



Universidade do Estado do Rio de Janeiro

Centro Biomédico

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Eliane de Paula Mendonça

Transtorno do estresse pós-traumático e alterações lipídicas

Rio de Janeiro

2014

Eliane de Paula Mendonça

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Dissertação apresentada como requisito parcial para obtenção do título de mestre, ao Programa de Pós-Graduação em Saúde Coletiva do Instituto de Medicina Social da Universidade do Estado do Rio de Janeiro. Área de concentração: Epidemiologia.

Orientador: Prof. Dr. Evandro da Silva Freire Coutinho

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2014

CATALOGAÇÃO NA FONTE
UERJ/REDE SIRIUS/CB/C

M539 Mendonça, Eliane de Paula
Transtorno do estresse pós-traumático e alterações
lipídicas / Eliane de Paula Mendonça. – 2014.
89 f.

Orientador : Evandro da Silva Freire Coutinho.

Dissertação (mestrado) – Universidade do Estado do Rio de
Janeiro, Instituto de Medicina Social.

1. Stress pós-traumático - Teses. 2. Colesterol - Teses. 3.
Stress pós-traumático - Tratamento – Teses. 4. Sistema
cardiovascular - Doenças – Teses. I. Coutinho, Evandro da
Silva Freire. II. Universidade do Estado do Rio de Janeiro.
Instituto de Medicina Social. III. Título.

CDU 159.942.5:612.397

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Assinatura

Data

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Aprovada em 31 de Março de 2014.

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2014

DEDICATÓRIA

Aos meus pais, com amor.

AGRADECIMENTOS

Ao Evandro da Silva Freire Coutinho, pela disponibilidade, atenção, paciência, dedicação e, principalmente, pela serenidade na condução de sua orientação.

Ao Ivan Figueira pela agradável parceria nos trabalhos que deram origem a esta dissertação, sempre muito atencioso e dedicado.

À Deborah Maia por compartilhar sua pesquisa, pelo bom humor e pela ajuda prestada.

A todos os meus professores pelo conhecimento transmitido, pois foram fundamentais para a minha formação.

Ao Caio Sequeira Machado, por todo amor, carinho e compreensão. Não foi à toa que neste período foi promovido de namorado a noivo e de noivo a marido!

À minha família, em particular aos meus pais, que sempre me apoiaram e não mediram esforços para que eu pudesse chegar até aqui.

Aos meus amigos, em especial ao Pedro Batalha e à Sabrina Borges, por sempre me incentivarem e dividirem comigo não só as alegrias, mas também as tristezas. *“Alegria compartilhada é alegria em dobro. Tristeza compartilhada é tristeza pela metade”*.

Aos colegas de turma, em especial à Ana Luisa e à Tatiana Henriques, pelos momentos felizes e “traumáticos” partilhados no mestrado. Essa jornada foi muito mais divertida por ter sido com vocês.

RESUMO

MENDONÇA, Eliane de Paula. *Transtorno do Estresse Pós-Traumático e alterações lipídicas*. 2014. 89 f. Dissertação (Mestrado em Saúde Coletiva) – Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro. Rio de Janeiro. 2014.

O transtorno do estresse pós-traumático (TEPT) e alterações lipídicas são as temáticas principais dessa Dissertação. Seu objetivo principal foi investigar a associação entre o TEPT e as concentrações séricas de colesterol total (CT), lipoproteína de baixa densidade (LDL), lipoproteína de alta densidade (HDL) e triglicerídeos (TG) através de uma revisão sistemática da literatura seguida de metanálise. Adicionalmente, a relação entre essas variáveis lipídicas e os grupos de sintomas do TEPT – *revivescência*, *esquiva/entorpecimento emocional* e *hiperestimulação autonômica* – foi avaliada em um segundo estudo com dados primários. A metanálise incluiu 18 artigos, totalizando 2.110 indivíduos com TEPT e 17.550 indivíduos sem TEPT. As diferenças de médias ponderadas (DMP) – mg/dL – dos parâmetros lipídicos foram calculadas por modelos de efeitos aleatórios e modelos de meta-regressão foram ajustados para investigar possíveis fontes de heterogeneidade. O estudo encontrou que o TEPT foi associado a um pior perfil lipídico quando comparados a controles sem o transtorno ($DMP_{CT} = 20,57$, IC 95% 12,21 – 28,93; $DMP_{LDL} = 12,11$, IC 95% 5,89 – 18,32; $DMP_{HDL} = -3,73$, IC 95% -5,97 – -1,49; $DMP_{TG} = 35,87$, IC 95% 21,12 – 50,61). A heterogeneidade estatística entre os resultados dos estudos foi alta para todos os parâmetros lipídicos e a variável que mais pareceu explicar essas inconsistências foi idade. O segundo artigo faz parte de um estudo maior conduzido em 2004 com 157 policiais do sexo masculino do Batalhão de Choque da Polícia Militar do Estado de Goiás (BPMCHOQUE). Somente oficiais de férias ou em dispensa – inclusive dispensa médica – não foram avaliados. O instrumento utilizado para o rastreio do TEPT foi a versão em português para civis da *Post-Traumatic Stress Disorder Checklist* (PCL-C). Trinta e nove participantes (25%) foram excluídos do estudo: dois porque falharam no preenchimento dos questionários e 37 cujas amostras de sangue não foram coletadas por vários motivos. Neste trabalho, encontrou-se uma forte correlação positiva entre as concentrações séricas de CT e LDL com o grupo de sintomas de hiperestimulação autonômica, somente no grupo TEPT: $\rho = 0,89$ ($p < 0,01$) e $\rho = 0,92$ ($p < 0,01$), respectivamente. Em suma, espera-se que os resultados dessa Dissertação possam colaborar para o estabelecimento de um melhor acompanhamento clínico de pacientes com TEPT, particularmente porque estes parecem estar sob um maior risco de doenças cardiovasculares devido a um pior perfil lipídico.

Palavras-chave: Transtorno do estresse pós-traumático. Perfil lipídico. Colesterol total. LDL. HDL. Triglicerídeos. Doenças cardiovasculares. Metanálise. Hiperestimulação autonômica.

ABSTRACT

MENDONÇA, Eliane de Paula. Post-traumatic stress disorder and worsened serum lipid profile. 2014. 89 f. Dissertação (Mestrado em Saúde Coletiva) – Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro. Rio de Janeiro. 2014.

Post-traumatic stress disorder (PTSD) and lipid profile changes are the main themes of this Dissertation, whose main purpose was to investigate the association between PTSD and serum lipid concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and Triglycerides (TGs). Additionally, the relationship between these serum lipid parameters and PTSD symptom clusters - *re-experiencing, avoidance and hyperarousal* – was assessed in a second study with primary data. The meta-analysis included 18 articles, for an overall number of 2,110 people with PTSD and 17,550 individuals without PTSD. Pooled weighted mean differences (WMD) - mg/dL - of serum lipid parameters were calculated using random effects model and meta-regression models were fitted to investigate the sources of heterogeneity. The study showed that PTSD was associated with worsened lipid profile when compared to controls without PTSD (DMP_{CT}= 20.57, IC 95% 12.21 – 28.93; DMP_{LDL}= 12.11, IC 95% 5.89 – 18.32; DMP_{HDL}= -3.73, IC 95% -5.97 – -1.49; DMP_{TG}= 35.87, IC 95% 21.12 – 50.61). Statistical heterogeneity between the results of the studies was high for all lipid parameters and the variable that most explained these inconsistencies was age. The second article is part of a larger study conducted in 2004 with 157 active duty male police officers of an elite unit of the Police Force of the State of Goiás-Brazil (BPMCHOQUE). Only officers on vacation or on leave – including those on sick leave – were not assessed. The diagnostic tool applied to screen for PTSD was a Portuguese version of the PTSD Checklist – Civilian Version (PCL-C). Thirty nine (25%) participants were excluded: 2 respondents who failed to fill out the questionnaires and 37 whose blood samples were not collected for various reasons. The study found a significant and strong positive correlation between TC and LDL-C with hyperarousal symptom cluster, only in the full PTSD group: $\rho = 0.89$ ($p < .01$) and $\rho = 0.92$ ($p < .01$), respectively. As a synthesis, the results found in this Dissertation can contribute to a better clinical follow-up of PTSD patients, especially because they appear to be at higher risk for cardiovascular diseases due to worsened serum lipid profile.

Key-words: Post-traumatic stress disorder. Lipid profile. Total Cholesterol. LDL. HDL. Triglycerides. Cardiovascular diseases. Meta-analysis. Hyperarousal.

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LISTA DE ABREVIATURAS E SIGLAS

BPMCHOQUE	Batalhão de Choque da Polícia Militar
CRH	Hormônio Liberador de Corticotropina
CT	Colesterol Total
DCV	Doença Cardiovascular
DMP	Diferença de Médias Padronizadas
DP	Desvio Padrão
DSM	Manual Diagnóstico e Estatístico de Transtornos Mentais (do inglês <i>Diagnostic and Statistical Manual of Mental Disorders</i>)
EP	Erro Padrão
EPM	Eliane de Paula Mendonça
ESFC	Evandro da Silva Freire Coutinho
HDL	Lipoproteína de Alta Densidade (do inglês <i>High-Density Lipoprotein</i>)
HPA	Hipotálamo-Hipófise-Adrenal (do inglês <i>Hypothalamic-Pituitary-Adrenal</i>)
IDH	Índice de Desenvolvimento Humano
IF	Ivan Figueira
JUB	José Ueleres Braga
LDL	Lipoproteína de Baixa Densidade (do inglês <i>Low-Density Lipoprotein</i>)
mg/dL	Miligramas por decilitro
mmol/L	Mili mol por litro
N	Tamanho amostral
PCL-C	Versão para civis da <i>Post-Traumatic Stress Disorder Checklist</i>
RJ	Rio de Janeiro
SI	Sistema Internacional de Unidades (do francês <i>Système International d'unités</i>)
SP	São Paulo
sTF	Fator Solúvel de Tecido
TC	<i>Total cholesterol</i>
TEPT	Transtorno do Estresse Pós-Traumático
TG	Triglicerídeos
UERJ	Universidade Estadual do Rio de Janeiro

VWF Fator de Von Willebrand

WMD *Weighted Mean Difference*

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INTRODUÇÃO

A presente Dissertação - **Transtorno do Estresse Pós-Traumático e Alterações Lipídicas** - é composta de dois subprojetos: (i) *Transtorno do Estresse Pós-Traumático e pior perfil lipídico: Revisão Sistemática e Metanálise* e (ii) *Dislipidemia e Grupos de Sintomas do Transtorno do Estresse Pós-Traumático: uma relação dose-resposta com os sintomas de hiperestimulação autonômica*.

