), used previously for similar purposes [14,23]. The adjusted QATQS was pilot tested

for clarity on five studies included and consisted of the following six domains: study design, selection bias, withdrawals and drop-outs, confounders, data collection and reporting. Although our research question differed from the majority of the research questions of the studies included, we assessed the quality of these studies in relation to our research question i.e. the association between environment characteristics and the outcome. Analysis or reporting of the results may, therefore, have been appropriate for the research question of the original paper, but not sufficient in light of the aim of this systematic review. Each domain was rated as strong, moderate, weak, or not applicable, which resulted in an overall quality score. Studies with at least three strong domains and no weak domains were classified as strong. Moderate was assigned to studies with two weak domains or fewer than three strong domains. Studies with more than two weak domains were rated as weak.

Data synthesis and analysis

A narrative of the findings from the studies included was written, structured around the type of outcome, the built-environment characteristics under study and the quality (strong/moderate versus weak). The meta-analyses were performed using R Studio version 0.99.896 and the Metafor package, using a random effects model. The pooled estimates in the forest plots were presented as mean differences with 95% confidence intervals between groups. The forest plots were grouped by study quality (moderate-strong, and weak) and by sex. Heterogeneity in study outcomes was assessed using the I^2 statistic. We assessed potential publication bias by evaluating the symmetry of funnel plots for each blood lipid under study. Since the included studies were published over a considerable time span (1980-2017) additional sensitivity analyses were performed in which we meta-analysed studies stratified by three time periods: from 1980-1999, 2000-2009 and from 2010-2017.

Results

Study selection

The search generated a total of 9,602 articles, of which 3,509 were duplicates, leaving 6,134 unique articles, (see Figure 1). We excluded 5,993 articles after screening the titles and abstracts, and reviewed the remaining 141 full-texts. Of those 141 full-texts, (i) 54 did not report on a relevant outcome; (ii) ten were in a language other than English, French or Dutch; (iii) ten studies were excluded because of study design; (iv) seven studies were excluded because of the study population; (v) seven studies were excluded because no relevant built-environment determinants were studied; and (vi) five studies reported on two of the same study populations, therefore three of these studies were excluded. As a result, a total of 50 studies met the eligibility criteria and

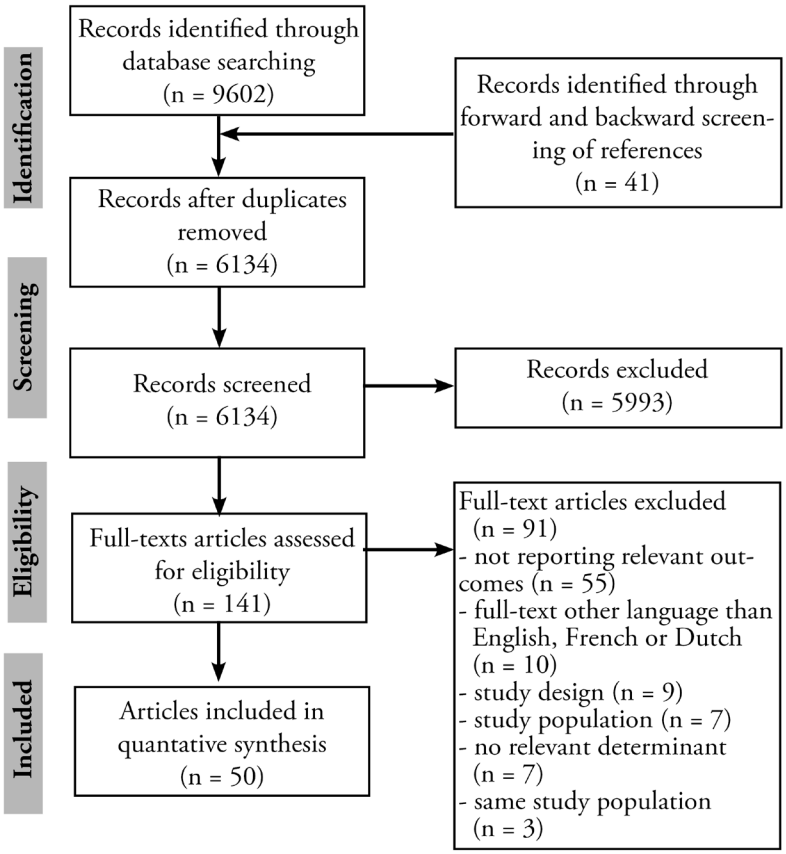

Figure 1: Flowchart.

were included. Evidence of heterogeneity across studies included in the meta-analysis was observed, I^2 ranged from 90.4 to 98.1%. The symmetry of the funnel plots (Figure 2) suggests the absence of publication bias. The plots also show some dispersion on top, indicating heterogeneity in outcomes between studies, which is in line with the observed I^2 statistic values.

Study characteristics

The majority of the studies included (47) reported on differences in blood lipids between urban and rural environments. The characteristics of these studies are summarised in Table 1. Most of these studies were conducted in Asia (30, of which 11 in India and ten in China), and Africa (10). With the exception of two studies [28,29] that had a longitudinal observational design, all urban/rural studies had a cross-sectional design and were published between 1980 and 2017, the median year of publication being 2009 (interquartile

Table 1: Characteristics of included "urban-rural" built environment characteristic studies.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Abdul-Rahim[46]	Palestina	CS	492	500					TC	5.23 ± 1.33			5.15 ± 1.11		
									HDL	0.90 ± 0.22			1.17 ± 0.45		
									LDL	3.75 ± 1.10			3.27 ± 1.32		
									TG	1.86 ± 2.66			1.53 ± 1.57		
Aguilar-Salinas[47]	Mexico	CS			167	81	56	40	TC		5.75 ± 1.12	5.6 ± 0.95		5.5 ± 1.1	5.02 ± 0.97
									HDL		1.26 ± 0.33	1.08 ± 0.26		1.26 ± 0.28	1.31 ± 0.36
									LDL		3.93 ± 1.08	3.86 ± 0.93		3.6 ± 1.1	3.2 ± 0.92
									TG		1.68 ± 0.42	1.96 ± 1.38		1.56 ± 0.49	1.65 ± 1.4
Al-Nuaim[48]	Saudi-Arabia	CS			864	875	584	601	TC		4.35 ± 1.5	4.2 ± 1.4		4.4 ± 1.5	4.4 ± 1.6
									HDL		1.2 ± 0.5	1.3 ± 0.6		1.3 ± 0.8	1.4 ± 0.8
									LDL		3.3 ± 1.3	3.1 ± 1.5		3.0 ± 1.5	2.5 ± 1.0
Cai[49]	China	CS							TC		5.14 ± 1.04	5.00 ± 0.98		4.96 ± 0.99	5.09 ± 1.09
									HDL		1.60 ± 0.48	1.37 ± 0.40		1.57 ± 0.41	1.37 ± 0.48
									LDL		3.32 ± 1.00	3.23 ± 0.95		3.14 ± 0.96	3.37 ± 1.11
									TG		1.35 ± 1.09	1.69 ± 1.51		1.32 ± 1.29	1.89 ± 2.37
Campos[50]	Costa Rica	CS			86	99	88	103	TC		4.89 ± 0.85	4.73 ± 0.80		4.63 ± 1.09	4.47 ± 0.88
									HDL		1.19 ± 0.26	1.01 ± 0.23		1.16 ± 0.23	1.09 ± 0.23
									LDL		3.05 ± 0.75	2.87 ± 0.78		2.84 ± 0.88	2.72 ± 0.80
									TG		1.41 ± 0.70	1.82 ± 0.89		1.32 ± 0.64	1.50 ± 0.71

Table 1 - continued.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Das[51]	India	CS			102	122	89	135	TC		4.97 ± 0.60	5.12 ± 0.76		5.28 ± 0.60	5.14 ± 0.74
									HDL		1.15 ± 0.12	1.18 ± 0.12		1.17 ± 0.13	1.17 ± 0.15
									LDL		3.07 ± 0.59	3.19 ± 0.75		3.42 ± 0.61	3.26 ± 0.76
									TG		1.63 ± 0.26	1.64 ± 0.32		1.51 ± 0.25	1.55 ± 0.32
Delisle[33]	Benin	CS			100	100	85	85	HDL		1.37 ± 0.40	1.22 ± 0.20		1.62 ± 0.37	1.29 ± 0.92
Du[52]	China	CS	2879	918					TC	4.34 (3.04-5.15)			4.20 (2.76-5.05)		
									HDL	1.15 (0.95-1.36)			1.03 (0.83-1.26)		
									LDL	2.77 (2.33-3.32)			2.78 (2.26-3.32)		
									TG	1.85 (1.13-3.94)			2.05 (1.27-4.13)		
Gharbi[30]	Tunesia	CS			201	168	155	146	TC		4.75 ± 1.50	4.51 ± 1.27		4.27 ± 1.13	4.05 ± 1.30
									HDL		1.07 ± 0.39	0.90 ± 0.13		1.05 ± 0.44	0.80 ± 0.15
									TG		1.41 ± 1.12	1.50 ± 1.42		1.06 ± 0.67	1.34 ± 0.91
Glew[53]	Nigeria	CS			77	55	79	42	TC		4.40 ± 0.77	4.09 ± 0.75		3.62 ± 0.80	3.62 ± 0.77
									HDL		1.29 ± 0.29	1.16 ± 0.27		1.06 ± 0.30	0.96 ± 0.34
									LDL		2.40 ± 0.70	2.17 ± 0.65		1.94 ± 0.71	1.91 ± 0.65
									TG		1.52 ± 0.74	1.67 ± 1.00		1.22 ± 0.74	1.65 ± 1.02
Gregory[54]	Guata-mala	CS			155	119	372	241	TC		4.26 ± 0.85	4.35 ± 0.91		4.21 ± 0.79	4.00 ± 0.83
									HDL		1.04 ± 0.26	0.86 ± 0.23		1.00 ± 0.28	0.88 ± 0.24
									LDL		2.42 ± 0.71	2.58 ± 0.82		2.33 ± 0.65	2.24 ± 0.69
									TG		1.82 ± 1.01	2.06 ± 1.15		1.91 ± 0.91	1.93 ± 1.00

