



# The role of fasting versus non-fasting triglycerides in ischemic stroke: a systematic review

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**Objective:** To synthesize results from pertinent studies and determine if fasting and/or non-fasting triglycerides are a risk factor for ischemic stroke. **Method:** We performed two independent systematic literature searches using the PubMed and ScienceDirect databases to identify studies examining the relationship between fasting and non-fasting triglyceride concentrations and ischemic stroke risk. A meta-analysis was performed using ischemic stroke as a primary endpoint.

**Results:** Twenty-five reports were identified, including 13 prospective cohort and 12 case-control studies. Baseline characteristics, study samples, methods, and primary outcomes varied. Of 13 prospective cohort studies, nine assessed triglyceride concentrations in the fasting state. Seven of these identified triglycerides as an independent risk factor for ischemic stroke risk ( $n = 1624$  ischemic cases). Three prospective cohort studies identified a positive association between elevated non-fasting triglyceride concentrations and ischemic stroke risk ( $n = 2050$  ischemic cases). One prospective cohort study that compared fasting and non-fasting triglycerides identified only non-fasting triglycerides as an independent risk factor for ischemic stroke. Of 12 case-control studies identified, five identified a positive relationship between ischemic stroke risk and elevated fasting triglycerides ( $n = 838$  cases). Seven case-control studies were included in the meta-analysis ( $n = 1996$  ischemic stroke cases), revealing an odds ratio of 1.15 (95% CI, 1.08–1.21). **Conclusions:** The available data are inconsistent. The relationship between triglyceride levels and ischemic stroke needs further investigation under standardized conditions. We recommend a standardized triglyceride tolerance test to further investigate the associations between fasting versus non-fasting triglyceride levels and ischemic stroke.

**Keywords:** ischemic stroke, triglycerides, epidemiology

## INTRODUCTION

Though it is well established that the number and severity of vascular risk factors contribute to stroke risk (Blumenfeld, 2002; Towfighi and Ovbiagele, 2008), it is clear that the list of known risk factors to date is not complete. Triglycerides are circulating lipid components that are among the many long-speculated modifiable risk factors for ischemic stroke (Albrink and Man, 1959; Zimmermann et al., 2004). However, the clinical usefulness of plasma triglyceride concentrations as an independent risk factor of ischemic stroke risk remains controversial (Tell et al., 1988; Ridker, 2008). Some claim that elevated triglyceride levels are strong independent factors increasing risk of ischemic stroke (Lindenstrom et al., 1994; Ahmed et al., 1999; Milionis et al., 2005) while others have found the relationship either to exist only in women (Bansal et al., 2007), men (Salonen et al., 1982), or not at all (Haheim et al., 1993; Bowman et al., 2003).

Some of the discrepancy in the literature could be due to genetic heterogeneity within study samples (Havasi et al., 2006). Indeed, lipid profiles can vary largely at the individual level, and are affected by factors like ethnicity, alcohol consumption, and menopausal

status (Austin, 1991; Sarwar et al., 2006; Ridker, 2008). Rhoads and Feinleib (1983), for instance, found that Puerto Rican and Japanese men had higher median triglyceride values than men of Caucasian descent. As larger samples of stroke patients of different ethnicities are being studied however (Sarwar et al., 2006), it is becoming increasingly apparent that methodological differences across studies might be playing a larger role (Bansal et al., 2007).

Traditionally measured in the fasting state to avoid variability (Ridker, 2008), mounting evidence supports the assessment of non-fasting triglyceride concentrations to determine stroke risk (Zilversmit, 1979; Ryu et al., 1992; Bengtsson et al., 1993; Stensvold et al., 1993; Jeppesen et al., 1998; Abdel-Maksoud and Hokanson, 2002). Because no consistent set of prospective cohort data specifically comparing fasting versus non-fasting triglycerides as a measure of stroke risk exist, it remains unclear which state is more efficacious.

It is also possible that risk could vary across genders, as one meta-analysis found that plasma triglyceride levels in women associated twice as strongly with cardiovascular disease risk than those in men (Hokanson and Austin, 1996).

The purpose of this review is to summarize and synthesize results from pertinent studies in an effort to determine if fasting and/or non-fasting triglycerides are a risk factor for ischemic stroke. We hypothesized that elevated non-fasting plasma triglyceride concentrations are indicative of stroke risk.