O primeiro estudo tem como objetivo investigar a associação entre o Transtorno do Estresse Pós-Traumático (TEPT) e a concentração sérica de lipídeos - colesterol total (CT), lipoproteína de baixa densidade (LDL), lipoproteína de alta densidade (HDL) e triglicérides (TG) - através de uma revisão sistemática da literatura seguida de metanálise.

O segundo estudo utilizou os dados primários de um projeto de acompanhamento psicológico e nutricional realizado em 2004 no Batalhão de Choque da Polícia Militar do Estado de Goiás (BPMCHOQUE). Este batalhão foi inicialmente escolhido por ser uma unidade especializada, acionada apenas em situações críticas. Neste trabalho, investigou-se a relação entre concentrações séricas de CT, LDL, HDL e TG com os diferentes grupos de sintomas do TEPT – *revivescência, esquiva e entorpecimento emocional e hiperestimulação autonômica* – em policiais da ativa.

Para apresentar a proposta de estudo e seus resultados, este documento está organizado em seis seções. A primeira seção define o Transtorno do Estresse Pós-Traumático (TEPT) e mostra suas principais opções de tratamento (1.1), distribuição (1.2) e sua relação com doenças cardiovasculares (CVD) e a dislipidemia (1.3). Em seguida, as seções 2 e 3 trazem a justificativa e os objetivos dessa dissertação, respectivamente.

A quarta seção deste trabalho (MATERIAL E MÉTODOS) traz informações sobre os aspectos metodológicos referentes aos dois trabalhos que deram origem a essa dissertação, com o intuito de fornecer ao leitor um maior detalhamento sobre as atividades que antecederam a análise e a interpretação dos dados.

A quinta e sexta seções contemplam os produtos dessa dissertação, apresentados na forma de dois artigos originais em vias de submissão para publicação.

Tendo como base os objetivos propostos, as considerações finais do projeto vêm para contextualizar e sintetizar o impacto potencial dos achados para a diminuição da morbimortalidade por doenças cardiovasculares decorrentes de alterações lipídicas em indivíduos com TEPT. Por fim, são apresentados os apêndices referentes ao primeiro estudo:

i. formulário de extração de dados dos estudos incluídos na metanálise (APÊNDICE A), ii. adaptação da *Newcastle–Ottawa scale* (NOS) para estudos de coortes utilizada para aferir a qualidade dos estudos seccionais (APÊNDICE B); e os anexos do segundo artigo: iii. termo de consentimento livre e esclarecido (ANEXO A), iv. questionário aplicado para o rastreamento do TEPT, a versão em português para civis da *Post-Traumatic Stress Disorder Checklist* (PCL-C) (ANEXO B).

1 O TRANSTORNO DO ESTRESSE PÓS-TRAUMÁTICO

De acordo com a quarta edição do Manual Diagnóstico e Estatístico de Transtornos Mentais, o DSM-IV, o Transtorno do Estresse Pós-Traumático (TEPT) é classificado como um transtorno de ansiedade, e seu diagnóstico é baseado em seis critérios (A-F) necessariamente presentes (Quadro 1). (DSM-IV)

O critério A define o transtorno como uma condição decorrente de um evento traumático reconhecível como um atentado à integridade física, própria ou alheia, que tenha sido experimentado direta ou indiretamente pela pessoa afetada e que tenha envolvido intenso medo, sensação de impotência e horror. (DSM-IV)

Três grupos de sintomas (critérios B, C e D) caracterizam o transtorno: *revivescência, esquiva e entorpecimento emocional e hiperestimulação autonômica*. (Figueira & Mendlowicz, 2003) Pelo menos, um dos cinco sintomas de *revivescência*, três dos sete de *esquiva* e dois dos cinco de *hiperestimulação* devem ser relatados ou observados pelo indivíduo. (DSM-IV)

O diagnóstico do transtorno é confirmado quando a duração da perturbação (sintomas dos critérios de *revivescência, esquiva e entorpecimento emocional e hiperestimulação autonômica*) é superior a um mês (critério E) e quando existe sofrimento clinicamente significativo ou prejuízo no funcionamento social ou ocupacional ou em outras áreas importantes da vida do indivíduo (critério F). (DSM-IV)

O TEPT é classificado como *agudo* se a duração dos sintomas é inferior a três meses, *crônico* se a duração dos sintomas é superior a três meses, e *com início tardio* se o início dos sintomas ocorre pelo menos seis meses após o evento estressor. (DSM-IV)

Quadro 1. Critérios diagnósticos do TEPT segundo o DSM-IV.

- A. Exposição a um evento traumático no qual os seguintes quesitos estiveram presentes:
1. A pessoa vivenciou, testemunhou ou foi confrontada com um ou mais eventos que envolvem morte ou grave ferimento, reais ou ameaçadores, ou uma ameaça à integridade física própria ou a de outros;
 2. A resposta da pessoa envolveu intenso medo, impotência ou horror.
- B. O evento traumático é persistentemente revivido em uma (ou mais) das seguintes maneiras:
1. Recordações aflitivas, recorrentes e intrusivas do evento, incluindo imagens, pensamentos ou percepções;
 2. Sonhos aflitivos e recorrentes com o evento;
 3. Agir ou sentir como se o evento traumático estivesse ocorrendo novamente (inclui um sentimento de revivência da experiência, ilusões, alucinações e episódios de *flashbacks* dissociativos);
 4. Sofrimento psicológico intenso quando da exposição a indícios internos ou externos que simbolizam ou lembram algum aspecto do evento traumático;
 5. Reatividade fisiológica na exposição a indícios internos ou externos que simbolizam ou lembram algum aspecto do evento traumático.
- C. Esquiva persistente de estímulos associados com o trauma e entorpecimento da responsividade geral (não presente antes do trauma), indicados por três ou mais dos seguintes quesitos:
1. Esforços no sentido de evitar pensamentos, sentimentos ou conversas associados com o trauma;
 2. Esforços no sentido de evitar atividades, locais ou pessoas que ativem recordações do trauma;
 3. Incapacidade de recordar algum aspecto importante do trauma;
 4. Redução acentuada do interesse ou da participação em atividades significativas;
 5. Sensação de distanciamento ou afastamento em relação a outras pessoas;
 6. Faixa de afeto restrita;
 7. Sentimento de um futuro abreviado (não espera ter uma carreira profissional, casamento, filhos ou período normal da vida).
- D. Sintomas persistentes de excitabilidade aumentada (não presentes antes do trauma), indicados por dois (ou mais) dos seguintes quesitos:
1. Dificuldade em conciliar ou manter o sono;
 2. Irritabilidade ou surtos de raiva;
 3. Dificuldade em concentrar-se;
 4. Hipervigilância;
 5. Resposta de sobressalto exagerada.
- E. A duração da perturbação (sintomas dos critérios B, C, e D) é superior a 1 mês.
- F. A perturbação causa sofrimento clinicamente significativo ou prejuízo no funcionamento social ou ocupacional ou em outras áreas importantes da vida do indivíduo.

Alguns trabalhos têm demonstrado que indivíduos com TEPT são mais suscetíveis ao divórcio, a reportar problemas em criar seus filhos, a envolver-se em agressões entre parceiros íntimos, a ter depressão e outros problemas psicológicos, a reportar pior qualidade de vida e problemas físicos de saúde, a envolver-se com o sistema judiciário, a ganhar menos e a trocar frequentemente de emprego. (Koss, et al., 1991; Jordan, et al., 1992; Walker, et al., 2003; Schnurr & Green, 2004) O TEPT, portanto, não é somente de uma condição bastante limitante para o indivíduo portador, mas que também afeta negativamente as pessoas em seu convívio e a comunidade num geral.

1.1 Tratamento

Dentre as atuais opções de tratamento do TEPT, destacam-se a Terapia Cognitivo-Comportamental (TCC), o uso de medicações antidepressivas e, mais recentemente, de drogas antiadrenérgicas. (Keane, et al., 2006) Devido sua relação mais estreita com o tema do projeto, somente o uso de antiadrenérgicos será comentado a seguir.

Consistente com a manifestação clínica de “hipervigilância persistente”, pacientes com TEPT exibem alterações na atividade nervosa autonômica, com aumento da função simpática e diminuição da parassimpática. (Wentworth, et al., 2013) Esse desequilíbrio autonômico com níveis mais elevados de catecolaminas – adrenalina, noradrenalina – aumenta o risco de aterosclerose e DCV por diferentes mecanismos e será abordado com mais detalhes na subseção 1.3.