Table 1 - continued.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Gu[55]	China	CS			4163	3730	3851	3796	TC		5.08 ± 1.23	5.00 ± 1.22		4.81 ± 1.24	4.72 ± 1.29
									HDL		1.36 ± 0.62	1.21 ± 0.61		1.36 ± 0.62	1.35 ± 0.65
									LDL		3.05 ± 1.23	3.03 ± 1.22		2.82 ± 1.24	2.75 ± 1.29
									TG		1.50 ± 1.23	1.75 ± 1.83		1.42 ± 1.24	1.38 ± 1.29
Gupta[56]	India	CS				199		202	TC			4.55 ± 1.11			4.27 ± 0.96
									HDL			1.11 ± 0.31			1.14 ± 0.31
									LDL			2.78 ± 1.01			2.50 ± 0.85
									TG			1.42 ± 0.62			1.38 ± 0.52
He[57]*	China	CS			4163	3730	3851	3796	TC		5.08	4.99		4.8	4.71
									HDL		1.35	1.21		1.36	1.34
									LDL		3.06	3.02		2.81	2.75
									TG		1.50	1.75		1.42	1.38
Htet[58]	Myan-mar	CS			379	376	362	369	TC		5.4 ± 0.95	5.5 ± 0.97		5.4 ± 1.75	5.0 ± 1.73
									HDL		1.1 ± 0.19	1.2 ± 0.19		1.3 ± 0.19	1.3 ± 0.38
									TG		1.6 ± 0.76	1.9 ± 1.36		1.4 ± 1.75	1.5 ± 1.34
Huang[59]	China	CS			2361	2552	2341	1631	TC		4.85 ± 1.00	4.73 ± 0.90		4.17 ± 0.92	4.25 ± 0.91
									HDL		1.46 ± 0.36	1.33 ± 0.32		1.37 ± 0.32	1.33 ± 0.33
Joshi[60]	India	CS	590	1452					TC	4.32 ± 1.11			3.98 ± 0.98		
									HDL	1.01 ± 0.31			1.01 ± 0.31		
									LDL	2.51 ± 0.85			2.3 ± 0.83		

Table 1 - continued.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Kodaman[61]	Ghana	CS			1293	972	583	469	TC		4.70 ± 1.09	4.41 ± 1.1		3.94 ± 0.95	3.68 ± 0.94
									HDL		1.27 ± 0.38	1.12 ± 0.34		1.20 ± 0.41	1.15 ± 0.38
									LDL		2.95 ± 0.97	2.75 ± 0.88		2.29 ± 0.84	1.98 ± 0.71
									TG		0.94 ± 0.64	0.87 ± 0.53		0.93 ± 0.59	0.93 ± 0.60
Lim[28]	South Korea	LT			2497	2523	2784	2240	TC		5.19 ± 0.97	5.33 ± 0.92		5.12 ± 0.93	4.86 ± 0.93
									HDL		1.34 ± 0.31	1.21 ± 0.27		1.30 ± 0.31	1.27 ± 0.33
									LDL		3.21 ± 0.89	3.37 ± 0.93		3.14 ± 0.88	2.86 ± 0.99
									TG		1.47 ± 0.93	1.92 ± 1.27		1.89 ± 1.40	1.63 ± 1.07
Mbaliaki[62]	Tanzania	CS			225	259	256	245	TC		4.5 ± 1.0	4.5 ± 1.1		3.8 ± 1.1	3.6 ± 1.0
									HDL		1.2 ± 0.3	1.1 ± 0.3		1.0 ± 0.4	0.9 ± 0.3
									LDL		2.7 ± 0.9	2.7 ± 1.0		2.1 ± 0.9	2.0 ± 0.8
									TG		1.4 ± 1.0	1.8 ± 1.2		1.4 ± 0.6	1.5 ± 0.8
Miranda[32‡]	Peru	CS	199	201					TC	5.04 ± 1.03			4.03 ± 0.86		
									HDL	1.15 ± 0.28			1.14 ± 0.34		
									LDL	3.10 ± 0.88			2.21 ± 0.70		
									TG	1.52 ± 1.23			1.28 ± 0.80		
Mohan[63]	India	CS			2229		2616		TC		4.90 ± 1.00			4.31 ± 0.79	

Table 1 - continued.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Mollentze[64]	Orange Free State	CS			468	290	574	279	TC		5.09 ± 1.15	4.99 ± 1.19		4.85 ± 1.12	4.72 ± 1.30
									HDL		1.36 ± 0.45	1.38 ± 0.51		1.20 ± 0.34	1.24 ± 0.49
									LDL		3.16 ± 1.06	2.94 ± 1.16		3.15 ± 1.11	2.80 ± 1.01
									TG		1.21 ± 0.93	1.52 ± 1.29		1.24 ± 0.66	1.48 ± 1.03
Ntandou[65]	Benin	CS			100	100	85	85	TG		0.75 ± 0.3	0.89 ± 0.4		0.72 ± 0.3	0.81 ± 0.4
Obirikoran[66]	Ghana	CS	312	360					TC	5.00 (4.65-5.50)			4.80 (4.55-5.20)		
									HDL	1.00 (0.80-1.20)			1.00 (0.80-1.20)		
									LDL	3.40 (3.05-3.80)			3.10 (2.70-3.60)		
									TG	1.20 (0.80-1.40)			1.35 (1.10-1.70)		
Oommen[67]	India	CS			1341	1058	2132	1667	TC		4.70 ± 1.08	4.91 ± 1.05		4.52 ± 1.10	4.53 ± 1.18
									HDL		0.87 ± 0.28	0.79 ± 0.34		1.03 ± 0.30	0.96 ± 0.31
									TG		1.40 ± 0.89	1.73 ± 1.20		1.27 ± 0.81	1.55 ± 1.28
Pandey[86]	India	CS			2008		2616		TC		4.67 ± 0.81			4.31 ± 0.93	
Patel[68]	Thailand	CS			2002	1130	1210	963	TC		5.71 ± 3.58	5.54 ± 3.70		5.18 ± 2.43	4.80 ± 2.48
									HDL		1.34 ± 0.89	1.19 ± 0.67		1.13 ± 0.67	1.06 ± 0.62
									LDL		3.71 ± 3.13	3.61 ± 3.70		3.28 ± 2.78	2.86 ± 2.48
									TG		1.51 ± 3.13	1.88 ± 2.17		1.73 ± 2.78	2.15 ± 2.02

Table 1 - continued.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Pongchaiyakul[69]	Thailand	CS			290	305	187	134	TC		5.28 ± 1.04	5.35 ± 1.10		4.98 ± 1.38	4.38 ± 1.08
									HDL		1.53 ± 0.34	1.36 ± 0.29		1.31 ± 0.29	1.32 ± 0.30
									LDL		3.16 ± 0.94	3.1 ± 1.00		2.85 ± 1.15	2.24 ± 0.88
									TG		1.26 ± 0.88	1.94 ± 1.24		1.80 ± 1.20	1.79 ± 0.96
Prabhakaran[70†]	India	LT	9504						TC		4.98 ± 0.97	4.96 ± 1.14		4.35 ± 1.01	4.93 ±1.09
Reddy[71]	India	CS				190		190	TC			4.62 ± 1.17			3.85 ± 0.92
									HDL			1.15 ± 0.31			1.13 ± 0.38
									LDL			2.67 ± 1.04			2.09 ± 0.77
									TG			1.70 ± 0.64			1.43 ± 0.49
Richter	South-Africa	CS			591	393	633	333	TC		5.02 (4.18-.09)	4.68 (3.84-5.71)		4.85 (4.11-5.95)	4.50 (3.81-5.53)
									HDL		1.36 (1.03-1.78)	1.50 (1.12-2.04)		1.39 (1.09-1.84)	1.45 (1.02-1.94)
									LDL		3.35 (2.55-4.12)	2.86 (2.17-3.73)		3.15 (2.50-4.09)	2.85 (2.9-3.62)
									TG		1.18 (0.87-1.78)	1.00 (0.78-1.46)		1.09 (0.81-1.49)	0.97 (0.76-1.35)
Russell-Jones[73]	Fijian Melanesian	CS			71	35	109	87	TC		5.2 ± 1.3	5.6 ± 1.6		4.0 ± 1.0	3.81 ± 1.0
Sarrafzade[74]	Iran	CS	4572	1751					TC		5.64 ± 1.35	5.33 ± 1.34		5.74 ± 1.38	5.46 ± 1.29
									HDL		1.24 ± 0.27	1.16 ± 0.26		1.27 ± 0.27	1.19 ± 0.25
									LDL		3.41 ± 1.10	3.13 ± 1.11		3.52 ± 1.14	3.34 ± 1.07
									TG		2.15 ± 1.14	2.25 ± 1.23		2.05 ± 1.09	2.04 ± 1.16

Table 1 - continued.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Seck[75]	Senegal	CS	557	469					TC	6.75 ± 0.52			5.38 ± 0.26		
Silambuselvi[76]	India	CS							TC		5.44			5.11	
									HDL		1.16			1.39	
									LDL		3.56			3.42	
									TG		1.84			1.80	
Singh[77]	India	CS			139	172	115	140	HDL		1.27 ± 0.24	1.25 ± 0.20		1.22 ± 0.15	1.18 ± 0.12
Snehalatha[78]	India	CS	1521	2145					TC	4.47 ± 0.94			3.93 ± 0.93		
									HDL	1.17 ± 0.26			1.09 ± 0.24		
									TG	1.39 ± 0.85			1.33 ± 0.89		
Song[29]	China	CS	19841	20029					TC		4.05 ± 6.24	4.66 ± 4.23		3.79 ± 5.21	4.54 ± 5.66
Tatsukawa[79]	Japan	CS			703	375	1688	676	TC		5.37 ± 0.92	5.03 ± 0.77		5.52 ± 1.00	5.33 ± 0.90
									HDL		1.52 ± 0.35	1.43 ± 0.34		1.67 ± 0.37	1.46 ± 0.37
									LDL		3.22 ± 0.84	2.92 ± 0.72		3.37 ± 0.89	3.22 ± 0.81
									TG		1.38 ± 0.75	1.49 ± 0.82		1.07 ± 0.61	1.41 ± 0.79
Tazi[80]	Morocco	CS	755	1047					TC	4.89 ± 1.16			4.42 ± 1.06		
Vrdoljak[81]	Croatia	CS	1824	642					TC	5.90			5.72		
									HDL	1.57			1.60		
									LDL	3.53			3.52		
									TG	1.80			1.94		

Table 1 - continued.

Study	Country	Study design	Number of participants						Blood lipid	Mean ± SD mmol/L per blood lipid					
			Urban			Rural				Urban			Rural		
			♀♂	♀	♂	♀♂	♀	♂		♀♂	♀	♂	♀♂	♀	♂
Wang[31]	China	CS			547	763	862	676	TC		4.32 ± 0.90	4.64 ± 0.98		4.10 ± 0.89	4.03 ± 0.94
											1.20 ± 0.30	1.05 ± 0.28		1.18 ± 0.31	1.09 ± 0.32
											2.52 ± 0.75	2.58 ± 0.95		2.43 ± 0.70	2.38 ± 0.78
											1.31 ± 1.00	2.28 ± 2.35		1.07 ± 0.73	1.24 ± 1.27
Weng[82]∂	China	CS			80	81	191	177	TC		4.45 ± 0.72	4.22 ± 0.72		3.39 ± 1.11	3.39 ± 1.73
									HDL		1.42 ± 0.54	1.09 ± 0.18		1.20 ± 0.41	1.22 ± 0.40
									LDL		2.73 ± 0.89	2.73 ± 0.72		1.99 ± 0.83	1.98 ± 1.60
									TG		1.04 ± 0.80	1.52 ± 0.99		0.78 ± 0.41	0.65 ± 0.67
Woo[83]	China	CS	116	116					TC	5.16 ± 0.96			5.14 ± 1.02		
									HDL	1.49 ± 0.36			1.33 ± 0.40		
									LDL	3.16 ± 0.87			3.21 ± 0.94		
									TG	1.08 ± 0.67			1.30 ± 1.04		
Wyatt[84]	Papua New Guinea	CS			23	86	49	22	TC		3.96 ± 0.88	3.64 ± 0.86		3.78 ± 1.09	3.57 ± 1.29
									TG		0.61 ± 0.25	0.63 ± 0.19		0.60 ± 0.38	0.60 ± 0.18
Xu[85]	China	CS	1467	890					HDL	1.30 ± 0.30			1.32 ± 0.31		
									TG	1.58 ± 1.18			1.49 ± 1.03		

Abbreviations: CS: cross-sectional. NR: not reported. TC: total cholesterol. HDL: high density lipoprotein. LDL: low density lipoprotein. TG: triglycerides. ♂: males. ♀: females ♀♂: males and females combined. SD: standard deviation. *Only SEM reported but no information on number of participants per group. †Longitudinal study. total number of participants of first and second wave reported. Urban levels of first wave are provided in the urban male cell. urban levels of second wave are depicted in the urban female cell. Accordingly the rural levels of the first and second wave are provided in the cells for rural males and females respectively. ‡Migration study. Only data on urban and rural levels are provided in this table[47]. *Migration study. Rural represents data of 'Yi farmers'. ∂: Urban represents 'Yi migrants'.