## MATERIALS AND METHODS

### SEARCHING DATA SOURCES

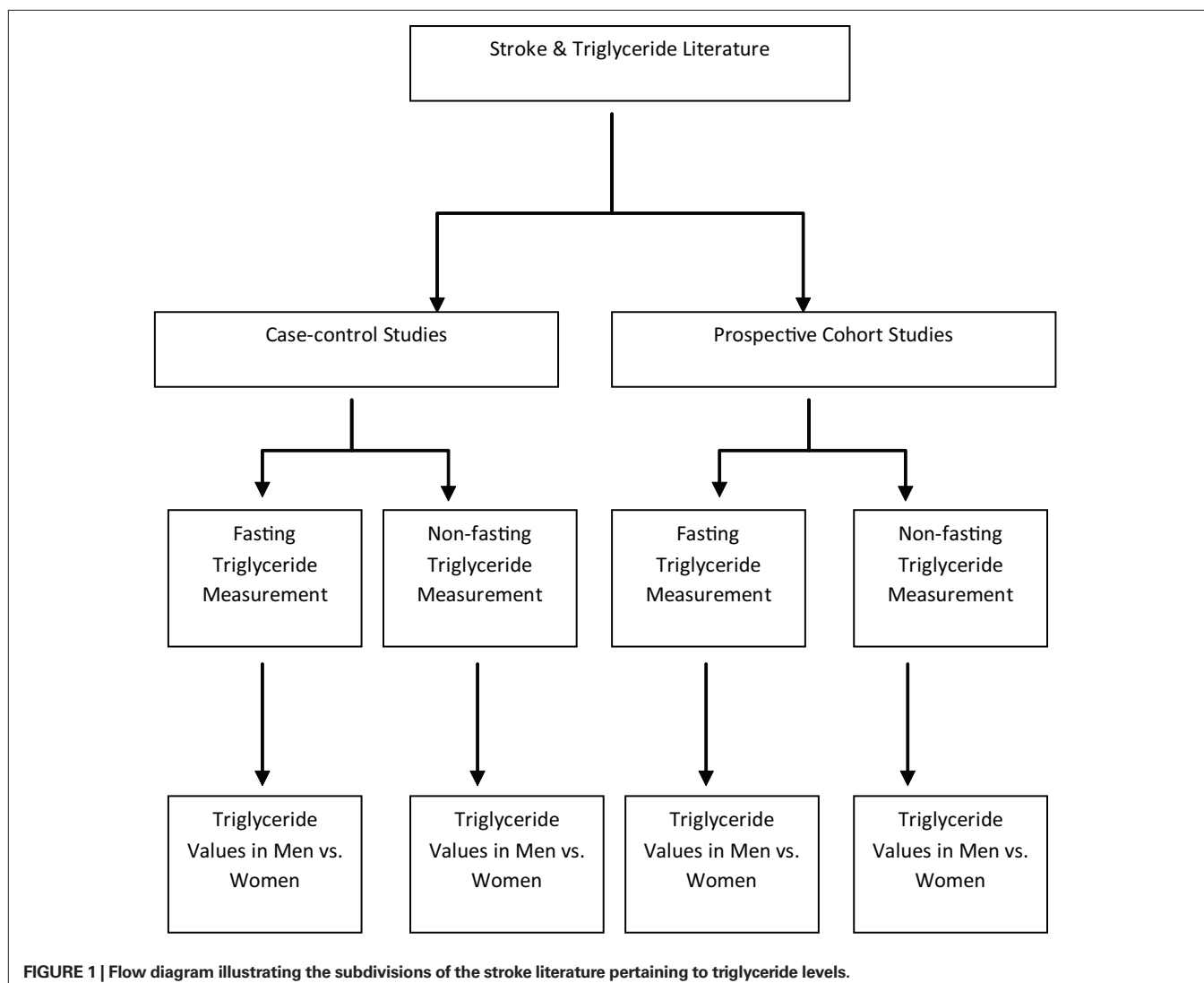
This review was conducted in accordance with MOOSE guidelines (Stroup et al., 2000). We identified original epidemiological studies assessing the relationship between stroke risk and fasting or non-fasting triglyceride concentrations using two independent computerized literature searches (**Figure 1**). The PubMed and ScienceDirect databases were searched by Christopher Leonards and Jana Batluk between April 14th and 27th April, 2010, using the medical subject heading (MESH) terms “triglycerides” and “stroke.” Hand searching was also performed of all included studies and relevant review articles. Unpublished studies were identified by searching the book of abstracts from the European Stroke Conferences ranging from the years 2006 through 2008.

### STUDY ELIGIBILITY

The review included any human prospective cohort, case-control, and nested case-control study having to do either directly or indirectly with ischemic stroke published or translated into the English language. Because this review focuses exclusively on ischemic stroke risk, studies were only eligible for inclusion if a computed tomography scan or magnetic resonance imaging had been performed on patients to distinguish between ischemic and hemorrhagic strokes.

### INCLUSION CRITERIA

Case-control and prospective cohort studies were included if they had at least 100 participants per group and a statistical analysis had been conducted measuring the relationship between triglyceride levels and stroke endpoint (fatal and/or non-fatal ischemic stroke and transient ischemic attack). Additionally, we excluded all studies that did not include a specific ischemic stroke patient subset within their study, thereby excluding studies that focused exclusively on other forms of stroke (e.g., subarachnoid hemorrhage). This was performed in an effort to minimize



potential confounds, as triglyceride levels have been more strongly connected with ischemic than hemorrhagic stroke risk (Austin et al., 2000; Sarti and Gallagher, 2006). When more than one publication using the same sample was found, the publication with the most recent, complete data set was included. Results from meta-analyses are discussed herein, but were excluded from our analyses.

### DATA EXTRACTION

The data extracted from eligible reports are exhibited in **Figure 2**. Data were extracted by one author (Christopher Leonards) and reviewed independently (Martin Ebinger) to assure accuracy. Authors were not contacted for additional or unpublished data. Studies were then categorized based on study design and the direction of association found (**Tables 1 and 2**).