Com o intuito de diminuir os efeitos deletérios na saúde causados pela crônica hiperativação simpática, o uso de agentes antiadrenérgicos tem recebido cada vez mais a atenção de médicos e pesquisadores tanto para o manejo de sintomas quanto para a prevenção do TEPT. Por exemplo, o alfa bloqueador prazosina demonstrou ser eficaz na redução do número de pesadelos, na melhora do sono, e também na redução geral de sintomas do TEPT. (Raskind, et al., 2003; Raskind, et al., 2007; Hudson, et al., 2012; Jeffreys, et al., 2012; Schoenfeld, et al., 2012; Raskind, et al., 2013) Já o beta bloqueador propranolol mostrou ser capaz de atenuar a memória traumática. (Tawa & Murphy, 2013) De acordo com o exposto, recentemente foi relatado que beta bloqueadores poderiam reduzir a incidência de TEPT, o que reforçaria a importância do desequilíbrio autonômico presente no transtorno e o uso potencial desses agentes como opção de tratamento. (Friedman, 2012)

1.2 Distribuição

Com o reconhecimento do impacto socioeconômico relacionado a morbidades psicológicas, há um aumento do interesse na investigação das estimativas regionais e mundiais de transtornos psiquiátricos, como o TEPT. (Leitão-Azevedo, et al., 2007)

Recentemente, Cabizuca (Cabizuca, 2013) estimou a prevalência mundial do TEPT na população geral através de uma revisão sistemática da literatura e metanálise. A prevalência combinada de TEPT na vida foi de 9% na América do Norte (n=5), 3% na Europa (n=11), 6% na América Central (n=2), América do Sul (n=3) e Oceania (n=1), 2% na África (n=2) e Oriente Médio (n=3) e 1% na Ásia (n=2).

Uma das maiores limitações na literatura do TEPT é a lacuna de estudos realizados com indivíduos em países de baixa e média renda, particularmente porque esses parecem estar sob um maior risco de sofrer eventos traumáticos. (de Girolamo & McFarlane, 1996) Ribeiro e colaboradores (Ribeiro, et al., 2013) estudaram a relação entre eventos traumáticos e a prevalência de transtornos mentais nas cidades de São Paulo (SP) e do Rio de Janeiro (RJ). O estudo transversal realizado entre 2007-2008 contou com 3744 entrevistas (2536 em SP e 1208 no RJ). Ao passo que aproximadamente 90% dos participantes já haviam vivenciado algum evento traumático, as estimativas do TEPT encontradas foram de 10% e 8,7% de prevalência na vida e 5% e 3,3% de prevalência no último ano para as cidades de SP e RJ, respectivamente.

1.3 TEPT, doenças cardiovasculares e pior perfil lipídico

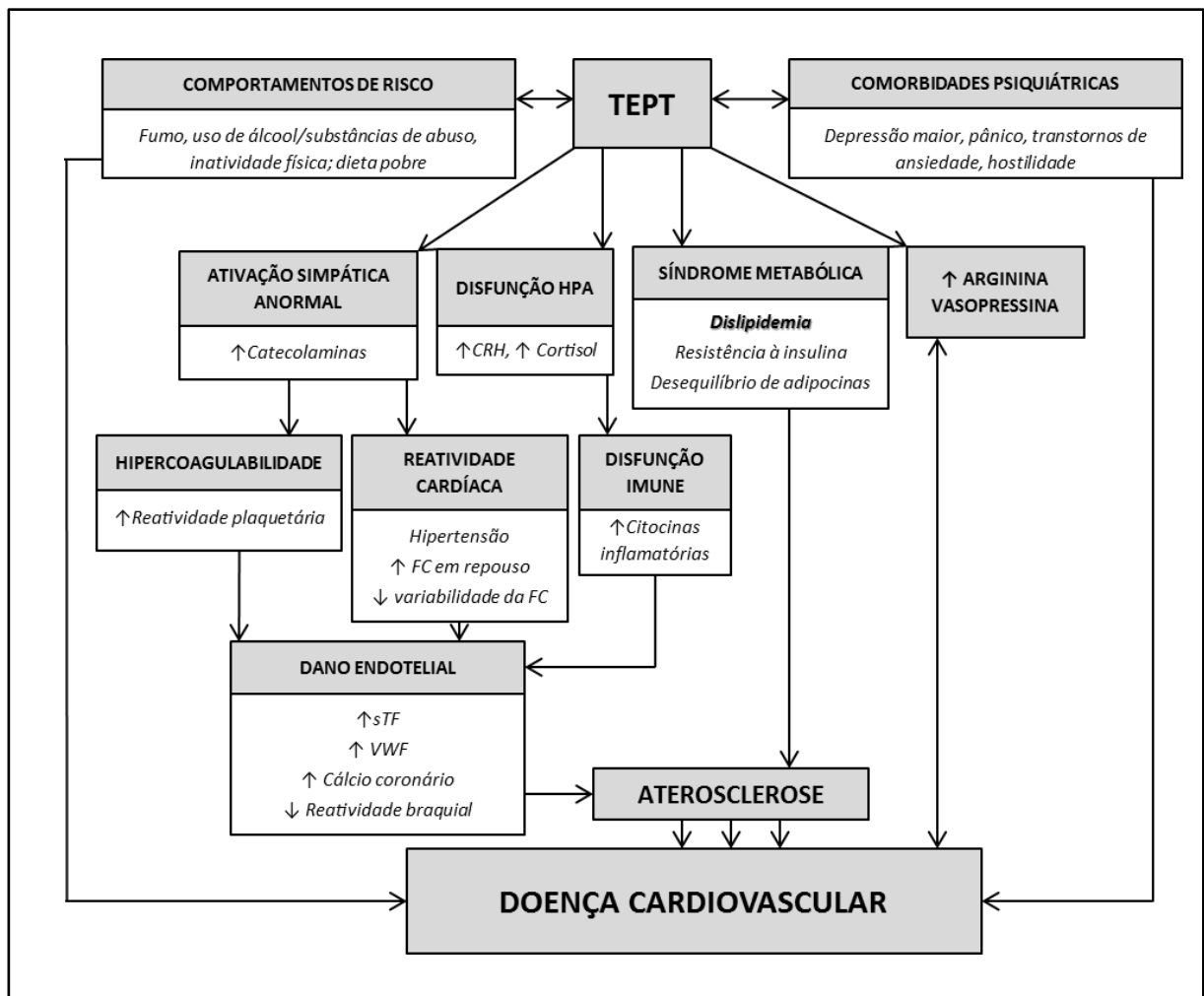
Além de causar grande prejuízo de âmbito psicossocial, o TEPT é também um fator de risco bem estabelecido para diversos desfechos negativos de saúde física, especialmente doenças cardiovasculares (DCV). (Boscarino, 2004; Dedert, et al., 2010) Estudos prospectivos de grande porte têm consistentemente demonstrado a associação entre o TEPT, DCV e mortalidade. (Kubzansky, et al., 2007; Boscarino, 2008; Scherrer, et al., 2010; Ahmadi, et al., 2011; Coughlin, 2011; Jordan, et al., 2011)

Jordan e colaboradores (Jordan, et al., 2011) examinaram as associações entre a exposição relacionada ao atentado de 11 de setembro de 2001, o TEPT, e o desenvolvimento subsequente de doenças do coração em um estudo prospectivo com 39.324 participantes. Neste estudo o TEPT foi associado a um risco elevado de doenças do coração, observando-se

uma relação dose-resposta com os sintomas do transtorno. Em outro estudo prospectivo, Ahmadi e colaboradores reportaram que o TEPT foi associado com a presença e a gravidade de aterosclerose coronariana, sendo preditor de mortalidade, independente de idade, sexo e outros fatores de risco já reconhecidos. (Ahmadi, et al., 2011)

Dado a consistência dos achados encontrados na literatura acerca do TEPT e DCV, diversos mecanismos patofisiológicos que conectam esses dois problemas de saúde têm sido propostos.

A figura 1 apresenta o modelo teórico sugerido por Wentworth e colaboradores (Wentworth, et al., 2013) com potenciais caminhos para o desenvolvimento de doenças cardiovasculares a partir do TEPT.



Conforme exposto, a dislipidemia é um dos fatores que pode mediar a relação entre o TEPT e DCV. A investigação acerca de mudanças nas concentrações lipídicas séricas em indivíduos acometidos por TEPT teve início a partir de observações clínicas e resultados de estudos epidemiológicos que indicaram um aumento da morbimortalidade cérebro/cardiovascular em sobreviventes de traumas prolongados e estresse de combates. (Kleinman, et al., 1992; Curin, 1996; Dimitrijevic, et al., 1999; Kadojic, et al., 1999; Koupil, et al., 2007) Diversos estudos têm demonstrado um pior perfil lipídico em populações com TEPT quando comparados a controles sem o transtorno (Kagan, et al., 1999; Karlovic, et al., 2004a; Karlovic, et al., 2004b; Trief, et al., 2006; Maia, et al., 2008; Heppner, et al., 2009; Jin, et al., 2009; Von Kanel, et al., 2010; Linnville, et al., 2011; Walczewska, et al., 2011). Os mecanismos propostos para explicar a relação entre o TEPT e um pior perfil lipídico geralmente envolvem a disfunção do eixo hipotálamo-hipófise-adrenal (HPA), o aumento da atividade nervosa simpática, a disfunção imune e fatores de risco comportamentais relacionados ao transtorno. (Kario, et al., 2003; Wentworth, et al., 2013) Como resultado da ativação crônica do eixo HPA, níveis mais baixos de cortisol plasmático e mais elevados de citocinas inflamatórias – ex. interleucina (IL)-6 fator de necrose tumoral (TNF)- α – são comumente observados em indivíduos com TEPT. (Wentworth, et al., 2013) Essas duas alterações são conhecidas por desregular o metabolismo de lipídeos. (Black, 2003; Fries, 2008) Além disso, a ativação crônica desse eixo também é associada a comer em excesso e à obesidade. (Dallman, et al., 2004; Nishitani & Sakakibara, 2006)