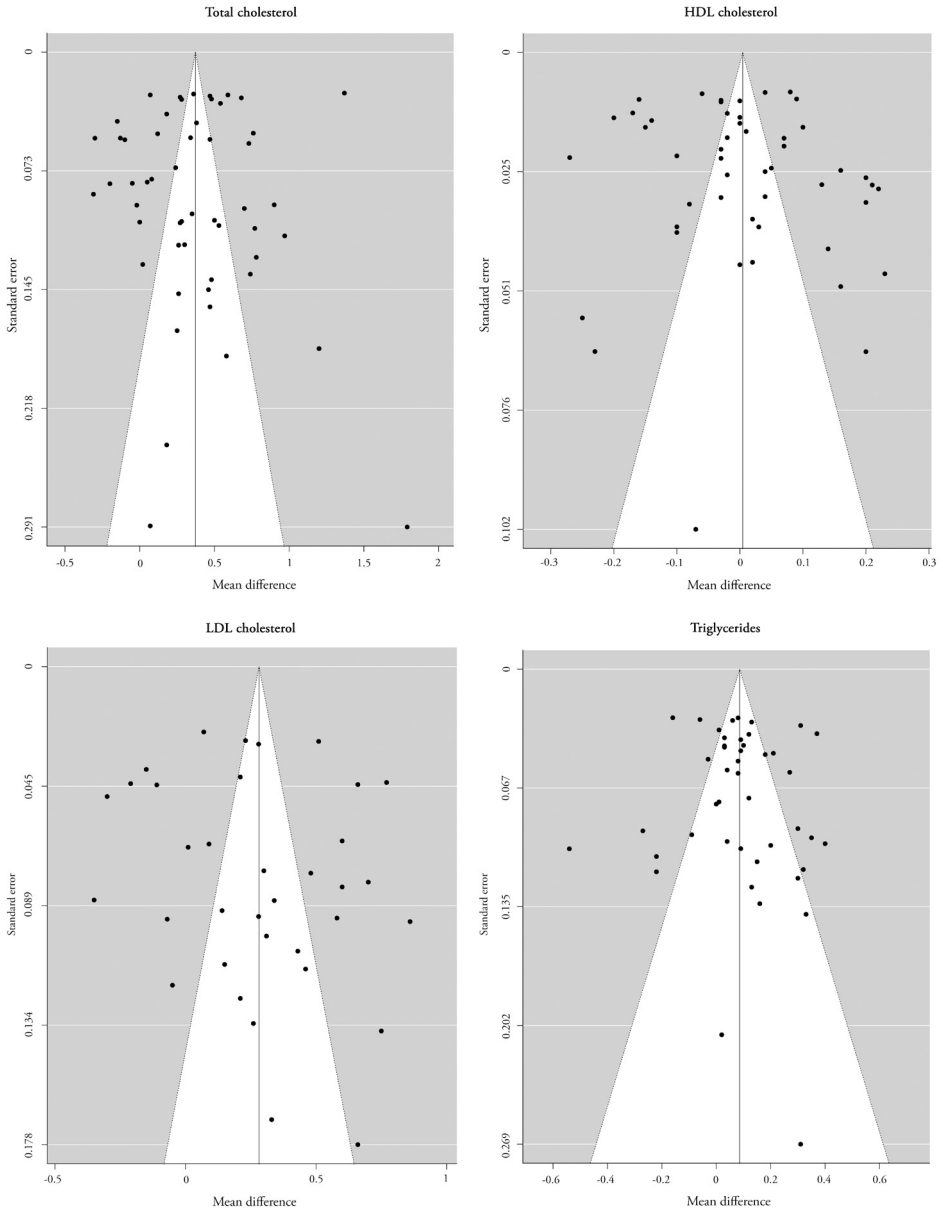

Figure 2: Funnel plots.

HDL: high density lipoprotein, LDL: low density lipoprotein.

range: 2001-2015). With the exception of one study published in French [30], all studies were published in English. Seven studies provided a reference for their operationalisation of urban and rural areas, most often citing a national statistics bureau (see Appendix C). The majority of the studies (30) only stated which cities and villages were considered to be urban and rural, the remainder

of the studies (10) reported no information on their definitions. Thirty-three studies reported blood lipid levels for men and women separately, 12 studies for men and women combined, three exclusively for women and two for men. Of the 47 studies that investigated urban- rural environment differences, two investigated differences between people who lived in rural areas and those who migrated to an urban area [31,32].The remaining studies included in this review focused on accessibility of markets/parks (1), community-based interventions (1) and walkability (1).

Quality assessment

The overall rating of 12 studies (24%) was weak, 37 moderate (74%) and one strong (2%)[33]. A summary of the quality assessment scores of the studies included is shown in Figure 3. The domain reporting was rated as weak in 22 studies (44%). The selection bias domain was assessed as strong in 7 studies (14%), as moderate in 26 studies (52%) and weak in 17 studies (34%). The ratings per domain per study are provided in Appendix D.

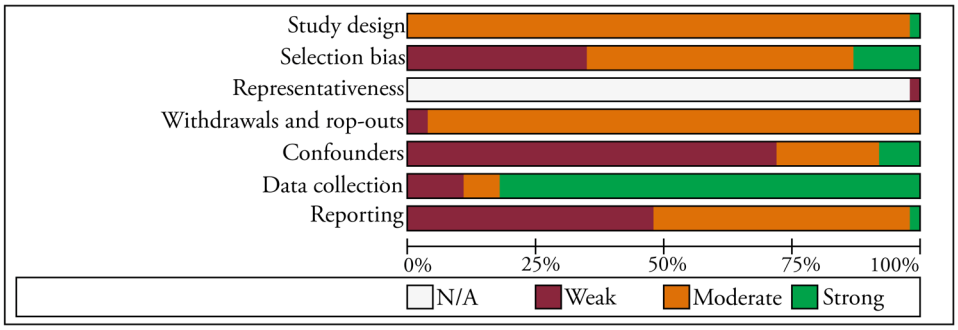

Figure 3: Quality assessment overview.

Environmental characteristics

Urban – rural

Total cholesterol

Forty studies provided information on total cholesterol levels, of which 30 were rated as being moderate in quality and ten as weak. The majority of the studies of moderate quality reported total cholesterol levels in urban areas to be significantly higher compared to rural areas. Of the studies that reported results for men and women combined (10), 63% found significantly higher total cholesterol levels in urban areas. Of the studies that were stratified by sex (25), in general, higher total cholesterol values were reported for women (65%) and men (81%) who lived in urban areas as compared to rural areas. More heterogeneous results were found for the studies classified as weak. The percentage of these studies that reported higher levels of total cholesterol in urban areas ranged from 33%-50%. Of the 32 studies that were eligible

for meta-analysis, 25 were rated as moderate and seven as weak. The meta-analysis of the studies of moderate quality showed significantly higher total cholesterol levels in urban areas as compared to rural areas (mean difference 0.37, 95%CI 0.27 – 0.48). Although the confidence interval of point estimates of the studies classified as weak was wider than the confidence interval of the moderate studies, the point estimate was still significantly higher for those residing in urban areas (mean difference 0.37 mmol/L, 0.04 – 0.69; see Figure 4).

HDL cholesterol

HDL cholesterol levels were reported in 36 studies. One such study was rated as strong 33, 27 as moderate and eight as weak. No clear pattern could be found in the results of the studies of moderate quality. The studies rated as of moderate and strong quality showed higher levels of HDL cholesterol in urban areas for women (47%), whereas for men, more studies reported higher HDL cholesterol levels in rural areas (41%). Most studies rated as weak (5 out of 8) found no statistically significant difference. The meta-analysis included 28 studies in total of which one was rated as strong, 22 as moderate and five as weak. No differences in HDL cholesterol levels according to urban-rural were observed (0.00 mmol/L, -0.03 – 0.04) (Figure 5).

LDL cholesterol

Information on LDL cholesterol levels was provided in 28 studies. Of these, 21 studies were rated as moderate and the remaining seven as weak. In about 60% of the studies of moderate quality, significantly higher LDL cholesterol was reported in urban areas. The number of studies that were classified as weak was low (7) and comparisons made in those studies generally showed no statistically significant difference between urban and rural areas. Twenty studies were eligible for meta-analysis, of which 16 were rated as moderate and four as weak. The mean difference in the studies of moderate quality was 0.29 mmol/L (0.17 – 0.41), see Figure 6, with higher levels in urban areas. Figure 4 shows that the patterns of the point estimates are similar across studies that reported on men and women separately or combined. The studies included that were rated as weak showed a mean difference between urban and rural areas of 0.25 mmol/L (0.01 – 0.48).