### META-ANALYSIS

We performed a meta-analysis of case-control studies that assessed plasma triglycerides and the risk of ischemic stroke using the MIX software package (Bax et al., 2006). Heterogeneity was assessed using the  $Q$  and  $I^2$  statistics and we calculated a pooled odds ratio within a fixed effect meta-analysis. Because stroke endpoint, fasting status, and statistical methods varied across studies, not all case-control studies were included.

<b>Report Characteristics</b>
Study & First author's names
Journal & Year of publication
Population Studied
Study Design
Selection of patients/Inclusion criteria
<b>Baseline Characteristics</b>
Overall sample size
Ischemic stroke sample size
Age
Gender
Lipid-profile levels for overall sample & ischemic stroke patients
<b>Method</b>
Blood sample collection
Fasting vs. nonfasting lipid profile measurements
Time spent fasting
Definition & identification of ischemic stroke (e.g. MRI)
Statistical methods
<b>Outcome</b>
Direction of association
Strength of association
Primary study outcome

**FIGURE 2 | Panel illustrating data extracted from eligible reports.**

For some case-control studies no logistic regression was performed and no odds ratios are reported. If only mean triglyceride values and SD's were given for cases and controls, we decided *not* to convert the corresponding standardized differences to odds ratios and thereafter include these studies in our meta-analysis. First, this would not yield adjusted odds ratios and, second, the corresponding model assumptions which justify such procedures (e.g., Hasselblad and Hedges, 1995; Whitehead, 2002) are very specialized and in practice difficult to test. Thus, we only included case-control studies that reported odds ratios.

### RESULTS

Of 6896 citations identified by the computerized literature search in ScienceDirect and 1065 in PubMed, 35 epidemiological human studies examining the relationship between triglyceride concentrations and stroke risk that were identified by review of the title, abstract, and hand searching of references (**Figure 3**). Of these 35 identified, 25 reports matched the inclusion criteria and are presented according to study design in **Table 1** (prospective cohort) and **Table 2** (case-control). The grounds for paper dismissal were lack of a specific ischemic stroke group ( $n = 6$ ) (Rhoads and Feinleib, 1983; Haheim et al., 1993; Njolstad et al., 1996; Wannamethee et al., 2000; Shearman et al., 2005; Tokuda and Stein, 2005), duplicated data sets ( $n = 2$ ) (Lindenstrom et al., 1994; Nordestgaard et al., 2007), and two full text papers could not be accessed (Lapidus et al., 1985).

#### PROSPECTIVE COHORT STUDIES

Thirteen prospective cohort studies (**Table 1**) were identified with a total of 99479 participants, and 4675 ischemic strokes that occurred during a mean follow-up period of 9.6 years. Samples varied regarding demographics and baseline characteristics. Nine of the prospective cohort studies measured triglyceride concentrations in the fasting state (Salonen et al., 1982; Aronow et al., 1988; Simons et al., 1998; Psaty et al., 2001; Tanne et al., 2001; Shahar et al., 2003; Onat et al., 2006; Nakamura et al., 2009), three non-fasting (Gordon et al., 1981; Iso et al., 2007; Freiberg et al., 2008), and one examined fasting versus non-fasting concentrations (Bansal et al., 2007). Fasting times across studies were variable, and ranged from 4 to 12 h.

#### NON-FASTING PROSPECTIVE COHORT STUDIES

Of the four studies that examined non-fasting triglyceride concentrations, three found that elevated triglyceride concentrations were independent risk factors for ischemic stroke in a sample including 1785 ischemic events after follow-up (Iso et al., 2007; Freiberg et al., 2008). One study found that triglyceride concentrations were not related to ischemic stroke risk in a sample of 150 ischemic stroke patients (Gordon et al., 1981). Of the three positive studies, one was conducted in women only and examined the risk of ischemic stroke across a fasting (minimum 8-h fast) and non-fasting group and found that in a sample including 265 ischemic events only non-fasting triglyceride concentrations were indicative of ischemic stroke risk (HR per 1-SD increase in triglyceride levels 1.98, 95% CI 1.21–3.25) (Bansal et al., 2007).

**Table 1 | Characteristics of prospective cohort studies assessing triglyceride concentrations and ischemic stroke risk.**