O aumento da ativação simpática com níveis mais elevados de catecolaminas – adrenalina, noradrenalina – pode impactar diretamente nas concentrações séricas de lipídeos por diferentes mecanismos. Sabe-se que a noradrenalina além de inibir a atividade da proteína lipase sanguínea – levando à diminuição da depuração de TG, diminuição dos níveis de HDL e aumento de LDL – também reduz a atividade da lipase hepática de triglicerídeos, promovendo um aumento na concentração sanguínea de lipoproteínas ricas em TG. (Stoney, 2007) Em adição, as catecolaminas estimulam diretamente a liberação para a corrente sanguínea de ácidos graxos livres e glicerol a partir de depósitos de gordura. (Stoney, 2007)

Outros caminhos plausíveis entre o TEPT e um pior perfil lipídico são através de distúrbios do sono, uma queixa bastante comum entre indivíduos com o transtorno. Por exemplo, sabe-se que o prejuízo do sono leva à diminuição dos níveis de leptina e aumento dos níveis de grelina, o que resulta em aumento da fome e do apetite. (Spiegel, et al., 2004; Pejovic, et al., 2010) Logo, mudanças na ingesta alimentar devem ser consideradas e podem

piorar o perfil lipídico. Em adição, a privação do sono aumenta os níveis de hidrocortisona e quando cronicamente elevada, favorece a deposição de gordura nos vasos sanguíneos e no abdômen. (McEwen, 2002)

Por fim, mas não menos importante, alguns fatores de risco comportamentais relacionados ao TEPT como o fumo, o uso de álcool e outras drogas, a atividade física diminuída, a má alimentação e o baixo auto-cuidado (Keane, et al., 2006; Dedert, et al., 2010; Wentworth, et al., 2013) também podem impactar negativamente nas concentrações séricas de lipídeos.

2 JUSTIFICATIVA

Primeiramente, a pertinência desse projeto baseia-se na alta prevalência na vida do Transtorno do Estresse Pós-Traumático (TEPT) e de suas consequências negativas sobre a saúde física e a qualidade de vida de seus portadores. Além da frequente presença de comorbidades psiquiátricas e da pobre resposta ao tratamento na maioria dos casos, a associação do TEPT com doenças cardiovasculares (DCV), principal causa de óbito no Brasil, surge como uma importante questão de saúde pública. Deve-se ainda considerar o impacto econômico gerado, seja pelo aumento do uso de serviços de saúde ou pela diminuição da capacidade laboral dos indivíduos acometidos por essa condição.

É crescente a informação científica disponível acerca do TEPT e alterações metabólicas, especialmente envolvendo desregulação lipídica. Para seu melhor aproveitamento, é importante que essas informações sejam transformadas em conhecimento, isto é, que tais informações sejam reunidas, organizadas, criticamente avaliadas e quantitativamente mensuradas.

O trabalho intitulado *Transtorno do Estresse Pós-Traumático e pior perfil lipídico: Revisão Sistemática e Metanálise* visa aumentar a precisão das estimativas de associação entre essas duas condições e, sobretudo, identificar e discutir as possíveis razões de resultados conflitantes. Por ser um transtorno bastante heterogêneo, a separação dos diferentes subgrupos clínicos do TEPT parece ser uma estratégia de pesquisa profícua para um melhor entendimento da relação entre o TEPT, a dislipidemia e doenças cardiovasculares. Sendo assim, estudos orientados nessa direção podem auxiliar na identificação de indivíduos sob um maior risco de desenvolvimento de DCV.

Seguindo o exposto, o trabalho intitulado *Dislipidemia e Grupos de Sintomas do Transtorno do Estresse Pós-Traumático: uma relação dose-resposta com os sintomas de hiperestimulação autonômica* avaliou a associação entre a concentração lipídica sérica e os diferentes grupos de sintomas do TEPT - *revivescência, esquiva e entorpecimento emocional e hiperestimulação autonômica* - em uma amostra urbana de policiais civis de Goiânia, regularmente exposta a incidentes críticos. Corroborada a hipótese levantada da associação do TEPT com um pior perfil lipídico, sugestões para a modificação dos protocolos de atendimento a pacientes com esta condição poderiam ser propostas, visando uma atenção mais adequada e um melhor acompanhamento clínico desses indivíduos que estariam sob um maior risco de DCV.

A implantação de uma rotina de mapeamento do perfil lipídico de indivíduos com TEPT, assim como a realização de medidas preventivas no intuito de diminuir o risco de aterosclerose e suas consequências, poderiam proporcionar uma diminuição da morbimortalidade entre seus pacientes.

3 OBJETIVOS

3.1 Geral

Investigar a associação entre o TEPT e a concentração sérica das seguintes variáveis lipídicas: i. colesterol total (CT); ii. lipoproteína de baixa densidade (LDL); iii. lipoproteína de alta densidade (HDL); iv. triglicerídeos (TG) através de uma revisão sistemática da literatura seguida de metanálise.

3.2 Específicos

Identificar variáveis que expliquem, pelo menos em parte, a heterogeneidade dos resultados dos estudos que investigaram a relação entre TEPT e perfil lipídico;

Investigar a relação entre as concentrações sanguíneas de CT, LDL, HDL e TG e os grupos de sintomas do TEPT - *revivescência*, *esquiva/entorpecimento emocional* e *hiperestimulação autonômica* - em uma amostra regularmente exposta a incidentes críticos.

4 MATERIAL E MÉTODOS

4.1 Estudo 1 - Transtorno do Estresse Pós-Traumático e pior perfil lipídico: Revisão Sistemática e Metanálise

4.1.1 Desenho

Foi realizada uma revisão sistemática seguida de metanálise de acordo com o protocolo *Preferred Reporting Items for Systematic Review and Metaanalyses* (PRISMA) (Liberati, et al., 2009).

4.1.2 Protocolo

Com o intuito de definir, acompanhar e documentar todos os passos a serem executados na presente revisão, elaborou-se inicialmente um protocolo que foi avaliado e aprimorado pela banca de qualificação deste projeto (ESFC, IF, JUB).

4.1.3 Critérios de elegibilidade

Tipo de estudo

A busca foi aberta a todos os estudos que tivessem um grupo controle, sendo estes de coortes, caso-controle ou seccionais.

Tipo de participante

Foram incluídos os estudos com adultos acima de 21 anos, de ambos os sexos.

Variável de exposição

A variável de exposição foi o Transtorno do Estresse Pós-Traumático (TEPT), desde que diagnosticado por médico psiquiatra ou através de instrumentos validados baseados no Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM III, III-R e IV) ou na Classificação Internacional de Doenças (CID – 10).

Grupos de comparação

Foram incluídos os estudos cujo grupo de comparação era constituído de indivíduos sem diagnóstico de TEPT. Aqueles formados por portadores de outras doenças psiquiátricas não foram excluídos da análise.

Desfecho

O desfecho de interesse foi o perfil lipídico: concentrações séricas de colesterol total (CT), lipoproteína de baixa densidade (LDL), lipoproteína de alta densidade (HDL) e triglicerídeos (TG).

4.1.4 Estratégias da busca

Foram pesquisadas as bases eletrônicas ISI/Thomson Reuters, PILOTS, PsycINFO, PubMed e LILACS para a captura dos artigos. A busca abrangeu os trabalhos publicados até outubro de 2012 (artigos na íntegra, resumos, dissertações/teses) e foi expandida às referências dos mesmos. A princípio não houve restrição quanto ao idioma. A chave da busca utilizada foi (ptsd OR "stress disorder*") AND (cholesterol OR triglycerides OR LDL OR HDL OR metabolic OR dyslipidemi* OR hyperlipidemi* OR hypercholesterolemi* OR lipid*).

4.1.5 Processo de seleção e coleta dos dados

Uma seleção preliminar foi conduzida com base na leitura dos títulos e resumos dos artigos. Quando havia dúvidas sobre o preenchimento dos critérios de elegibilidade, o artigo completo era avaliado. Em seguida, construiu-se um formulário de extração de informações (ANEXO A1) para os artigos selecionados, incluindo:

- a. Referência bibliográfica
- b. Ano de publicação
- c. Local de estudo
- d. Tipo de publicação – Artigo na íntegra; Resumo; Estudo não publicado; Dissertação/Tese; Outro
- e. Desenho do estudo – Coorte; Seccional; Caso-controle
- f. Perfil dos participantes – Representativos da população geral; População específica (ex. veteranos)

- g. Número de participantes
- h. Proporção de homens
- i. Fonte dos controles – A mesma que deram origem aos casos; Diferente
- j. Idade
- k. Instrumento diagnóstico para o TEPT – Entrevista estruturada; Escala auto preenchida; Médico psiquiatra
- l. Comorbidades psiquiátricas no grupo TEPT – Presente; Ausente
- m. Comorbidades psiquiátricas no grupo controle – Presente; Ausente
- n. Características do trauma – Misto; Específico
- o. Método de ajuste – Restrição; Pareamento; Estratificação; Modelagem
- p. Variáveis controladas
- q. Médias dos parâmetros lipídicos de interesse e respectivas medidas de dispersão
- r. Percentual de perdas
- s. Conflito de interesse – Declarado; Não declarado

Um autor (EPM) extraiu os dados dos estudos incluídos e outro autor (ESFC) reavaliou essas informações. Discordâncias foram resolvidas por consenso entre os dois. Na ausência de informações necessárias para a análise, os autores dos artigos selecionados foram contatados. No intuito de evitar dupla contagem de dados de uma mesma amostra publicados em estudos diferentes, os nomes dos autores foram justapostos e as características das amostras comparadas. Em paralelo foi permitido que um mesmo estudo participasse mais de uma vez na análise, desde que tivesse mais de um grupo TEPT e mais de um grupo controle que atendessem aos critérios de inclusão. Caso houvesse mais de um grupo controle para um mesmo grupo TEPT, a escolha daquele baseou-se nos critérios de idade mais próxima e uso mais balanceado de estatinas e antipsicóticos.