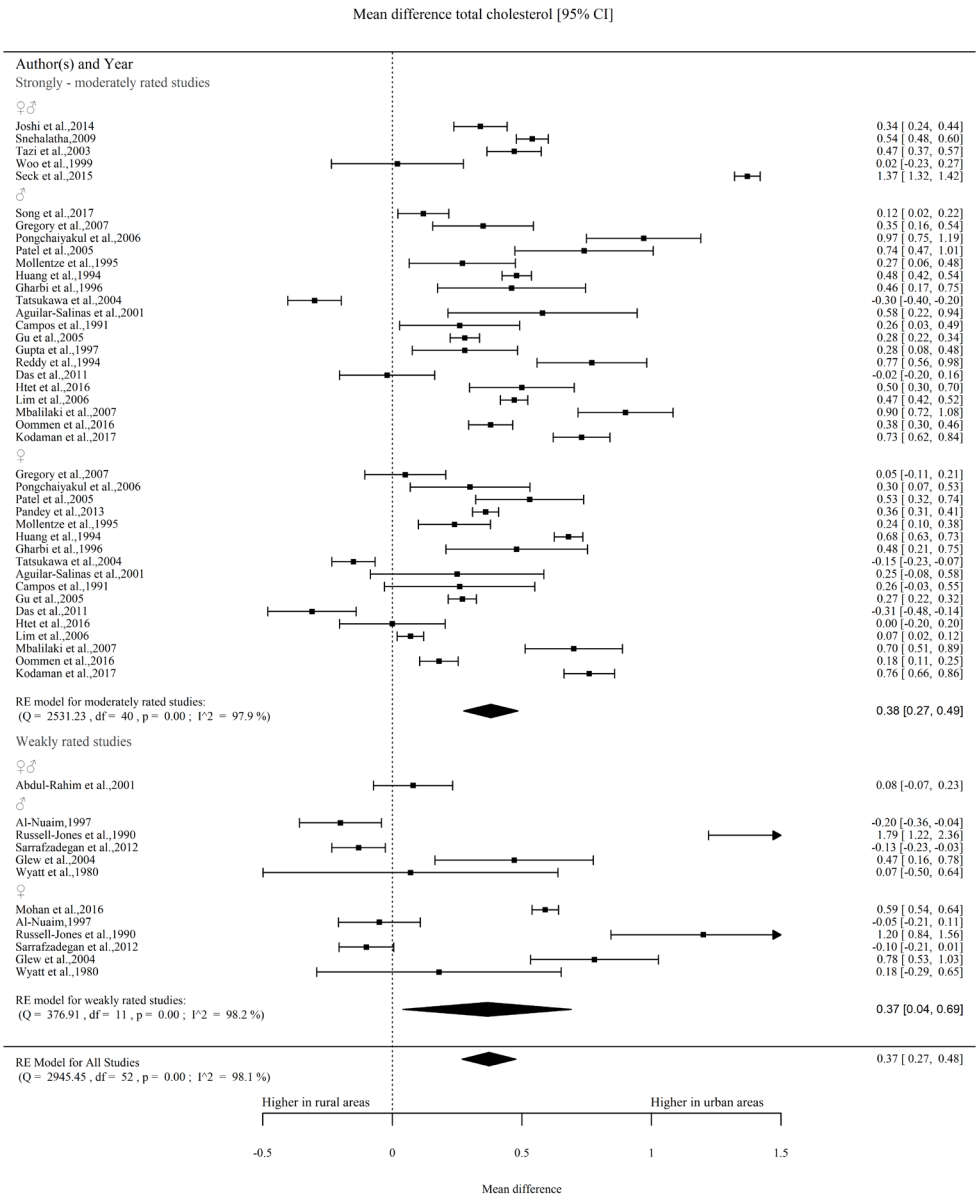

Figure 4: Forest plot total cholesterol.

Triglycerides

Of the 33 studies that reported triglyceride levels, 26 were rated as moderate and seven as weak. Mixed results were found for studies that were rated as moderate and reported separately for women. In 30% of the comparisons (6), higher levels of triglycerides were found in urban areas; however,

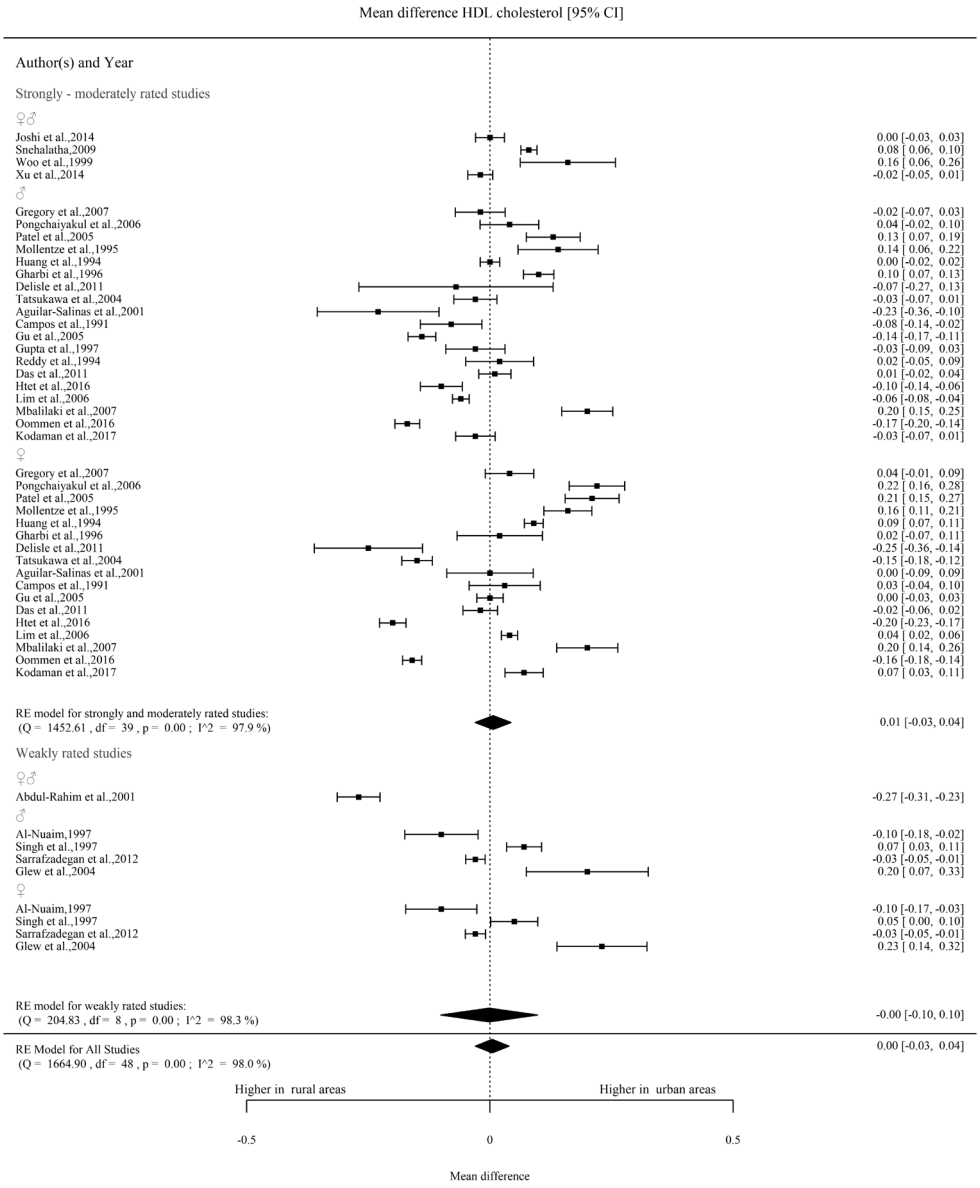

Figure 5: Forest plot HDL cholesterol.

HDL: high density lipoprotein

38% reported no differences. Comparisons made by studies that reported triglycerides of men found 48% higher levels in urban areas. More than half of the comparisons (6 or 55%) of the studies of weak quality reported higher levels in urban areas. Three out of four studies that made separate comparisons for men did not show statistically significant differences

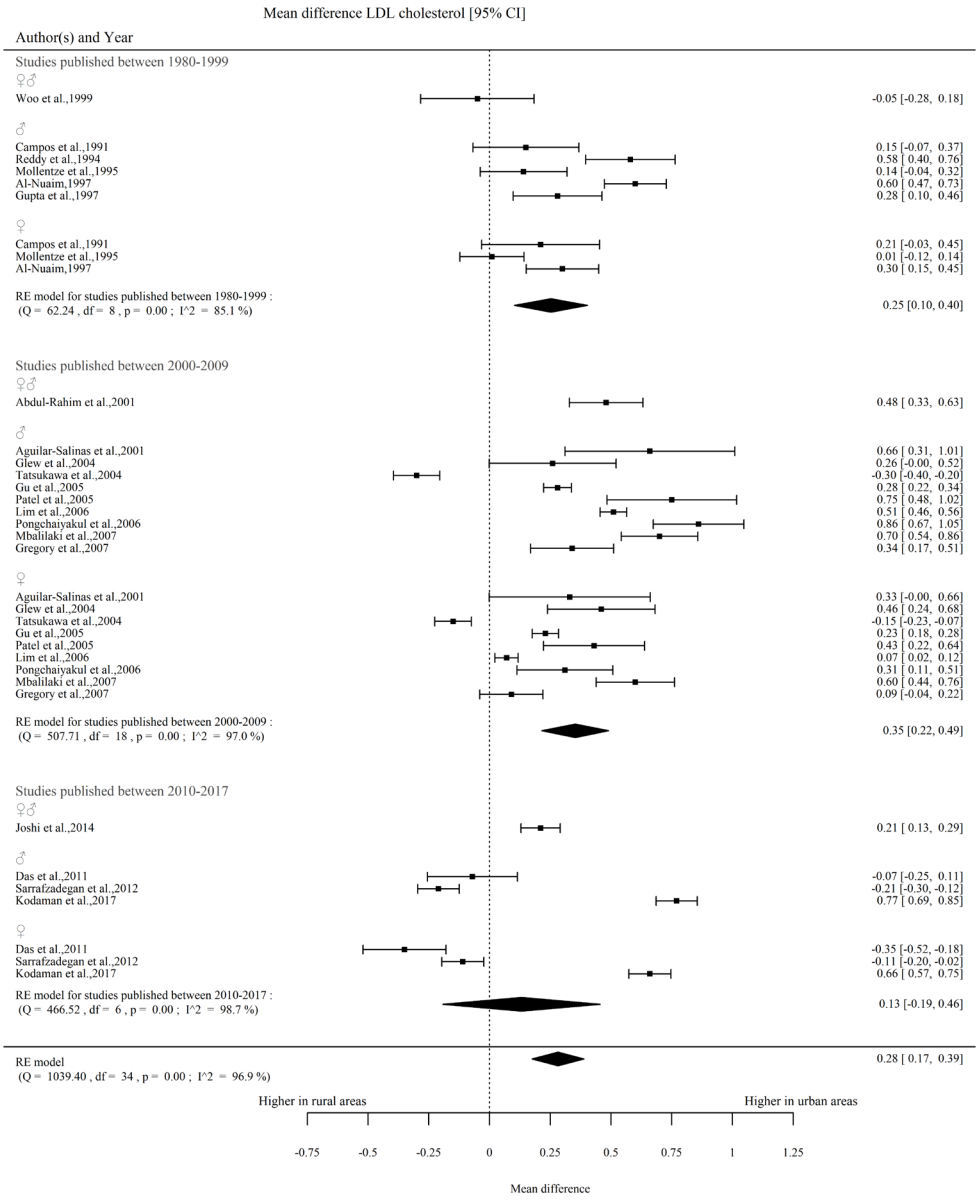

Figure 6: Forest plot LDL cholesterol.

LDL: low density lipoprotein

between urban and rural areas. The meta-analysis included 25 studies, of which 21 were rated as moderate and four as weak. The forest plot of the moderately rated studies shows significantly higher triglyceride levels in urban areas as compared to rural areas (mean difference 0.08 mmol/L, 0.02 –0.14, Figure 7). The studies that were rated as weak showed higher

triglyceride levels in urban areas (mean difference 0.13 mmol/L, 0.04 –0.21).