Source	Study name (data set used)	Endpoint: IS Yes/No (additional endpoints)	Association identified between TG and stroke	Fast at baseline (h)	Total n	n total ischemic stroke pts	Mean age and SD (total sample size)	TG Mean (mmol/L) and SD for subjects without stroke	TG Mean (mmol/L) and SD for subjects with stroke	p value comparing Pts with and without stroke	OR/HR/RR	Adjustments
Aronow et al. (1988)	-	Yes	No	Yes (14)	708	708	82 ± 8	-	-	-	-	-
Bonaventure et al. (2009)	Three city study	No (HS and IHD)	No (TG did inversely associate with HS)	Yes	8393	186 total, 143 IS	≥65	-	-	-	HR for IS with increasing TG per 1 mmol/L (95% CI), 1.13 (0.88–1.47)	Age, gender, center, MI, SS, PAD, alcohol, weight, BP, DM, apo E, low-dose aspirin intake, and lipid-lowering therapy
Bansal et al. (2007)	Women's health study	No (cardiovascular events: IS, non-fatal MI, CR, CD)	Yes, Non-fasting TGs were sig. risk factor	half/half (≥8)	26509	265	Fasting: 54.5 ± 7.2, Non-fasting: 53.3 ± 6.6	Total (including subjects with and without stroke) Median, Fasting = 1.29 ± 0.92–1.91 Median, Non-fasting = 1.50 ± 1.05–2.21	-	-	HR (per 1 SD increase in TG; 95% CI) Fasting TG, 1.11 (0.92–1.34), $p = 0.30$ Non-fasting TG, 1.67 (1.18–2.35), $p = 0.004$	Total cholesterol, HDLC, and signs of IR, DM, BMI, and high-sensitivity C-reactive protein
Freiberg et al. (2008)	Copenhagen city heart study	Yes	Yes	No (0)	13956	1529	age range 30–74	Median, Men = 1.67; Women = 1.44	Median, Men = 2.16, Women = 1.89	Men, $p < 0.01$ ; Women, $p < 0.05$	HR for IS with increasing TG (95% CI); Multivariate-analysis HR in men: 1.21 (0.9–4.6) 2.11 (0.7–1.9) 3.16 (0.9–2.7) 4.16 (0.8–3.0) 5.22 (1.0–4.7) $p$ for Trend = 0.005 in Women: 1.1 (Reference) 2.51 (1.6–16.2) 3.11 (0.8–1.6) 4.17 (1.1–2.6) 5.10 (0.5–2.3)	

6. 2.2 (0.8–6.2 p for Trend = 0.006	Total cholesterol level, alcohol consumption, SS, hypertension, atrial fibrillation, and lipid-lowering therapy, with further adjustment in women for postmenopausal status and hormone therapy																																								
Gordon et al. (1981)	Framingham study	Yes (IS, HS, CHD, CHF, IC)	No	No (0)	5209	150	Range 59–82	–	–	–	Multivariate logistic regression analysis (regression of IS on TG): Men, 0.102 Women, 0.227 “not significant”																														
Iso et al. (2007)	–	No (IS, IHD)	Yes	No (0)	9087	256	Men = 55.3, Women = 574	Men = 1.58 ± 0.02, Women = 1.48 ± 0.01	Men = 1.69 ± 0.09, Women = 1.59 ± 0.08	“not significant”																															
Nakamura et al. (2009)	Yamanashi University Hospital Pts (02–04)	Yes (in metabolic syndrome Pts)	Yes	Yes (12)	1024 Total, 290 on follow-up	22	64 ± 8	Median: 1.60	–	–	Univariate Cox proportional analysis: (mg/dL) 4.7 (95% CI, 1.5–15.1) p < 0.001																														

(Continued)

Table 1 | Continued.

Source	Study name (data set used)	Endpoint: IS Yes/No (additional endpoints)	Association identified between TG and stroke	Fast at baseline (h)	Total n	n total ischemic stroke pts	Mean age and SD (total sample size)	TG Mean (mmol/L) and SD for subjects without stroke	TG Mean (mmol/L) and SD for subjects with stroke	p value comparing Pts with and without stroke	OR/HR/RR	Adjustments
Okamura et al. (2010)	The Suita study	Yes (MI, IS, death, leaving Suita city)	Yes	Yes (10)	5098 Total	116	range: 30–79	Baseline survey median, men = 1.29 mmol/L (range, 0.9–1.9) women = 0.98 (range, 0.73–1.41)	–	–	Multivariate-adjusted HR (95% CI) in high TG group, 1.63 (1.03–2.56)	Age, BMI, hypertension, DM, HDL, SS, alcohol
Onat et al. (2006)	Turkish adult risk factor Study	No (CVD)	Yes	Yes (>11)	2682	341	Total 43 ± 14, Men 43.1 ± 14.3, Women 42.8 ± 14.4	Men: 1.55 ± 1.00, Women: 1.36 ± 0.85	–	–	RR (lowest compared with highest TG quintile), 2.16 (95% CI, 1.38; 3.39), “borderline significant” (First, lowest compared with fourth TG quintile), 1.56 (95% CI, 0.984; 2.47), “not significant”	–
Psaty et al. (2004)	Cardiovascular health study	Yes (MI, IS, HS, and total mortality)	Yes	Yes (8–12)	5201	332	Men = 73.0 ± 5.7, Women = 72.3 ± 5.3	–	Mean, Men = 1.55 ± .86, Women = 1.56 ± 0.80	–	HR, 1.10 (95% CI, 1.01–1.20), p = 0.046	Age, gender, DM, SS, CD, and systolic BP
Salonen et al. (1982)	North Karelia project	No (CS and MI)	Yes	Yes (4)	4948	59 All stroke	Age range: 30–59	–	–	–	Participants were stratified according to age, Group 1 (ranged from 30 to 49 years of age) included 3038 men, RR = 2.7 (95% CI, 1.0–7.1) Group 2 (ranged from 50 to 59) included 1066 men; RR = 1.1 (95% CI, 0.4–2.7)	–