4.1.6 Avaliação da qualidade dos estudos

Foi realizada uma adaptação da escala *Newcastle-Ottawa Scale* (NOS) para estudos de coorte para aferir a qualidade dos estudos seccionais (ANEXO A2). Esta etapa foi realizada por dois avaliadores trabalhando em conjunto (EPM, ESFC). A representação gráfica desta qualidade fez uso de uma adaptação dos gráficos de risco de vieses propostos no *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins JPT).

4.1.7 Análise dos dados

Inicialmente investigou-se a simetria da distribuição dos dados utilizando-se a proposta de Altman e Bland (Altman & Bland, 1996): para escalas que iniciam em zero, não há evidência de assimetria quando o dobro do desvio-padrão é menor que a média. As análises foram baseadas nas médias de lipídios - mg/dL - em cada grupo e respectivos desvios-padrão. Dois estudos forneceram o erro-padrão, que foi convertido em desvio-padrão segundo a fórmula: $DP = EP * \sqrt{N}$. Seis estudos apresentaram as concentrações séricas de lipídios em mmol/L que foram convertidas para mg/dL segundo o Sistema Internacional de Unidades (SI): as medidas de CT, LDL e HDL foram divididas por 0,02586 e as de TG por 0,01129. (Young, 1990)

Além da inspeção visual dos gráficos de *forest-plot*, a magnitude e significância da heterogeneidade foram avaliadas pela estatística I^2 de Higgins e pelo teste Q de Cochran, respectivamente (Borenstein, et al., 2009).

Para a obtenção das medidas-sumário (diferenças de médias entre grupos TEPT e não-TEPT em relação às variáveis CT, LDL, HDL e TG), os dados individuais dos estudos foram combinados por modelos de efeitos aleatórios. Os resultados foram representados graficamente através de *Forest Plots*.

Modelos de meta-regressão foram ajustados incluindo variáveis relativas às amostras e aos desenhos de estudo visando identificar possíveis fontes de heterogeneidade. As variáveis investigadas nessa etapa foram:

- a. Média de idade do grupo TEPT
- b. Proporção de homens no grupo TEPT
- c. Índice de Desenvolvimento Humano (IDH)
- d. Critério diagnóstico de TEPT - Entrevista estruturada; Escala auto preenchida; Médico psiquiatra
- e. Comorbidade psiquiátrica no grupo TEPT – Sim; Não
- f. Comorbidade psiquiátrica no grupo controle – Sim; Não
- g. Fonte dos controles – A mesma do grupo TEPT; Diferente
- h. Tipo de trauma – Relacionado à guerra ou combate; Outros
- i. Método de ajuste para confundimento – Nenhum; Restrição; Pareamento
- j. Variáveis de ajuste – Nenhuma; Sexo ou idade; Sexo e idade; Sexo, idade e outras

Os dados foram analisados utilizando o programa STATA/IC 12.0.

4.2 **Estudo 2 - Dislipidemia e Grupos de Sintomas do Transtorno do Estresse Pós-Traumático: uma relação dose-resposta com os sintomas de hiperestimulação autonômica.**

4.2.1 Desenho

Trata-se de um estudo seccional, com dados primários.

4.2.2 População

Participaram do estudo 157 policiais do gênero masculino da ativa do Batalhão de Choque da Polícia Militar do Estado de Goiás (BPMCHOQUE). O grupo foi restrito ao sexo masculino porque nenhuma policial feminina participava dos serviços operacionais da unidade no período.

4.2.3 Aspectos éticos

O projeto foi aprovado pelas Comissões de Ética em Pesquisa do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro e da Polícia Militar do Estado de Goiás. Todos os participantes assinaram termo de consentimento livre e esclarecido (ANEXO B1).

4.2.4 Medidas

Foi utilizada uma versão em Português para civis da *Post-Traumatic Stress Disorder Checklist* (PCL-C) (Berger, et al., 2004) para o rastreamento do TEPT (ANEXO B2). Para seu preenchimento, o examinado deve mensurar o quanto tem sido perturbado no último mês pelos sintomas descritos, utilizando uma escala de gravidade que varia de 1 a 5 (nada até muito). A PCL é uma ferramenta validada para o diagnóstico do TEPT. (Blanchard, et al., 1996) Os grupos “TEPT” e “não-TEPT” foram determinados segundo critério do DSM-IV: para “TEPT” foram considerados os scores iguais ou maiores que 3 (médio) para pelo menos um dos sintomas do grupo revivescência (grupo B), pelo menos 3 sintomas de esquiva/entorpecimento emocional (grupo C), e pelo menos 2 sintomas de hiperestimulação autonômica (grupo D). No primeiro dia da avaliação, a nutricionista entrevistou os voluntários sobre seus hábitos alimentares, consumo de álcool e tabaco, antes de qualquer orientação nutricional. Eles também foram solicitados a coletar as amostras de sangue após uma noite de

jejum. A punção venosa foi conduzida com os voluntários na posição sentada com um torniquete, entre 7:00h e 10:00h da manhã, após jejum de 12h.

4.2.5 Análise estatística

A correlação de Spearman foi estimada entre os parâmetros lipídicos e os grupos de sintomas do TEPT - *revivescência, esquiva/entorpecimento emocional e hiperestimulação autonômica*. Diferenças foram consideradas estatisticamente significativas para p-valores $<0,05$ e de significância limítrofe para a faixa $0,05 < p\text{-valor} < 0,10$.

5 ARTIGO 1: POST-TRAUMATIC STRESS DISORDER AND WORSENERED LIPID PROFILE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Resumo

Introdução: O transtorno do estresse pós-traumático (TEPT) é um fator de risco bem estabelecido para doenças cardiovasculares. Diversas pesquisas têm demonstrado um pior perfil lipídico em populações com TEPT, o que pode ser um elo importante entre o TEPT e doenças cardiovasculares. O objetivo desse estudo foi investigar a associação entre o TEPT e concentrações séricas de colesterol total (CT), lipoproteína de baixa densidade (LDL), lipoproteína de alta densidade (HDL) e triglicerídeos (TG), assim como identificar modificadores de efeito dessa relação. **Métodos:** Realizou-se uma revisão sistemática da literatura através das bases eletrônicas ISI/Thomson Reuters, PILOTS, PsycINFO, PubMed e LILACS. Uma adaptação da *Newcastle-Ottawa Scale* (NOS) para estudos de coorte foi realizada para avaliar a qualidade dos estudos seccionais. As diferenças de médias ponderadas (DMP) dos parâmetros lipídicos foram calculadas usando modelos de efeitos aleatórios e modelos de meta-regressão foram ajustados para investigar possíveis fontes de heterogeneidade. **Resultados:** Dezoito estudos atenderam aos critérios de inclusão, totalizando 2.110 indivíduos com TEPT e 17.550 controles sem TEPT. As DMP – mg/dL – para concentrações séricas de lipídeos e respectivos intervalos de confiança de 95% foram: $DMP_{CT} = 20,57$ (12,21 – 28,93), $DMP_{LDL} = 12,11$ (5,89 – 18,32), $DMP_{HDL} = -3,73$ (-5,97 – -1,49) e $DMP_{TG} = 35,87$ (21,12 – 50,61). A heterogeneidade estatística entre os estudos foi alta para todas as variáveis lipídicas e a variável que mais pareceu explicar as inconsistências entre os resultados foi idade.

Palavras-chave: TEPT, Colesterol, LDL, HDL, Triglicerídeos, Lipídeos, Metanálise.

Abstract

Background: Post-Traumatic Stress Disorder (PTSD) is a well-established risk factor for cardiovascular diseases. Several researches have shown worsened serum lipid profile in PTSD populations, which may be an important link between PTSD and cardiovascular diseases. We aimed to investigate the association between PTSD and serum lipid concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein

cholesterol (HDL-C) and Triglycerides (TGs), and also, to identify effect modifiers of this relationship. **Methods:** We performed a systematic review/meta-analysis searching ISI/Thomson Reuters, PILOTS, PsycINFO, PubMed and LILACS databases. We adapted the *Newcastle-Ottawa Scale* (NOS) for cohort studies to assess the quality of the cross-sectional ones. Pooled weighted mean differences (WMD) of serum lipid parameters were calculated using random effects model and meta-regression models were fitted to investigate the sources of heterogeneity. **Results:** Eighteen articles met inclusion criteria, for an overall number of 2,110 people with PTSD and 17,550 controls without PTSD. The WMD - mg/dL - for serum lipid concentrations and respective 95% confidence interval were: $WMD_{TC} = 20.57$ (12.21 – 28.93), $WMD_{LDL-C} = 12.11$ (5.89 – 18.32), $WMD_{HDL-C} = -3.73$ (-5.97 – -1.49) e $WMD_{TGs} = 35.87$ (21.12 – 50.61). Statistical heterogeneity between studies was high for all lipid parameters. The variable that most explained the inconsistency of the results was age.

Keywords: PTSD, Cholesterol, LDL-C, HDL-C, Triglycerides, Lipids, Meta-analysis.

Introduction

Posttraumatic stress disorder (PTSD) is not only associated to a wide variety of mental disorders but also to physical health impairments, especially cardiovascular diseases (CVD). (Boscarino, 2004; Dedert, et al., 2010; Boscarino, 2011; Jordan, et al., 2011; Boscarino, 2012) Some large prospective studies have shown that people suffering from this disorder are at higher risk of CVD and mortality. (Kubzansky, et al., 2007; Boscarino, 2008; Scherrer, et al., 2010; Ahmadi, et al., 2011; Coughlin, 2011; Jordan, et al., 2011) Although the evaluation of mechanisms linking both of these conditions deserves further investigation, several behavioral, psychosocial and biological mechanisms have been proposed to explain the relationship between PTSD and CVD. (Edmondson, et al., 2013; Wentworth, et al., 2013)

Dyslipidemia is a well-established risk factor for atherosclerosis and consequently for CVD (Fruchart, et al., 2004). Several researches have shown worsened serum lipid profile – higher levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and lower levels of high-density lipoprotein cholesterol (HDL-C) – in both veteran and civilian PTSD populations. (Kagan, et al., 1999; Karlovic, et al., 2004a; Karlovic, et al., 2004b; Trief, et al., 2006; Maia, et al., 2008; Heppner, et al., 2009; Jin, et al., 2009; Von Kanel, et al., 2010; Linnville, et al., 2011; Walczewska, et al., 2011) However,

some studies have shown inconclusive results and the knowledge concerning the relationship between PTSD and lipid profile is not robust. Accordingly, the purpose of this work is to systematically investigate the association of PTSD with serum lipid profile and to identify potential factors that can modify this association. If the hypothesis of worsened serum lipid profile in PTSD populations is confirmed, together with a better understanding of possible effect modifiers of this relationship, a more appropriate medical monitoring should be proposed aiming to improve health and life expectancy of individuals with PTSD.

Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. (Liberati, et al., 2009) First, we elaborated a protocol to specify and document the procedures to be used in the investigation.

Eligibility criteria

The literature search was opened to all types of studies with a control group i.e. cohort, case-control and cross-sectional designs. We considered male and female adults for the analyses. We only included studies that used a validated diagnostic/screening tool for PTSD - based on the Diagnostic and Statistical Manual of Mental Disorders (DSM III, III-R and IV) or the International Classification of Diseases (ICD 10) – or the ones in which PTSD was diagnosed by a psychiatrist.

Search of studies

We performed a bibliographic search of Thomson Reuters Web of Knowledge (formerly ISI), PILOTS, PsycINFO, PubMed and LILACS electronic databases. We did not apply any restriction regarding to language, publication date or publication status. Last search was run on 16 October 2012. We used the following search strategy: (ptsd OR "stress disorder*") AND (cholesterol OR triglycerides OR LDL OR HDL OR metabolic OR dyslipidemi* OR hyperlipidemi* OR hypercholesterolemi* OR lipid*). We also hand-searched the reference lists of all included articles to ensure a comprehensive coverage.

Study selection

An initial screening was conducted by reading titles and abstracts. If doubts about the fulfillment of inclusion criteria still remained, the full text of paper was assessed. This stage

was performed by one review author (EPM). When in doubt, a second author (ESFC) was consulted.

Data extraction

We developed a data extraction sheet including the most relevant information about the samples and study design. One author (EPM) extracted the data from included studies and a second author (ESFC) checked these information. Disagreements were solved by discussion between the two reviewers. We contacted one author requesting numerical data that had only been presented graphically in his paper. As we got no response, we had to exclude this study from analysis. To avoid double counting and piecing together data from multiple reports of the same study, we juxtaposed author names and compared the general features of samples and study design. In parallel, we allowed the same study to participate twice in the analyses if there were two different PTSD groups and two different control groups that met inclusion criteria. If there was more than one control group, we chose the one most similar to the PTSD group as regard as age, use of lipid-lowering drugs and/or psychotropic medication.

We extracted information from each selected study including: (i). characteristics of the participants (e.g. age, gender, sample size, type of trauma, psychiatric comorbidities and representativeness of general population); (ii) characteristics of the study (e.g. year and type of publication, local, study design, source of controls, method of diagnosis, controlled variables and method for adjustment, proportion of loss and conflict of interest); (iii) outcome measurement: mean values of serum lipid concentrations and respective measures of dispersion.

Methodological quality of individual studies

To assess the quality of selected studies, we adapted the Newcastle-Ottawa scale (NOS) for cohort studies into the cross-sectional design. Although a few studies were longitudinal, they were evaluated as cross-sectional because lipid data were only depicted once. We graphically represented this quality using the Review Manager (RevMan) software adapting the graphs of risk of bias proposed in Higgins & Green (Higgins JPT). This entire section was conducted by two authors working together (EPM and ESFC), and disagreements were solved by consensus.

Statistical analysis

The pooled measures - weighted mean differences (WMD) - were obtained by random effect models. To investigate the symmetry of data distribution, we followed Altman & Bland's proposition: when a scale starts from zero, the standard deviation, when multiplied by two, is less than the mean. (Altman & Bland, 1996) Data from six studies were originally presented using mmol/L and were converted to mg/dL according to the International System of Units (SI). (Young, 1990) In two studies the standard deviation was obtained from the standard-error using the formula: $SD = SE * \sqrt{N}$. Heterogeneity between studies was initially evaluated by visual inspection of forest-plots. Statistical significance of heterogeneity was assessed by Q-test whilst the proportion of true heterogeneity to total variance was calculated by the Higgins I^2 statistic. (Borenstein, et al., 2009) We adjusted models of meta-regression including variables related to the samples and study design aiming to identify possible sources of inconsistency – *heterogeneity* – between the studies. We also conducted post-hoc sensitivity analyses to evaluate the impact of removing/including studies on the pooled measures. Data was analyzed using Stata/IC 12.0 software.

Direction of graphs

All association measures were calculated as the mean differences (MD) of serum lipid concentrations between PTSD and non-PTSD groups. Thus, MD>0 for TC, LDL-C and TGs and MD<0 for HDL-C indicate a worsened serum lipid profile in PTSD populations. In the forest-plots, this means that the pooled measure will be on the right of the line of no effect for TC, LDL-C and TGs and on the left for HDL-C.

Results

Study selection

A total of 167, 159, 131, 110, and 9 studies were found in ISI/Thomson Reuters, PubMed, PILOTS, PsycINFO, and LILACS electronic databases, respectively. After duplicates were removed, a first screening based on titles and abstracts identified 36 articles as potentially relevant. At this point, one Japanese study was discarded because it could not be feasibly translated. Then, we assessed the full text of the 35 remaining papers and 17 were excluded: 16 did not meet inclusion criteria and one assessed the same sample of another selected article. Finally, 18 studies met inclusion criteria and were included in the meta-analysis. These studies originated 19 comparison groups (15 for TC, 15 for LDL-C, 18 for

HDL-C and 19 for TGs). No unpublished relevant studies were identified. The flow diagram of study selection is depicted in Figure 1.

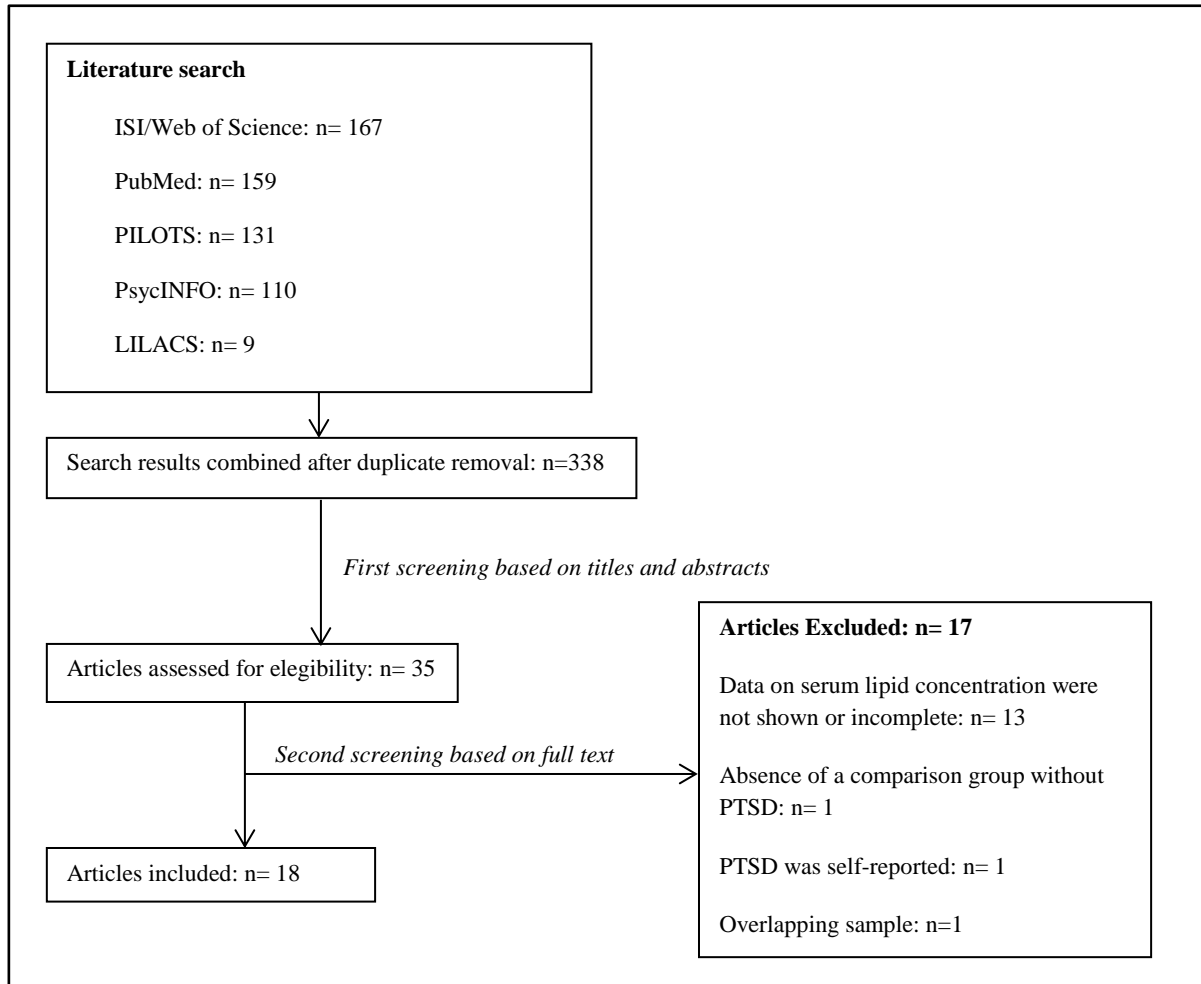


Figure 1: Flow diagram of search results. PTSD: posttraumatic stress disorder.