Sensitivity analyses with time periods

Studies performed in different time periods were quite consistent, apart from some small non-significant differences (Appendix E1 – E4).

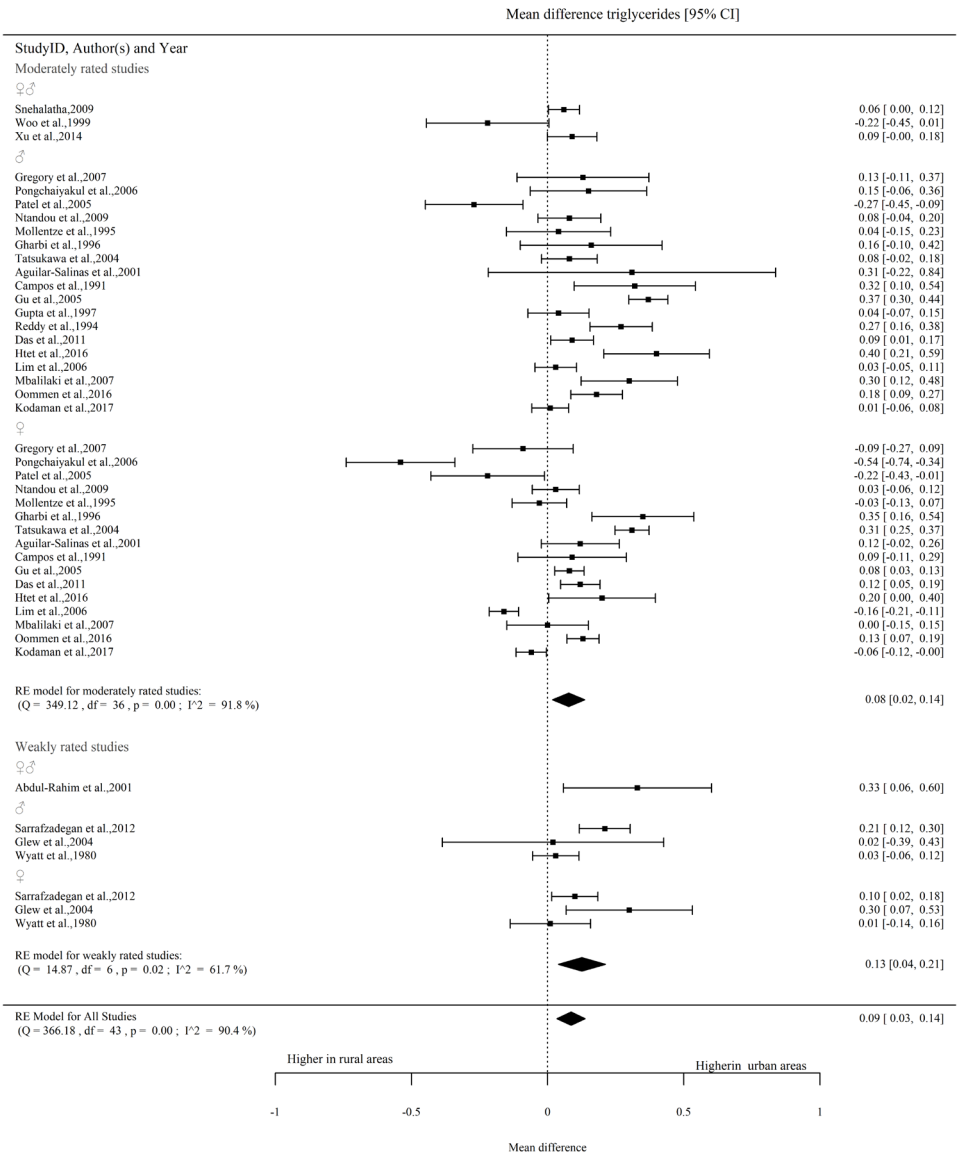

Figure 7: Forest plot triglyderides.

Migration studies

Two studies focused on migration to urban areas [31,32]. In their investigation, Miranda et al. (2011) categorised three groups; urban residents, rural residents, and those who migrated to urban areas at least five years ago. They found that total and LDL cholesterol, and triglyceride levels were similar in urban and migrant residents, but both were significantly higher than rural areas. The HDL cholesterol levels were approximately 1.44 mmol/L across all resident groups. In the other migration study, similar patterns were reported, with the exception of HDL cholesterol levels in men, which were significantly lower in urban residents [32].

Miscellaneous

We identified three studies investigating accessibility to parks, the impact of community-based interventions and walkability, and blood lipid levels. The study investigating accessibility of parks and markets reported a positive association between distance to markets and HDL cholesterol [74].

The community-based obesity and chronic disease prevention intervention study initiated various interventions on the physical, economic, social and political environments depending on the needs of the community. Slight improvement in blood lipid levels were reported after a three-year follow-up [75]. Increased walkability scores were unexpectedly found to be associated with increased triglyceride levels in the Multi-Ethnic Study of Atherosclerosis [76].

Discussion

The studies on built-environment characteristics and blood lipid levels that are available to date focus predominantly on urban-rural differences. The current review reveals that LDL and total cholesterol and triglyceride levels are consistently less favourable in urban areas as compared to rural areas. No overall differences in HDL-cholesterol were found between urban and rural areas. In the studies meta-analysed here, the pooled mean urban-rural differences in LDL, total cholesterol and triglyceride levels were 0.28 (0.17 – 0.39), 0.37 (0.27 – 0.47) and 0.09 (0.03 – 0.14) mmol/L. Guidelines from the National Cholesterol Education Program (NCEP) classify LDL cholesterol levels of <2.59 mmol/L as optimal, the range of LDL cholesterol levels of the included studies in the meta-analysis ranged from 1.06 to 3.93 mmol/L [77].Total cholesterol levels below 5.18 mmol/L are considered desirable and triglyceride levels below 1.69 mmol/L are classified as normal by the NCEP guidelines. The range of total cholesterol and triglyceride levels of studies included in the meta-analysis ranged from 3.57 to 6.75 mmol/L and from 0.60 to 2.15 mmol/L respectively. On an individual level,–the pooled mean differences may be considered small, but at a population level, and from a public health

policy perspective, this can be regarded as relevant [78]. Although quantification in terms of the population attributable risk is difficult to estimate for our study population, a previous meta-analysis investigating the effect of statin use to reduce blood lipid levels identified a decrease of 1.00 mmol/L in LDL cholesterol to reduce the risk of ischemic heart disease events by 11% [79]. In addition, Rodger et al., state that although associations of total cholesterol levels and risk of cardiovascular diseases attenuate with age, they remain strong and positive in the oldest age groups; 1 mmol/L lower cholesterol is associated with 15-20% lower stroke risk and 20-25% lower ischemic heart disease[80]. Anyway, differences in urban and rural areas are likely to become even more relevant as it is projected that 70% of the world's population will reside in urban areas by 2050 [26,27].

Potential explanations for the urban-rural differences in blood lipids include differences in socio-economic status, diet, as well as occupational activities [10,26,81,82]. To date, most of the studies on this topic have been carried out in LMIC, in which there is a stark contrast between the socio-economic position of various inhabitants. In LMIC, living in certain urban areas –often referred to as slums— poses grave health risks due to the poor living conditions in such neighbourhoods and may negatively impact individuals' lifestyles [83]. In addition, urban areas, in general are characterised by a relatively high availability of (fast-)food outlets and are conducive to the adoption of more western diets, rich in salt, sugar and saturated fat, potentially contributing to the unfavourable blood lipids observed [10,82,84]. Another possible explanation is that in urban areas, occupations often involve office work that generally requires less physical activity as compared to labour in rural, agricultural settings [85]. Some of the studies included selected very remote places as research contexts, where traditional dietary habits and frequent occupation-related physical activity (due to agriculture) are more prevalent. This may have introduced some selection bias that increased the contrast between urban and rural areas. Also, less heterogeneity might exist between urban and rural areas in non-LMIC at the level of occupation-related physical activity, food availability and dietary habits, and social-economic status in comparison with LMIC. However, only few studies from high-income countries were included in this review.

This systematic literature review and meta-analysis provides strong evidence of an association between the built environment and lipid levels on the basis of a meta-analysis of 36 studies and 133.966 subjects. The findings contribute to our understanding of the relationship between urban versus rural areas, as a characteristic of the built environment, and blood lipid levels. Our study also has certain limitations: the majority of the studies included were cross-

sectional, preventing us from drawing causal inferences. The available studies to date, in general, do not allow for adjustment for potential confounding variables such as age, sex and socio-economic position. Reliance on the quality, as well as the reporting, of the original studies is, however, an inherent aspect of any systematic review. The large heterogeneity of settings and variation in quality of included studies made pooling of the results and synthesis challenging. However, reporting separately for studies rated as of weak and moderate/high quality provides at least some quantitative assessment of the overall association. Moreover, the findings were quite consistent, even across different time periods. The distribution curve for population blood lipid levels likely changed in the timespan that the included studies were published in (1980-2017). However, as we investigate associations of urban versus rural areas with these blood lipid levels, changes in population levels over time may not have a large impact. Another potential limitation is that there is no generally accepted definition of urban and rural. The majority of the included studies merely provided names of places and abstained from providing any definition of concepts or explaining why certain places were considered to be either rural or urban. Even when studies referred to census data, these data were not comparable between studies. It is, therefore, unclear as to whether relative rurality in a certain country is linearly associated with blood lipid levels or if there is a more absolute threshold level.

This comprehensive review shows a consistent association between LDL and total cholesterol and triglyceride levels and urban areas. The current focus of research on built-environment characteristics and blood lipids is largely on urban and rural differences, especially in LMIC. The lack of evidence on the association between urbanisation and blood lipid levels in more high-income countries needs to be addressed. Further study of the way in which urbanisation affects blood lipid levels is warranted in order to better inform and guide policy makers and urban planners to help diminish unfavourable blood lipid levels and, in doing so, combat associated non-communicable disease.

Conflict of interest:
The authors have no conflicts of interest to declare

Contributions
RdG, KvdH, WLAMdK, JB and JL conceived and designed the study. RdG, LJS and JL developed the search strategy. RdG and JL screened and performed the assessment of bias. RdG extracted the data. RdG, KvdH, WLAMdK, JB and JL interpreted the data. All authors gave final approval of the version to be published and have contributed to the manuscript. RdG is the guarantor.

Funding
This study was financially supported by a Product and Process Development Grant (PPOC-14-028) from Sanquin Blood Supply Foundation and by the VU University Medical Center. Competing interests None declared.