Simons et al. (2001)	Dubbo study	Yes	Yes	Yes (12)	2805	326	72.6 ± 7.2	1.73 ± 1.09	1.94 ± 1.53	<0.05	HR, All ages: 1.13 (95% CI, 1.00–1.28); 60–69 years old: 1.18 (95% CI, 0.97–1.43); 70–79 years old: 1.19 (1.00–1.42); >80 years old: 0.72 (0.47–1.10)	-
Tanne et al. (2001)	BISP	Yes (includes TIA)	Yes	Yes (12)	11177	487	61.8 ± 6.5	1.85 ± 1.15	2.01 ± 1.22	<0.01	Adjusted OR For 1-natural-log-unit increase, 1.39 (95% CI, 1.16–1.68) Adjusted OR for TG 200 mg/dL: 1.47 (95% CI, 1.19–1.80)	Age, gender, lipid-lowering medications, previous myocardial infarction, diabetes mellitus, hypertension, smoking status, peripheral vascular disease, and body mass index

Abbreviations: BP, blood pressure; CHF, congestive heart failure; CR, coronary revascularization; CD, cardiovascular death; CS, cerebral stroke; CVD, cerebrovascular disease; DM, diabetes mellitus; Glc, glucose; HDL, high density lipoprotein; HS, hemorrhagic stroke; IC, intermittent claudication; IHD, ischemic heart disease; IR, insulin resistance; IS, ischemic stroke; LDL, low density lipoprotein; MI, myocardial infarction; Pt, patient; SS, smoking status; TIA, transient ischemic attack; TG, triglycerides.

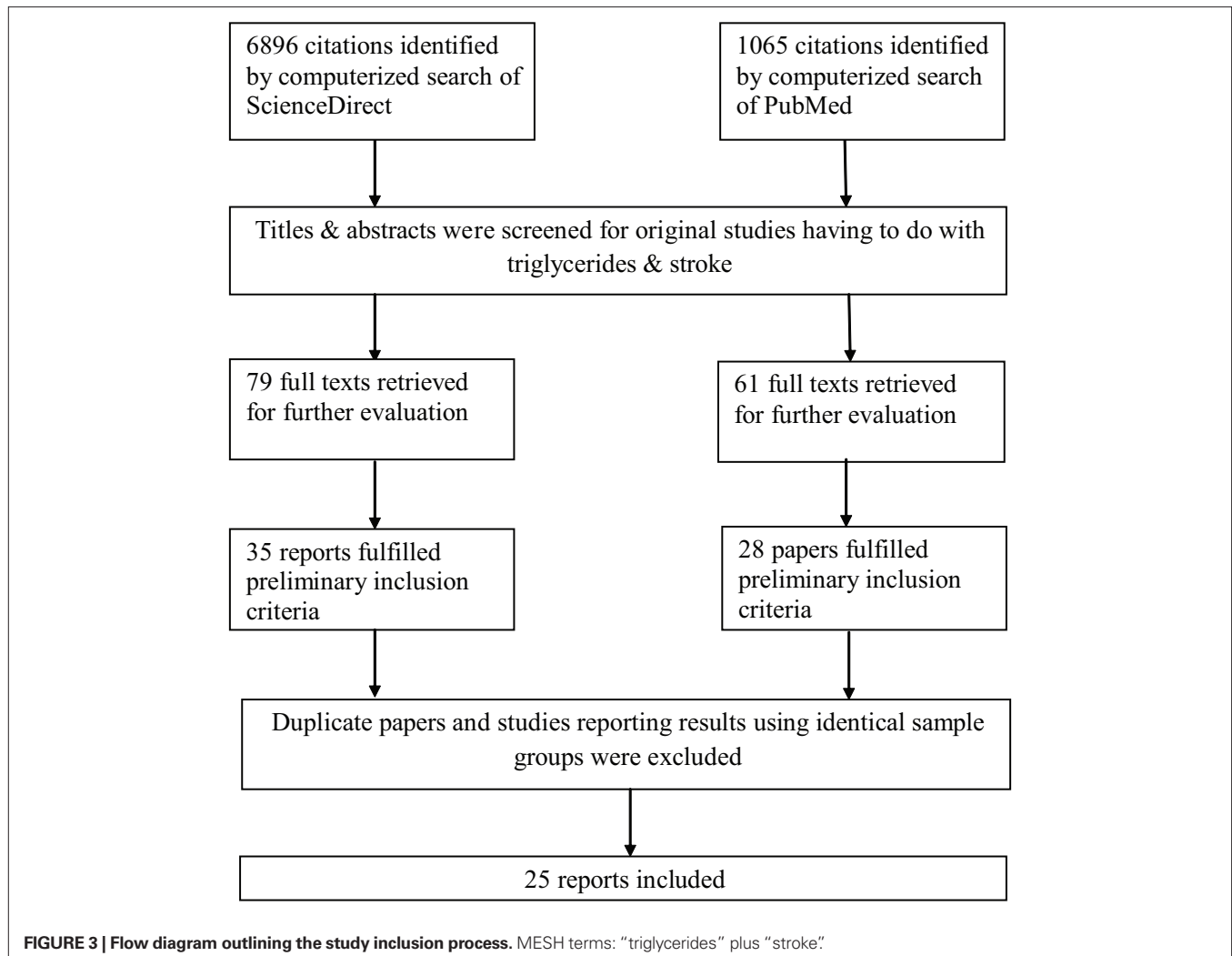
**Table 2 | Characteristics of case-control studies assessing triglyceride concentrations and ischemic stroke risk.**