Study characteristics:

All 18 studies selected for meta-analysis had cross-sectional data and were published in English. The years of publication ranged from 1997 to 2012. Nine articles were from United States of America (USA), five from Croatia, two from Germany, one from Bosnia and Herzegovina, one from Brazil, one from Japan and one from Poland. Restrictions regarding to smoking, alcohol, drugs and medication usage (e.g. statins and antipsychotic) varied across studies. Detailed characteristics of included studies are presented in table 1.

Table 1. Characteristics of studies included in meta-analysis.

Reference	Country	Recruitment PTSD; control	Mean age \pm SD PTSD; control	Male gender PTSD; control	PTSD diagnosis	Lipid assessment	Main findings PTSD vs control	Matching	Medication, alcohol and tobacco
FILAKOVIC 1997	Croatia	32 hospitalized soldiers with PTSD; 32 hospitalized patients with psychoneurosis	34.1 \pm 7.1; 33 \pm 7.5	100% (overall sample)	PTSD Questionnaire according to DSM-III R, and Los Angeles Symptom Checklist (adult version-LASC 01)	Blood drawn in the morning after patients admission	TC: 239.75 \pm 42.54 vs. 204.95 \pm 34.8 LDL-C: 150.81 \pm 27.07 vs. 135.34 \pm 38.67 HDL-C: 38.67 \pm 11.6 vs. 50.27 \pm 7.73 TGs: 256.86 \pm 203.72 vs. 132.86 \pm 44.29	Age, sex and education	Not informed.
SOLTER 2002	Croatia	103 inpatients with combat-related PTSD; 92 inpatients with major depressive disorder	32.0 \pm 4.6; 33 \pm 5.1	100% (overall sample)	Structured clinical interview - Watson's PTSD interview based on DSM-III-R criteria.	Blood drawn in the morning after an overnight fast of 12h and serum concentrations for lipid variables were enzymatically determined.	TC: 252.9 \pm 47.95 vs. 208.82 \pm 42.15 LDL-C: 173.63 \pm 40.99 vs. 133.8 \pm 35.96 HDL-C: 37.12 \pm 6.96 vs. 44.47 \pm 9.28 TGs: 225.86 \pm 60.23 vs. 153.23 \pm 68.2	Age and BMI	Various medications, but none that influence serum lipid concentration. Nicotine dependence.
TOCHIGI 2002	Japan	8 civilians with PTSD due to Tokyo subway sarin poisoning; 34 healthy controls mainly recruited from staff of the Tokyo University Hospital.	45.5 \pm 16.8; 43.7 \pm 12.5	62.5%; 52.9%	Clinician-Administered PTSD Scale (CAPS).	Used standard methods of clinical laboratories.	TC: 186 \pm 25 vs. 194 \pm 43 LDL-C: 108 \pm 16 vs. 110 \pm 31 HDL-C: 64.6 \pm 11.8 vs. 64.4 \pm 16.5 TGs: ---	Age	Not informed.
KARLOVIC (a) 2004	Croatia	53 patients with combat-related PTSD; 49 soldiers without combat experience without PTSD or other psychiatric or medical problems.	34 \pm 5.4; 35 \pm 4.3	100% (overall sample)	Structured clinical interview based on DSM-IV; Watson's PTSD interview based on DSM-III-R criteria.	Blood drawn in the morning after an overnight fast of 12h and serum concentrations for lipid variables were enzymatically determined. LDL-C concentrations were calculated by the following formula: LDL-C=cholesterol-(HDL-C -tryglicerides/5)	TC: 263.7 \pm 48.6 vs. 226.2 \pm 24.3 LDL-C: 168.9 \pm 43.3 vs. 136.8 \pm 25.1 HDL-C: 42.9 \pm 13.5 vs. 62.2 \pm 18.2 TGs: 195.6 \pm 80.5 vs. 138.1 \pm 36.5	None	Various, but none that influence serum lipid concentration. Nicotine dependence.
KARLOVIC (b) 2004 - 1	Croatia	43 veterans with chronic combat-related PTSD receiving treatment; 39 healthy individuals (mostly hospital workers)	41.3 \pm 8.3; 43.8 \pm 10.1	100% (overall sample)	Structured clinical interview based on DSM-IV criteria. *Additional criteria to diagnose PTSD was Clinician Administered PTSD Scale (CAPS) based on DSM-IV criteria.	Blood drawn in the morning after an overnight fast of 12h and serum concentrations for lipid variables were enzymatically determined. LDL-C concentrations were calculated by the following formula: LDL-C=cholesterol-(HDL-C -tryglicerides/5)]	TC: 239.9 \pm 46.4 vs. 205.1 \pm 42.5 LDL-C: 157.5 \pm 33.7 vs. 123.7 \pm 30.1 HDL-C: 38.6 \pm 11.2 vs. 54.1 \pm 11.6 TGs: 203.5 \pm 123.9 vs. 123.9 \pm 61.9	None	Various, but none that influence serum lipid concentration. Nicotine dependence.
KARLOVIC (b) 2004 - 2	Croatia	37 veterans with chronic combat-related PTSD comorbid with major depressive disorder (MDD); 38 veterans with combat-experiences with MDD.	42.9 \pm 7.3; 46.2 \pm 11.3	100% (overall sample)	Structured clinical interview based on DSM-IV criteria. *Additional criteria to diagnose PTSD was Clinician Administered PTSD Scale (CAPS) based on DSM-IV criteria.	Blood drawn in the morning after an overnight fast of 12h and serum concentrations for lipid variables were enzymatically determined. LDL-C concentrations were calculated by the following formula: LDL-C=cholesterol-(HDL-C -tryglicerides/5)]	TC: 243.8 \pm 50.3 vs. 197.4 \pm 38.7 LDL-C: 161.2 \pm 33.7 vs. 135.1 \pm 26.2 HDL-C: 42.5 \pm 10.3 vs. 50.3 \pm 12.9 TGs: 194.7 \pm 106.2 vs. 115.1 \pm 53.1	None	Various, but none that influence serum lipid concentration. Nicotine dependence.
DAVID 2004	USA	55 veterans with chronic PTSD; 38 veterans with alcohol dependence. Subjects were recruited from a rehabilitation unit for chronic PTSD and alcohol dependence, respectively.	49.7 \pm 5.7; 48.3 \pm 8	100% (overall sample)	Psychiatric diagnoses were assessed with the Structured Clinical Interview for DSM-III-R (SCID) (5) and then DSM-IV.	Blood tests were performed.	TC: 213 \pm 38.7 vs. 188.5 \pm 38.3 LDL-C: --- HDL-C: --- TGs: 292.1 \pm 225.8 vs. 149.3 \pm 62.9	None	Alcohol, intravenous drug and smoking.