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Supplementary files

Appendix A - Search strategy

Search strategy in PubMed October 9th, 2017 (read from bottom-up)

Set	Search terms	Result
#3	#1 AND #2	2,862
#2	"Environment Design"[Mesh] OR "City Planning"[Mesh] OR "Spatial Analysis"[Mesh] OR "Geographic Information Systems"[Mesh] OR "Noise"[Mesh] OR "Parks, Recreational"[Mesh] OR "Crowding"[Mesh] OR green space*[tiab] OR greenspace*[tiab] OR green environment*[tiab] OR green infrastructure*[tiab] OR natural space*[tiab] OR natural environment*[tiab] OR natural infrastructure*[tiab] OR environment design[tiab] OR environmental influence*[tiab] OR environmental determinant*[tiab] OR environmental support*[tiab] OR environmental approach*[tiab] OR environmental variable*[tiab] OR environmental attribute*[tiab] OR environmental barrier*[tiab] OR environmental characteristic*[tiab] OR environmental correlat*[tiab] OR environment design*[tiab] OR city planning*[tiab] OR urban design[tiab] OR urban planning*[tiab] OR urban form[tiab] OR town planning*[tiab] OR neighbourhood*[tiab] OR neighborhood*[tiab] OR geospatial[tiab] OR local environment*[tiab] OR rural environment*[tiab] OR urban environment*[tiab] OR objective environment*[tiab] OR perceived environment*[tiab] OR measured environment*[tiab] OR obesogenic environment*[tiab] OR built environment*[tiab] OR physical environment*[tiab] OR geoepidemiology[tiab] OR spatial analysis[tiab] OR land use[tiab] OR spatial access[tiab] OR residential environment*[tiab] OR urban-rural epidemiology[tiab] OR geographic cluster*[tiab] OR residential factor*[tiab] OR residence characteristic*[tiab] OR geographic information system*[tiab] OR geographical information system*[tiab] OR sprawl[tiab] OR zoning[tiab] OR residential location*[tiab] OR residential proximit*[tiab] OR population densit*[tiab] OR food outlet*[tiab] OR grocery store*[tiab] OR fast food density[tiab] OR fast food restaurant*[tiab] OR retail densit*[tiab] OR walkability[tiab] OR cyclability[tiab] OR sidewalk*[tiab] OR pedestrian[tiab] OR cycle path*[tiab] OR cycling lane*[tiab] OR recreational facilit*[tiab] OR recreation facility*[tiab] OR worksite*[tiab] OR sports facilit*[tiab] OR food environment*[tiab] OR food suppl*[tiab] OR public open space*[tiab] OR crowding[tiab] OR park access[tiab] OR urban park*[tiab] OR noise pollution[tiab] OR contextual research[tiab] OR ecological stud*[tiab] OR ecological analys*[tiab] OR remoteness[tiab] OR aesthetic*[tiab] OR active travel*[tiab] OR passive travel*[tiab] OR travel to work[tiab] OR transport to work[tiab] OR public transport*[tiab] OR transportation network*[tiab]	183,891
#1	"Cholesterol"[Mesh] OR "triglycerides"[MeSH Terms] OR "Lipids"[Mesh:NoExp] OR "Lipoproteins, HDL"[Mesh] OR "Lipoproteins, LDL"[Mesh] OR "Hypertriglyceridemia"[Mesh] OR "Dyslipidemias"[Mesh] OR cholesterol*[tiab] OR epicholesterol*[tiab] OR hdl[tiab] OR ldl[tiab] OR ldl1[tiab] OR ldl2[tiab] OR triglycerid*[tiab] OR lipid[tiab] OR lipids[tiab] OR hypertriglyceride*[tiab] OR triglyceride*[tiab] OR triacylglycerol*[tiab] OR lipoprotein*[tiab] OR dyslipidemi*[tiab] OR dyslipoprotein*[tiab] OR hyperlipemi*[tiab] OR hyperlipidemi*[tiab] OR lipidemi*[tiab] OR lipemi*[tiab] OR hypercholesterolemi*[tiab] OR hypercholesterolaemi*[tiab] OR hypercholesteremi*[tiab] OR hypercholesteraemi*[tiab] OR hyperlipoproteinemi*[tiab] OR hypoprebetalipoproteinemi*[tiab]	723,701

Search strategy in Embase.com October 9th, 2017 (read from bottom-up)

Set	Search terms	Result
#4	#3 NOT 'conference abstract'/it	4,972
#3	#1 AND #2	5,867
#2	'environmental planning'/exp OR 'city planning'/exp OR 'spatial analysis'/exp OR 'geographic information system'/exp OR 'noise pollution'/exp OR 'land use'/exp OR 'neighborhood'/exp OR 'recreational park'/exp OR 'crowding (area)'/exp OR 'green space*':ab,ti OR greenspace*:ab,ti OR 'green environment*':ab,ti OR 'green infrastructure*':ab,ti OR 'natural space*':ab,ti OR 'natural environment*':ab,ti OR 'natural infrastructure*':ab,ti OR 'environment* design*':ab,ti OR 'environment* influence*':ab,ti OR 'environment* determinant*':ab,ti OR 'environment* support*':ab,ti OR 'environment* approach*':ab,ti OR 'environment* variable*':ab,ti OR 'environment* attribute*':ab,ti OR 'environment* barrier*':ab,ti OR 'environment* characteristic*':ab,ti OR 'environment* correlat*':ab,ti OR 'city planning*':ab,ti OR 'urban design*':ab,ti OR 'urban form*':ab,ti OR 'urban planning*':ab,ti OR 'town planning*':ab,ti OR neighbourhood*:ab,ti OR neighborhood*:ab,ti OR geospatial:ab,ti OR 'local environment*':ab,ti OR 'rural environment*':ab,ti OR 'urban environment*':ab,ti OR 'objective environment*':ab,ti OR 'perceived environment*':ab,ti OR 'measured environment*':ab,ti OR 'obesogenic environment*':ab,ti OR 'built environment*':ab,ti OR 'physical environment*':ab,ti OR geoepidemiology:ab,ti OR 'spatial analysis':ab,ti OR 'land use':ab,ti OR 'spatial access':ab,ti OR 'residential environment*':ab,ti OR 'urban rural epidemiology':ab,ti OR 'geographic cluster*':ab,ti OR 'residential factor*':ab,ti OR 'residence characteristic*':ab,ti OR 'geographic* information system*':ab,ti OR sprawl:ab,ti OR zoning:ab,ti OR 'residential location*':ab,ti OR 'resident* proximit*':ab,ti OR 'population densit*':ab,ti OR 'food outlet*':ab,ti OR 'grocery store*':ab,ti OR 'fast food densit*':ab,ti OR 'fast food restaurant*':ab,ti OR 'retail densit*':ab,ti OR walkability:ab,ti OR cyclability:ab,ti OR sidewalk*:ab,ti OR pedestrian:ab,ti OR 'cycle path*':ab,ti OR cyclepath*:ab,ti OR 'recreation* facilit*':ab,ti OR worksite*:ab,ti OR 'sport* facilit*':ab,ti OR 'food environment*':ab,ti OR 'food suppl*':ab,ti OR 'public open space*':ab,ti OR crowding:ab,ti OR 'park access':ab,ti OR 'urban park*':ab,ti OR 'noise pollution':ab,ti OR 'contextual research':ab,ti OR 'ecological stud*':ab,ti OR 'ecological analys*':ab,ti OR remoteness:ab,ti OR aesthetic*:ab,ti OR 'active travel*':ab,ti OR 'passive travel*':ab,ti OR 'travel to work':ab,ti OR 'transport to work':ab,ti OR 'public transport*':ab,ti OR 'transportation network*':ab,ti	289,726
#1	'cholesterol'/exp OR 'lipid'/de OR 'triacylglycerol'/exp OR 'high density lipoprotein'/exp OR 'low density lipoprotein'/exp OR 'hypertriglyceridemia'/exp OR 'dyslipidemia'/exp OR cholesterol*:ab,ti OR epicholesterol*:ab,ti OR hdl:ab,ti OR ldl:ab,ti OR ldl1:ab,ti OR ldl2:ab,ti OR triglycerid*:ab,ti OR lipid:ab,ti OR lipids:ab,ti OR hypertriglyceride*:ab,ti OR triglyceride*:ab,ti OR triacylglycerol*:ab,ti OR lipoprotein*:ab,ti OR dyslipidemi*:ab,ti OR dyslipoprotein*:ab,ti OR hyperlipemi*:ab,ti OR hyperlipidemi*:ab,ti OR lipidemi*:ab,ti OR lipemi*:ab,ti OR hypercholesterolemi*:ab,ti OR hypercholesterolaemi*:ab,ti OR hypercholesteremi*:ab,ti OR hypercholesteraemi*:ab,ti OR hyperlipoproteinemi*:ab,ti OR hypoprebetalipoproteinemi*:ab,ti	947,830

Search strategy in Web of Science Core Collection,October 9th, 2017 (read from bottom-up)

Set	Search terms	Result
#4	#2 AND #1 refined by: research areas: (acoustics or gastroenterology hepatology or allergy or anthropology or geriatrics gerontology or pathology or health care sciences services or pediatrics or hematology or physical geography or behavioral sciences or immunology or biomedical social sciences or life sciences biomedicine other topics or psychology or public environmental occupational health or cardiovascular system cardiology or sport sciences or endocrinology metabolism or transportation or nursing or nutrition dietetics or environmental sciences ecology or women s studies)Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years	1,768
#3	#1 AND #2	5,126
#2	TS=("environment design*" OR "city planning*" OR "spatial analysis" OR "geographic information system*" OR “noise” OR “crowding” OR “green space*” OR greenspace* OR "green environment*" OR "green infrastructure*" OR "natural space*" OR "natural environment*" OR "natural infrastructure*" OR "environmental influence*" OR "environmental determinant*" OR "environmental support*" OR "environmental approach*" OR "environmental variable*" OR "environmental attribute*" OR "environmental barrier*" OR "environmental characteristic*" OR "environmental correlat*" OR "urban design*" OR "urban planning*" OR "urban form" OR "town planning*" OR neighbourhood* OR neighborhood* OR “geospatial” OR "local environment*" OR "rural environment*" OR "urban environment*" OR "objective environment*" OR "perceived environment*" OR "measured environment*" OR "obesogenic environment*" OR "built environment*" OR "physical environment*" OR “geoepidemiology” OR "spatial analysis" OR "land use" OR "spatial access" OR "residential environment*" OR "urban-rural epidemiology" OR "geographic cluster*" OR "residential factor*" OR "residence characteristic*" OR "geographic information system*" OR "geographical information system*" OR “sprawl” OR “zoning” OR "residential location*" OR "residential proximit*" OR "population densit*" OR "food outlet*" OR "grocery store*" OR "fast food density" OR "fast food restaurant*" OR "retail densit*" OR “walkability” OR “cyclability” OR sidewalk* OR “pedestrian” OR "cycle path*" OR cyclepath* OR "recreational facilit*" OR "recreational park*" OR "recreation facility*" OR worksite* OR "sports facilit*" OR "food environment*" OR "food suppl*" OR "public open space*" OR “crowding” OR "park access" OR "urban park*" OR "noise pollution" OR "contextual research" OR "ecological stud*" OR "ecological analys*" OR “remoteness” OR aesthetic* OR "active travel*" OR "passive travel*" OR "travel to work" OR "transport to work" OR "public transport*" OR "transportation network*")	1,768
#1	TS = (cholesterol* OR triacylglycerol* OR “hypertriglyceridemia” OR epicholesterol* OR “hdl” OR “ldl” OR “ldl1” OR “ldl2” OR triglycerid* OR “lipid” OR “lipids” OR hypertriglyceride* OR triglyceride* OR lipoprotein* OR dyslipidemi* OR dyslipoprotein* OR hyperlipemi* OR hyperlipidemi* OR lipidemi* OR lipemi* OR hypercholesterolemi* OR hypercholesterolaemi* OR hypercholesteremi* OR hypercholesteraemi* OR hyperlipoproteinemi* OR hypoprebetalipoproteinemi*) Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years	838,514

Appendix B - Adapted Quality Assessment Tool for Quantitative Studies (QATQS)

Section A -Selection Bias (paper level)

Q1. Are the individuals selected to participate in the study likely to be representative of the target population ?