Source	Study name (data set used)	Cases = ischemic stroke only Yes/No	Association identified between TG and stroke	Fast at Baseline (h)	Total n	n total ischemic stroke pts	Mean age and SD (total sample size)	ControlTG Mean (mmol/L) and SD	PTTG Mean (mmol/L) and SD	p value comparing Pt and controlTGs	OR, HR, RR, Regression analysis	Adjustments
Ahmed et al. (1999)	MONICA surveys	No (IS and HS)	Yes	Yes (4)	119 Cases, 233 Controls	98 (IS) 21 (HS)	55.1 ± 7.7	1.4 ± 0.6	1.7 ± 1	0.017	–	–
Amaranco et al. (2006)	GENIC study	Yes	No	Yes (-)	510 Cases, 510 Controls	492	66	1.64 ± 0.71	1.55 ± 0.63	0.15	Raw OR for highest TG quartiles; 1.53 (95% CI, 1.02–2.18) <i>p</i> = 0.04, Adjusted OR for highest TG quartiles, 1.33 (95% CI, 0.86–2.05), <i>p</i> = 0.19	LDL, HDL, cholesterol, and apo A-I and apo B
Bowman et al. (2003)	Physicians' health study	Yes	No	No	296 Cases, 296 Controls	296	61.0 ± 8.3	1.77 ± 1.05	2.17 ± 1.76	<0.01	OR after adjustment; First quartile (lowest); 1, Second quartile; 0.77 (0.47–1.27), Third quartile; 1.21 (0.76–1.93), Fourth quartile (highest); 1.34 (0.84–2.14)	Age, smoking status, randomization Status (i.e., aspirin, beta-carotene, both, or neither), BMI, hypertension, diabetes mellitus, exercise level, and alcohol
Chen et al. (2003)	–	Yes	Yes	Yes (overnight)	100 Cases, 150 Controls	100	65.9 ± 11.0	1.54 ± 0.90	1.96 ± 1.27	0.003	OR after adjustment (multivariate analysis) 1st quartile (lowest); 1.00 Second quartile; 0.68 (0.39–1.19) Third quartile; 0.97 (0.57–1.64) Fourth quartile (highest); 1.07 (0.63–1.82)	–
Laloux et al. (2004)	–	Yes (IS was divided into cardioembolic, large vessel, small vessel)	Yes	Yes (-)	485	240	66.2 ± 12.0	1.39 ± 0.70	1.77 ± 0.77	<0.001	–	–
Lipska et al. (2007)	–	Yes	No	Yes (-)	214 Cases, 96 Controls	214	35 ± 7	1.23 ± 0.76	1.61 ± 0.94	<0.001	First multivariable logistic regression for TG and IS in IS Pts compared with community controls, OR (95% CI), .70 (0.37–1.32), <i>p</i> = 0.27, Second OR for TG and IS in IS Pts compared with hospital controls, OR (95% CI) 0.67 (0.4–1.11), <i>p</i> = 0.12	Age, gender, antihypertensive agents, lipid-and/or blood sugar-lowering treatment



Author (Year)	Study	Yes (n)	No (n)	Yes (overnight)	Yes (n)	No (n)	OR (95% CI)	p-value	Multivariate logistical regression analyze OR (95% CI)	Adjustment factors
Millionis et al. (2005)	-	Yes	No	Yes	163 Cases, 166 Controls	78	1.41 ± 0.90	1.97 ± 0.84	<0.001	Age, gender, BMI, hypertension, DM, MS, SS, lipidemic parameters (TC, TG, HDL, apo A-I, apo B, Lp(a)), fibrinogen, uric acid, albumin, total bilirubin and ferritin
Patel et al. (2005)	PROGRESS	Yes (IS, IS, MI, and HF)	No	Half/night (-)	895 Cases, 1011 Controls	66.5	1.95 (95% CI, 1.88-2.01)	1.95 (95% CI, 1.86-2.04)	0.99	First adjusted OR (95% CI) for IS (in tertiles) First tertile; 1 Second tertile; 0.95 (0.73-1.24) Third tertile; 0.91 (0.69-1.20) p = 0.54, Second adjusted OR (95% CI) with 1 mmol/L increase in TG, 0.93 (0.81-1.07)
Sacco et al. (2001)	Northern Manhattan	Yes	No	Yes (-)	539 Cases, 905 Controls	69.9 ± 11.5	1.66 ± 0.95	1.72 ± 0.82	0.16	-
Saidi et al. (2007)	-	Yes	Yes	Yes (-)	216 Cases, 282 Controls	62.94 ± 12.2	1.25 ± 0.62	1.39 ± 0.66	0.026	Gender, BMI, CPK, Glc, TC, and HDL
Shimo-Nakanishi et al. (2001)	-	Yes	No	Yes (12)	177 Cases, 177 Controls	62.23 ± 10.79	1.37 ± 0.12	1.53 ± 0.06	"not significant"	-
Woo et al. (1991)	-	No (IS and HS were combined)	No	Yes (12)	304 Cases, 304 Controls and HS)	Range: 60-80	1.60 ± 0.08	1.70 ± 0.07	<0.05	OR for developing stroke according to TG quintile at 95% CI, First quintile; Reference Second quintile; 1.6 (0.80-3.16) Third quintile; 2.4 (1.18-4.75) fourth quintile; 1.8 (0.90-3.5) Fifth quintile; 2 (1.10-4.71) p < 0.05, different from first quintile (reference)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CPK, creatine phosphokinase; DM, diabetes mellitus; Glc, glucose; HDL, high density lipoprotein; HF, heart failure; LDL, low density lipoprotein; LVH, left ventricular hypertrophy; MS, metabolic syndrome; Pt, patient; SS, smoking status; TG, triglycerides.