1.Very likely
2.Somewhat likely
3.Not likely (selected group of users e.g., volunteers)
4.Can't tell (no information provided)
5.Not applicable (using an existing database and authors refer to design

Q2 What percentage of selected individuals agreed to participate?

1.80 - 100% agreement
2.60 – 79% agreement
3.less than 60% agreement
4. Can't tell
5.Not applicable

Rating selection bias:

Strong: Q1 is 1 and Q2 is 1
Moderate: Q1 is 1 or 2 and Q2 is 1 or 2. Q1 is 1 or 2 and Q2 is 4. Q1 is 5 and Q2 is 1 or 2
Weak: Q1 is 3. Q2 is 3. Q1 is 4. Q2 is 4
No rating: Q1 is 5 and Q2 is 5.

Section B – Study Design (paper level)

Q3. The study design is:

1. Experimental
   Individual-randomised
   Group-randomised
   Non-randomised
2. Observational
   Individual-randomised
   Cross-sectional
   Longitudinal (also natural experiment or pre-post tests)
   Case-control
3. Any other method or did not state method (i.e. pre-post test without control group).

Q4 Was the study described as randomized?

1. Yes - proceed
2. No - go to question 9

Q5 Was the method of randomization described?

1. Yes
2. No

Q6 Was the method appropriate?

1. Yes
2. No

Q7 Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1. Yes
2. No
3. Can't tell

Q8 Were the study participants aware of the research question?

1. Yes
2. No
3. Can't tell

Rating study design:

Strong: Q3 is 1.
Moderate: Q3 is 2.
Weak: Q3 is 3.

Rating blinding:

Strong: Q4 and Q5 are 2.
Moderate: Q4 is 2. Q5 is 2. Q4 and Q5 are 3.
Weak: Q4 or Q5 are 1.

Section C - confounding

Q8 Were analyses appropriately adjusted for confounders? (the table in which information for our research question is presented)

1. For most confounders (meaning at least age and sex/or education or SES)
2. For some confounders (meaning at least two of the following: age, sex education or SES.
3. No or can't tell.

Rating confounding:

Strong: Q8 is 1.
Moderate: Q8 is 2.
Weak: Q8 is 3.

Section D - blinding
This section is incorporated in section B study design as these questions are only applicable for intervention studies (Q7 and Q8).

Section E - data collection (paper level)
The following question is only applicable if blood was collected.

Q9 Were the participants fasting before the blood sample was taken?

1. Yes
2. No
3. Can't tel

Rating data collection:

Strong: Q9 is 1.
Moderate: Q9 is 2.
Weak: Q9 is 3.

Section F – Representativeness (withdrawals and drop-outs) (paper level)
Q10 Were withdrawals and drop-outs reported in terms of numbers and reasons per group?

1. Numbers and reasons provided
2. Numbers but no reasons provided
3. Can't tell (if longitudinal data)
4. Not applicable (if cross-sectional data or if using an existing database and authors refer to design article)

If Q10 is 1 or 2, proceed to Q11. Otherwise, proceed to Q12.

Q11 What was the loss to follow-up/percentage completing the study? (If % differs by groups, record the lowest)

1. 80-100%
2. 60-79%
3. Less than 60%
4. Can't tell
5. Not applicable (i.e. retrospective case control)

Rating representativeness:

Strong: Q11 is 1.
Moderate: Q11 is 2 or Q11 is 5.
Weak: Q11 is 3 or Q11 is 4.

Section I – Reporting
Q12 Are the hypothesis/aim/objective of the study clearly described? (paper level)

1. Yes.
2. No.

Q 13Were inclusion/exclusion criteria specified and number of exclusions reported? (paper level)

1. Criteria and number of exclusions reported
2. Criteria or number of exclusions not reported
3. Criteria and number not reported

Q14 Were the methods to measure the lipid profile discussed?

1. Yes
2. No

Q15 Were the important descriptive statistics for lipid variables reported ?

1. The mean, SD/SEM or the median, IQR and the N per urban-rural category are reported.
2. No.

The following question is only applicable if the study concerns an urban-rural comparison.

Q16 Is a definition of urban – rural provided? (paper level)

1. Yes (for example, definition used from national statistics office)
2. No, only the names of the places are stated
3. No

Rating reporting:

Strong: Q12 is 1 and Q13 is 1 and Q14 is 1 and Q15 is 1 and if applicable Q16 is.

Moderate: :Q12 is 1, Q13 is 1 or 2, Q14 is 1 or 2 and Q15 is 1 or 2 and if applicable Q16 is 1 (In case of Q12-Q16 at least 3 questions are 1 and in case of Q12-Q15 at least 2 questions are 1).

Overall rating - 7 ratings:

Strong: No weak + at least four strong.
Moderate: Two weak or fewer than four strong.
Weak: More than two weak.

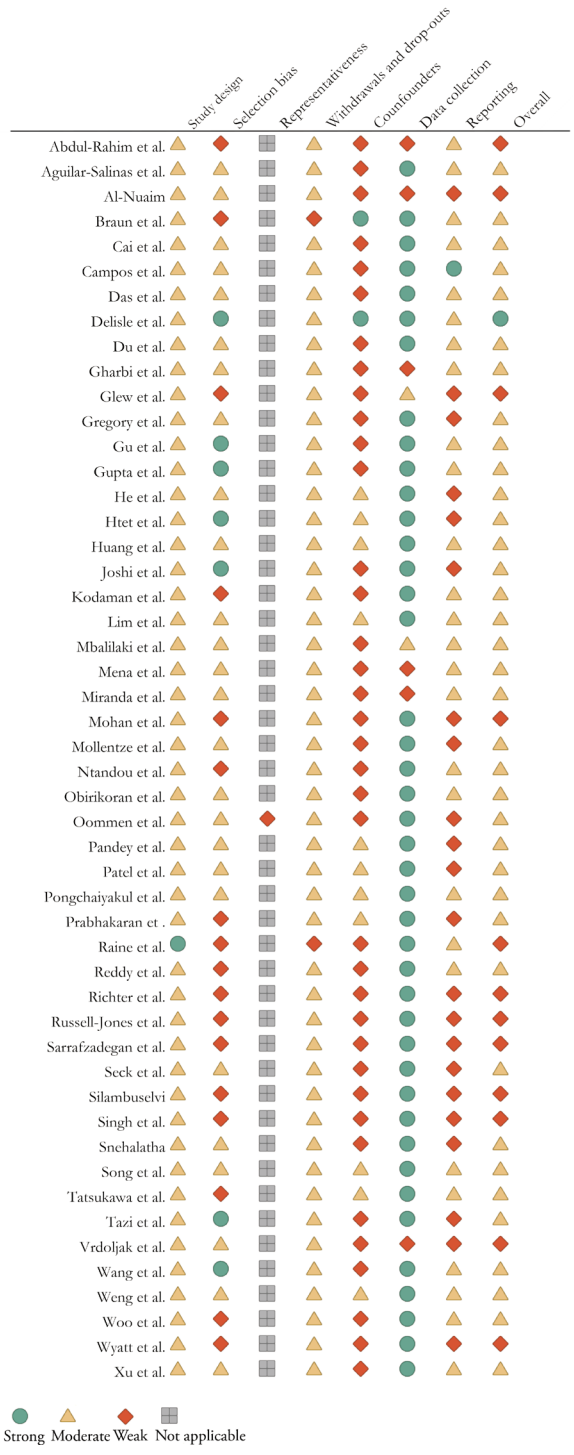
Appendix C - Definitions provided about urban - rural

Authors	Definition urban-rural
Aguilar-Salinas et al.	Reference to the National Institute of Statistics, Geographics and Informatics
Abdul-Rahim et al.	Reference to the Palestinian Central Bureau of Statistics
Ntandou et al.	Reference to definition of Government of Benin
Campos et al.	Reference to Center of Census and Statistics of Costa Rica
Gharbi et al.	Reference to the National Institute of Statistics of Tunis
Al-Nuaim	Reference to National Population Census
Song et al.	Reference to China National Bureau of Statistics and the China Ministry of Health
Statistics	
Das et al.	Only names of places reported
Delisle et al.	Only names of places reported
Kodaman et al.	Only names of places reported
Sarrafzadegan et al.	Only names of places reported
Glew et al.	Only names of places reported
Xu et al.	Only names of places reported
Miranda et al.	Only names of places reported
Mbalilaki et al.	Only names of places reported
He et al.	Only names of places reported
Du et al.	Only names of places reported
Wyatt et al.	Only names of places reported
Huang et al.	Only names of places reported
Joshi et al.	Only names of places reported
Obirikoran et al.	Only names of places reported
Cai et al.	Only names of places reported
Lim et al.	Only names of places reported
Silambuselvi	Only names of places reported
Weng et al.	Only names of places reported
Woo et al.	Only names of places reported
Mollentze et al.	Only names of places reported
Pandey et al.	Only names of places reported
Tatsukawa et al.	Only names of places reported
Mohan et al.	Only names of places reported
Wang et al.	Only names of places reported
Snehalatha	Only names of places reported
Gu et al.	Only names of places reported
Reddy et al.	Only names of places reported
Russell-Jones et al.	Only names of places reported
Pongchaiyakul et al.	Only names of places reported

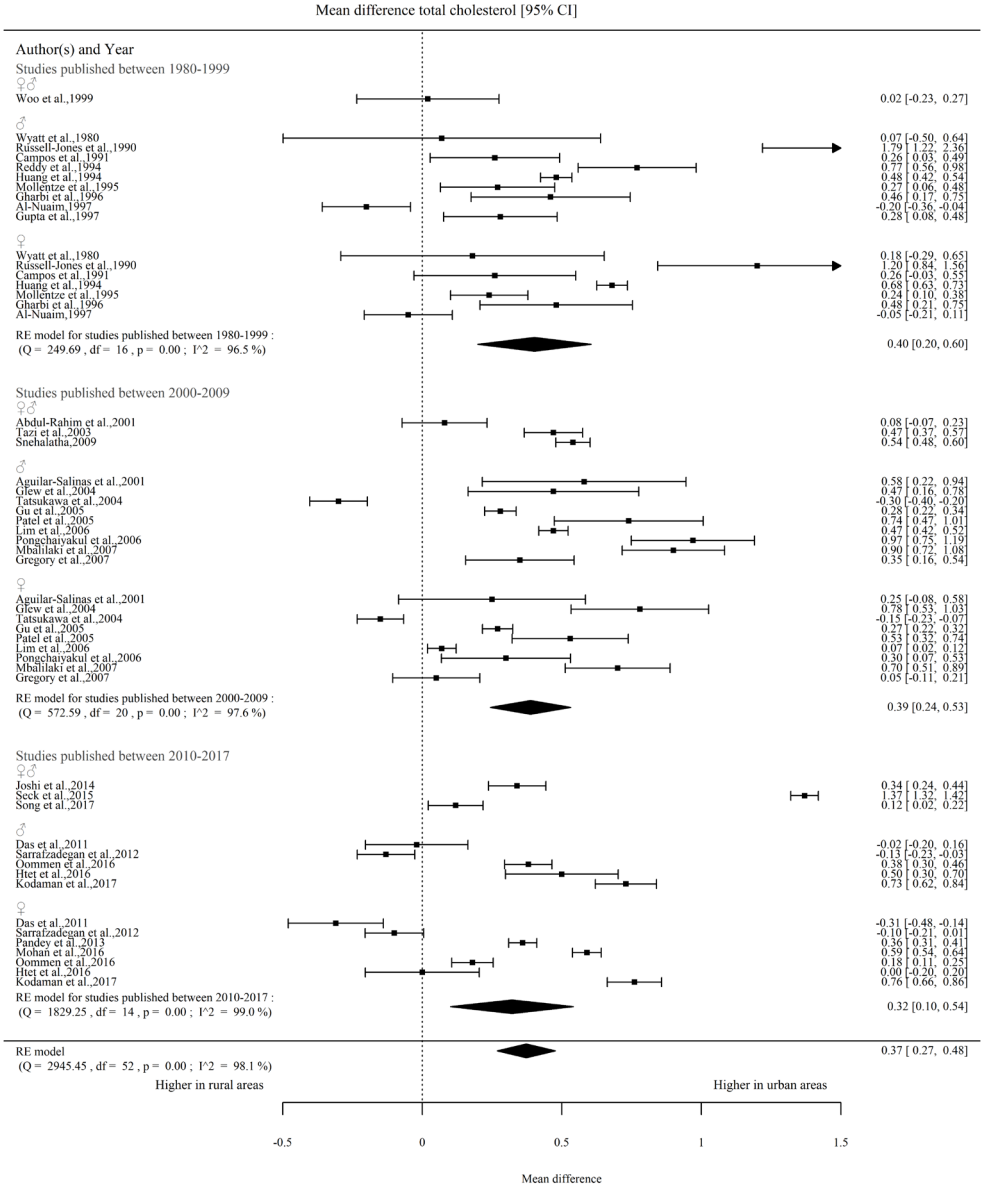
Appendix B - continued

Authors	Definition urban-rural
Tazi et al.	None
Vrdoljak et al.	None
Gregory et al.	None
Prabhakaran et .	None
Htet et al.	None
Oommen et al.	None
Seck et al.	None
Singh et al.	None
Richter et al.	None
Patel et al.	None

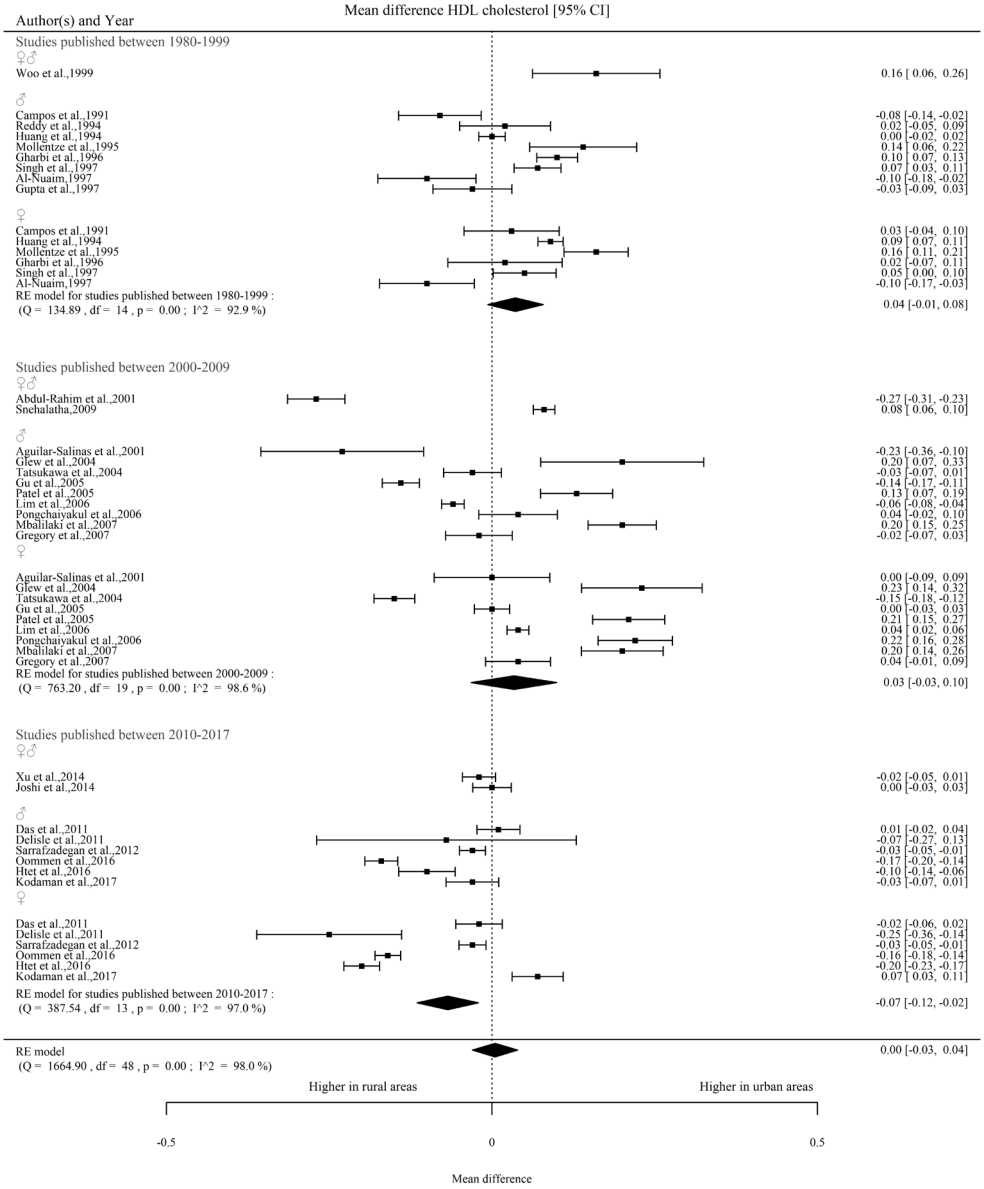
Appendix D - Quality assessment per domain per study



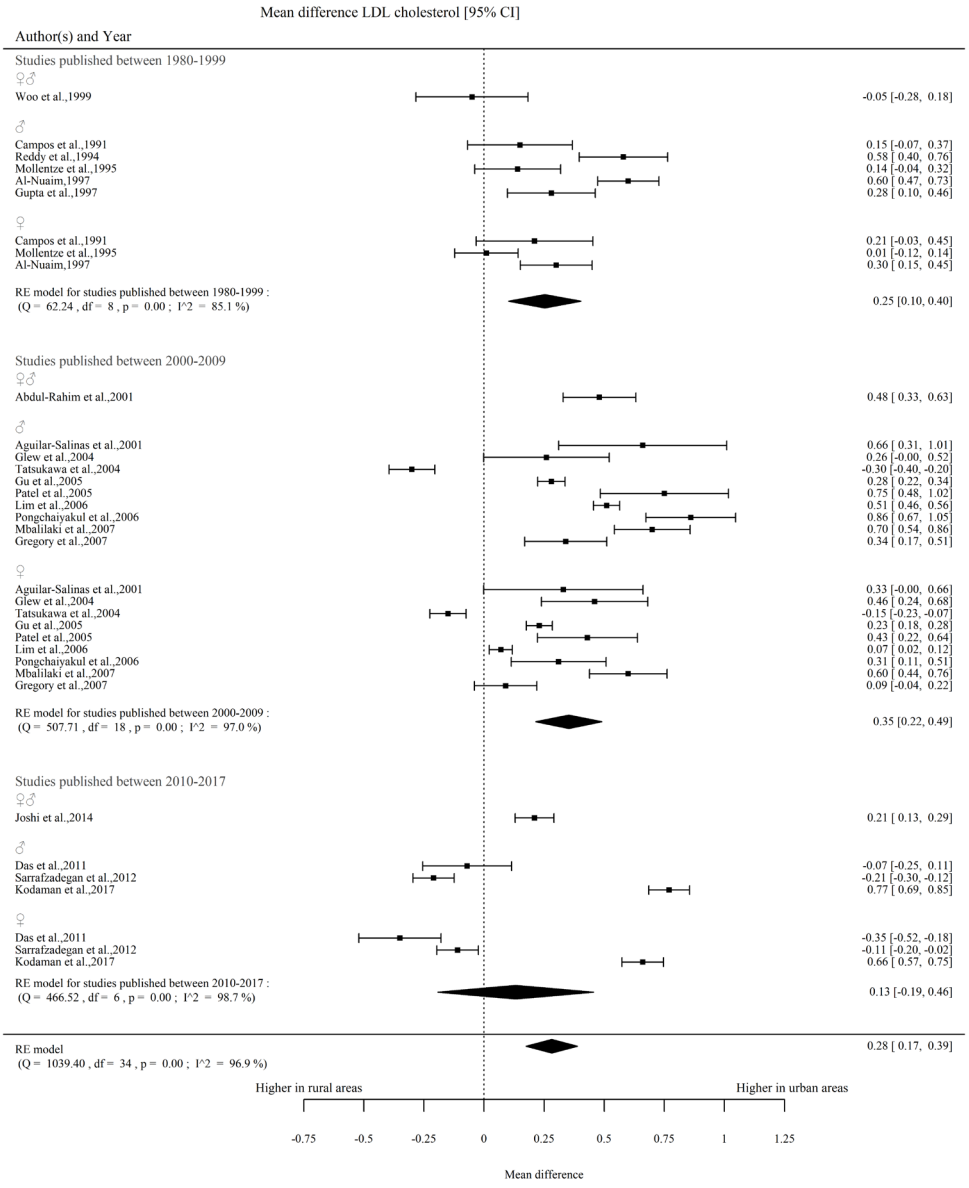
Appendix E1 - Sensitivity analyses total cholesterol with time periods



Appendix E2 - Sensitivity analyses high density lipoprotein (HDL) with time periods



Appendix E3 - Sensitivity analyses low density lipoprotein (LDL) with time periods



Appendix E4 - Sensitivity analyses triglycerides with time periods