### FASTING PROSPECTIVE COHORT STUDIES

Seven of the nine prospective cohort studies that measured triglycerides in the fasting state identified elevated plasma triglyceride concentrations as an independent risk factor for ischemic stroke with 1624 combined ischemic events (Salonen et al., 1982; Simons et al., 1998; Psaty et al., 2001; Tanne et al., 2001; Onat et al., 2006; Nakamura et al., 2009). Two studies, with 1013 combined ischemic events, found no association to exist between ischemic stroke risk and elevated triglyceride levels (Aronow et al., 1988; Shahar et al., 2003).

### CASE-CONTROL STUDIES

Twelve case-control studies were identified (Table 2) including 3841 cases and 4715 controls. Three studies were nested within randomized clinical trials (Ahmed et al., 1999; Bowman et al., 2003; Patel et al., 2005), and baseline characteristics varied as did sample populations. One study (Bowman et al., 2003) measured triglycerides in the non-fasting status.

Another study (Patel et al., 2005) measured both fasting and non-fasting plasma triglyceride concentrations. All other studies measured triglycerides in the fasting state only. Length of fasting varied between 4 and 12 h and was often not reported ( $n = 5$ ).

### NON-FASTING CASE-CONTROL STUDIES

Two studies reported on triglyceride levels in the non-fasting state (Bowman et al., 2003; Patel et al., 2005). Both found no relationship between ischemic stroke risk and elevated plasma triglyceride concentrations (1191 cases). Interestingly however, though one study (Patel et al., 2005) reported no significant relationship to exist, Bowman et al. (2003) reported a significant difference between mean baseline non-fasting triglyceride concentrations in cases and controls, reporting a mean control group triglyceride concentration of  $1.77 \pm 1.05$  mmol/L and mean case concentration of  $2.17 \pm 1.76$  mmol/L ( $p < 0.01$ ).

### FASTING CASE-CONTROL STUDIES

Ten of the 12 case-control studies measured triglycerides in the fasting state (Table 2), two of which, assessed triglyceride concentrations in the acute stroke state ( $\leq 48$ -h post ictus) (Woo et al., 1991; Shimo-Nakanishi et al., 2001). Of these 10 fasting state studies, five (838 ischemic cases) reported a positive association between increased plasma triglyceride levels and ischemic stroke risk (Ahmed et al., 1999; Chen et al., 2003; Laloux et al., 2004; Milonis et al., 2005; Saidi et al., 2007), and four (883 ischemic

cases) found no relationship to exist (Woo et al., 1991; Sacco et al., 2001; Shimo-Nakanishi et al., 2001; Patel et al., 2005). One study combining ischemic and hemorrhagic cases found no relationship between fasting triglyceride levels and stroke (Woo et al., 1991).

### GENDER DIFFERENCES

A number of studies have directly investigated the relationship between triglycerides and stroke in both men and women with varying results. In a study conducted by Njolstad et al. (1996), elevated fasting plasma triglycerides were significant risk factors for ischemic stroke in women. A women's study conducted by Bansal et al. (2007) showed similar findings measuring non-fasting triglycerides. Of five men's studies, three found no relationship between ischemic stroke and non-fasting triglycerides to exist (Rhoads and Feinleib, 1983; Haheim et al., 1993; Wannamethee et al., 2000) and two identified a positive relationship (Salonen et al., 1982; Iso et al., 2007). Taking both genders into account, several studies have found both fasting and non-fasting triglycerides to be an independent risk factor for ischemic stroke (Ahmed et al., 1999; Iso et al., 2007; Freiberg et al., 2008).

### META-ANALYSIS

Seven case-control studies (Woo et al., 1991; Bowman et al., 2003; Milionis et al., 2005; Patel et al., 2005; Amarenco et al., 2006; Lipska et al., 2007; Saidi et al., 2007) were included in the meta-analysis, with a total of 5263 participants (for odds ratios, see Figure 4).

Based on the Q-statistic, the null-hypothesis that all seven studies share a common odds ratio could not be rejected ( $Q = 6.57$ ,  $p = 0.36$ ). There was no significant excess variation. The very low value for  $I^2$  ( $I^2 = 8.76\%$ ) indicated that only a very small proportion of the observed variance reflected real differences between the seven

odds ratios. There was, however, an uncertainty in  $I^2$  corresponding to a broad 95% CI. The pooled odds ratio within a fixed effect model (1.15, 95% CI, 1.08–1.21) and the estimated mean odds ratio within a random effects model (1.13, 95% CI, 1.02–1.25) were very close. Removing the only study (Bowman et al., 2003) with non-fasting TG values in a sensitivity analysis did not change the result. However, when another study was excluded (Milionis et al., 2005) sensitivity analysis revealed loss of significance (for study inclusion criteria, see section Materials and methods).

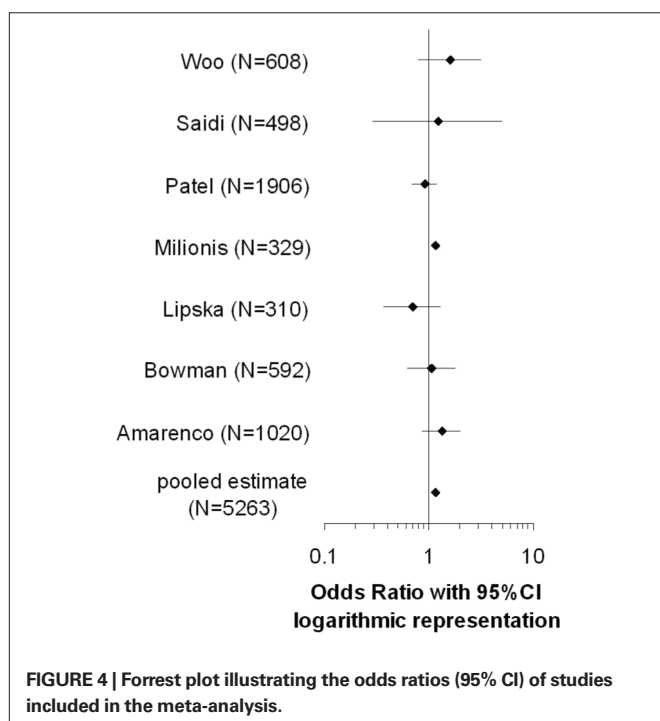
### DISCUSSION

This review revealed that a vast array of conflicting results exist in the literature with regard to the impact that triglycerides have on ischemic stroke risk (Tables 1 and 2). Out of 12 case-control studies only seven studies that reported odds ratios were included in our meta-analysis. It revealed a significant odds ratio of 1.15 (95% CI, 1.08–1.21) but the significance was attributable to a single study (Milionis et al., 2005) only. A sensitivity analysis revealed that this study contributed with a high weight to our meta-analysis and therefore strongly influenced our findings. In fact, significance was lost after the removal of this study [pooled odds ratio with 95% CI within a fixed effect model: 1.03 (0.85, 1.25), estimate for the mean odds ratio with 95% CI for a random effects model: 1.03 (0.85, 1.26)]. Our literature search showed that very few ( $n = 3$ ) original studies have specifically compared fasting with non-fasting triglyceride levels in relation to ischemic stroke risk (Patel et al., 2005; Bansal et al., 2007; Nordestgaard et al., 2007). Moreover, we observed that neither the time elapsed since the most recent meal, nor the content of that meal have been standardized.

Thus, to quell the debate between fasting versus non-fasting triglycerides, it might be beneficial to develop a standardized paradigm for measuring triglycerides. An oral triglyceride tolerance test (oTTT) has recently been suggested as a possible approach (Mohanlal and Holman, 2004; Bansal et al., 2007; Ridker, 2008; Ebinger et al., 2010).

Our review and meta-analysis have a few limitations. First, only those studies published in the English language were included. Secondly, though we specified our inclusion and exclusion criteria no further method quality appraisal was performed. Third, various final endpoints were included in this review (ischemic stroke was the only endpoint used in our meta-analysis). Fourth, we did not differentiate between studies on first versus recurrent stroke.

One advantage of our meta-analysis is that we examined only ischemic stroke. As stroke is a heterogeneous condition, it is possible that plasma triglyceride concentrations correlate differently to various subtypes. Studies performed by Bonaventure et al. (2009) and Psaty et al. (2004) have found an inverse relationship between triglyceride concentrations and hemorrhagic stroke. This distinction between ischemic and hemorrhagic stroke could be of importance, as studies that combine all forms of stroke may be negating possible significant associations. Future work might include examining triglycerides as a risk factor for all stroke subtypes and across the various subtypes of ischemic stroke. We did not differentiate between the embolic, thrombotic, or lacunar subtypes of ischemic stroke as we found very little published information on the topic (Laloux et al., 2004).



While other reviews (Nordestgaard et al., 2007; Antonios et al., 2008; Labreuche et al., 2009) suggested that triglycerides may be associated with ischemic stroke, we concluded that the available data are inconsistent. The relationship between triglyceride levels and ischemic stroke needs further investigation under standardized conditions. Though the available data are mainly composed of studies performed using fasting triglyceride values, some elegant non-fasting prospective cohort studies identified a correlation between non-fasting triglycerides and ischemic stroke risk (Bansal et al., 2007; Freiberg et al. 2008). Therefore, further

studies examining the possible benefit of non-fasting triglyceride measurement, ideally differentiating between stroke subtypes, may be especially warranted.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 04 June 2010; accepted: 15 September 2010; published online: 25 October 2010.

Citation: Leonards C, Ebinger M, Batluk J, Malzahn U, Heuschmann P and Endres M (2010) The role of fasting versus non-fasting triglycerides in ischemic stroke: a systematic review. *Front. Neur.* 1:133. doi: 10.3389/fneur.2010.00133

This article was submitted to *Frontiers in Stroke, a specialty of Frontiers in Neurology*.

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