TRIEF 2006 - 1	USA	480 diabetic PTSD veterans; 11,613 diabetic veterans with no PTSD and no depression.	61.1 ± 9.7; 69.32 ± 999	100% (overall sample)	Psychiatric diagnoses were based on ICD-9-CM and were noted by providers as the purpose for a visit.	Medical records.	TC: 172 ± 41.63 vs. 168 ± 43.1 LDL-C: 98.1 ± 32.86 vs. 95.7 ± 32.33 HDL-C: 38.2 ± 13.14 vs. 38.9 ± 10.78 TGs: 194 ± 18.18 vs. 186 ± 193.97	None	Insulin, diabetes and psychiatric medication.
TRIEF 2006 - 2	USA	649 diabetic veterans with PTSD and depression; 1696 diabetic veterans with depression.	59.6 ± 9.3; 64.3 ± 11.8	100% (overall sample)	Psychiatric diagnoses were based on ICD-9-CM and were noted by providers as the purpose for a visit.	Medical records.	TC: 175 ± 43.31 vs. 169 ± 41.18 LDL-C: 99.7 ± 33.12 vs. 95.1 ± 32.95 HDL-C: 38.2 ± 12.74 vs. 37.5 ± 12.35 TGs: 214 ± 18.85 vs. 203 ± 189.44	None	Insulin, diabetes and psychiatric medication.
MAIA 2008	Brazil	11 police officers with full PTSD; 117 police officers with non-PTSD symptoms.	35.73 ± 7.3; 33.12 ± 5.26	100% (overall sample)	Self-report checklist: PTSD checklist civilian version (PCL-C) according to DSM-IV criteria.	Blood drawn in the morning after an overnight fast of 12h and lipid parameters were enzymatically determined.	TC: 217.4 ± 54.1 vs. 183.4 ± 39.9 LDL-C: 134.6 ± 45.2 vs. 111.9 ± 34.2 HDL-C: 44.8 ± 13.3 vs. 48.3 ± 9.2 TGs: 224.8 ± 160.8 vs. 122.7 ± 76.9	None	Alcohol, tobacco and beta-blockers. None were in use of statins.
KULENOVIC 2008	Bosnia and Herzegovina	50 veterans with PTSD; 50 veterans with combat exposures without PTSD.	40 – 50 (overall sample)	100% (overall sample)	Mini International Neuropsychiatric Interview (MINI), version 5.0.0, Mini Mental State Examination (MMSE)	Blood drawn in the morning after an overnight fast of 12 hours. Lipid levels were enzymatically determined.	TC: 215.39 ± 46.4 vs. 218.87 ± 43.31 LDL-C: 131.48 ± 40.6 vs. 135.34 ± 39.83 HDL-C: 45.63 ± 6.57 vs. 50.66 ± 10.05 TGs: 198.41 ± 127.55 vs. 170.06 ± 119.57	None	No drugs that affect plasma lipid levels. All participants were smokers.
HEPPNER 2009	USA	139 veterans with PTSD; 114 veterans without PTSD.	51.5 ± 9; 51.5 ± 9	92% (overall sample)	CAPS along with DSM-IV criteria.	Blood drawn after 12h fasting and assayed within the hospital clinical laboratory.	TC: --- LDL-C: --- HDL-C: 42.5 ± 10.6 vs. 43 ± 12 TGs: 194.6 ± 154.7 vs. 183.3 ± 124.7	None	Nicotine, alcohol and substance use/abuse.
JENDRICKO 2009	Croatia	66 veterans with PTSD; 33 veterans without PTSD* Subjects were either inpatients or outpatients from psychiatric services.	37.6 ± 4.7; 37.4 ± 4.2	100% (overall sample)	Structured Clinical Interview for DSM-IV (SCID) and CAPS.	Blood drawn in the morning after 12 h of fasting.	TC: 224.28 ± 52.98 vs. 215 ± 45.24 LDL-C: 143.08 ± 47.95 vs. 136.5 ± 39.06 HDL-C: 46.79 ± 22.04 vs. 46.02 ± 16.24 TGs: 173.6 ± 103.63 vs. 160.32 ± 146.15	None	Various, including psychotropic medication. None were on lipid lowering drugs.
SPITZER 2010	Germany	55 subjects with PTSD; 2,994 subjects without PTSD. *Participants were recruited from general population.	55 ± 16.4; 53.5 ± 15	29%; 48%	Structured Clinical Interview for DSM-IV (SCID) and Mini Mental State Examination (MMSE) and the Composite International Diagnostic-Screener (CID-S).	TC and HDL-C were measured applying a precipitation procedure and TGs were enzymatically determined.	TC: 224.28 ± 61.87 vs. 177.88 ± 42.54 LDL-C: --- HDL-C: --- TGs: 256.86 ± 283.44 vs. 124 ± 53.14	None	Various medications, including statins. Alcohol and smoking.
JIN 2011	USA	31 patients with PTSD and psychotic symptoms; 68 controls with schizophrenia and psychotic symptoms.	59.6 ± 11.2; 56.9 ± 9.7	87%; 87%	Primary psychiatrists (the patients met DSM-IV criteria).	Blood drawn in the early morning, after at least 12 hours of fasting. Laboratory testing was done at a certified clinical laboratory.	TC: 192.6 ± 48.6 vs. 186.2 ± 41.1 LDL-C: --- HDL-C: 45.9 ± 14.1 vs. 44.5 ± 17.1 TGs: 131.6 ± 77.8 vs. 152.1 ± 118.1	None	Various medications, including antipsychotic and statins. Smoking.
LINNVILLE 2011	USA	89 repatriated prisoners of war with PTSD; 196 repatriated prisoners of war without PTSD.	61 ± 6 (overall sample)	100% (overall sample)	Impact of Event Scale-Revised (IES-R) and DSM-IV criteria.	Medical record.	TC: --- LDL-C: --- HDL-C: 51.4 ± 13.2 vs. 51.4 ± 14.1 TGs: 175.2 ± 175.5 vs. 140.3 ± 77.9	None	Lipid lowering and tobacco. Alcohol abuse were excluded.
WALCZEWSKA 2011	Poland	80 patients with PTSD resulting from deportation to Siberia during childhood; 70 subjects without traumatic history from.	69.3 ± 5.9; 70.8 ± 4.9	50%; 50%	The diagnosis was made during a direct interview by a psychiatrist and was based (verified) using DSM-IV criteria.	Levels of TC, LDL-C, HDL-C, and TGs were extracted from medical records. Samples were collected when such data were not available or in whom they were taken more than 6 months before the study.	TC: 215.39 ± 46.4 vs. 213.46 ± 36.35 LDL-C: 131.48 ± 40.6 vs. 133.41 ± 32.1 HDL-C: 45.63 ± 6.57 vs. 47.18 ± 8.51 TGs: 198.41 ± 127.55 vs. 164.75 ± 108.95	Year of birth and gender	Tobacco.

MUHTZ 2011	Germany	25 refugees of WWII with PTSD; 25 refugees of WWII without PTSD.	71 ± 0.5; 71 ± 0.4	36%; 36%	Structured Diagnostic Interview according to DSM-IV.	Blood drawn after fasting in the morning. Serum HDL-C, LDL-C and TGs were measured by standard laboratory methods.	TC: --- LDL-C: 140.9 ± 5.4 vs. 129.6 ± 6.6 HDL-C: 69.1 ± 3.5 vs. 67.3 ± 3.7 TGs: 104.4 ± 7.2 vs. 134.9 ± 12.8	Age and gender	Various medications, including lipid drugs. Smoking and alcohol.
WEISS 2011	USA	46 patients with current PTSD; 199 patients without current PTSD.	43.7 ± 10.98; 46 ± 11.86	30%; 40%	CAPS and DSM-IV criteria.	Blood drawn in the morning.	TC: --- LDL-C: 101.2 ± 26.3 vs. 107.8 ± 41.1 HDL-C: 51.7 ± 20.5 vs. 48.2 ± 16.2 TGs: 116.4 ± 59.5 vs. 126.4 ± 130.6	None	Medication for diabetes, hypertension and hyperlipidemia.
DEDERT 2012	USA	63 individuals with PTSD; 71 without PTSD.	40.4 ± 12.9 (overall sample)	0% (overall sample)	CAPS and the Structured Clinical Interview for DSM-IV.	Blood drawn after 12 h of fasting. TGs were enzymatically determined, HDL-C assays used a precipitation procedure and LDL-C concentrations were calculated by the following formula: LDL-C=cholesterol-(HDL-C - tryglicerides/5)	TC: --- LDL-C: 128 ± 37.7 vs. 116.2 ± 35.4 HDL-C: 54.6 ± 52.1 vs. 50.5 ± 12.5 TGs: 108.6 ± 68.4 vs. 89 ± 48.7	None	Antipsychotic medication. Current alcohol or other substance dependence/abuse were excluded.

Weighted mean differences of serum lipid concentrations - PTSD vs non-PTSD groups:

Included studies involved 19,660 participants: 2,110 with PTSD and 17,550 from the comparison groups. With only one exception of TGs measurement (Muhtz, et al., 2011), all studies that did not show a worsened serum lipid profile in PTSD populations were inconclusive. Figures 2 to 5 display the forest plots with the weighted mean differences (WMD) - mg/dL - of serum lipid concentrations. Pooled data showed statistically significant higher levels of TC, LDL-C and TGs and lower levels of HDL-C in PTSD groups. Statistical heterogeneity between studies was high - I^2 above 85% - for all lipid parameters.

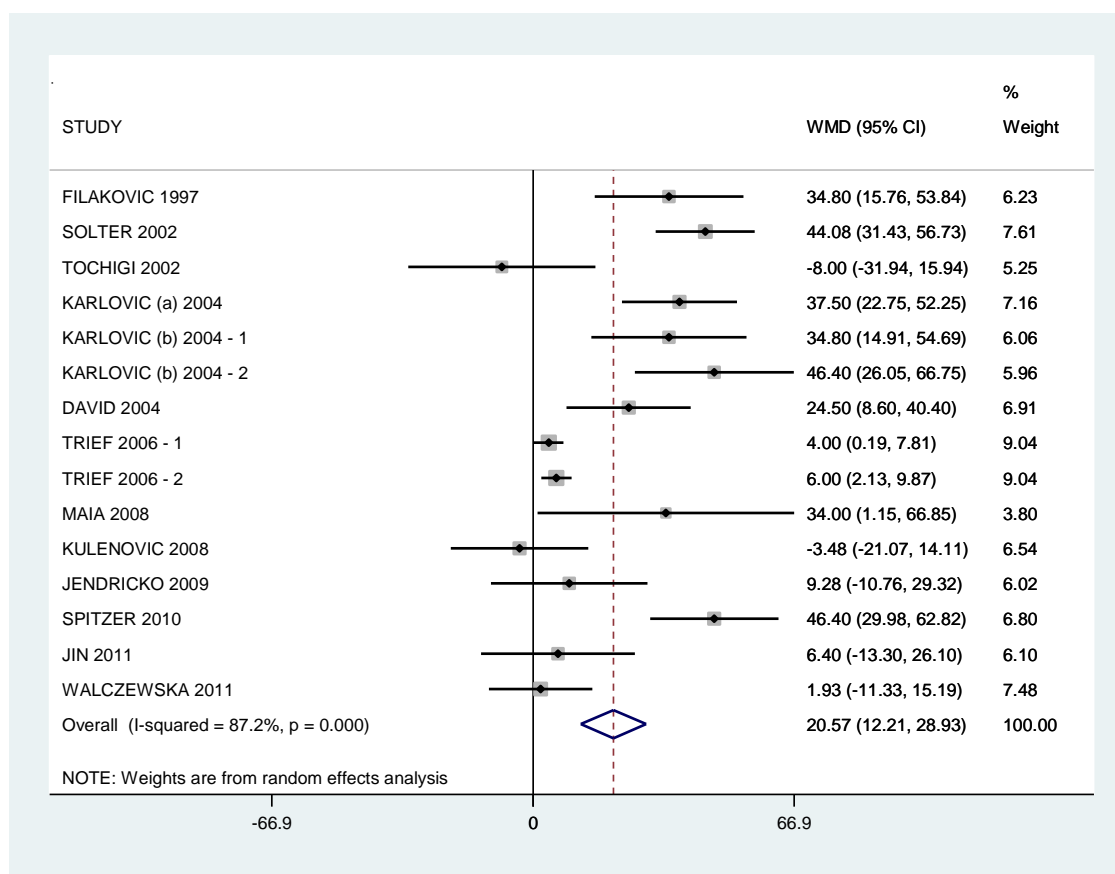


Figure 2: Forest-plot. Weighted mean difference (WMD) of total cholesterol (TC) - mg/dL - and respective 95% confidence interval (CI). PTSD vs non-PTSD populations. PTSD: posttraumatic stress disorder.

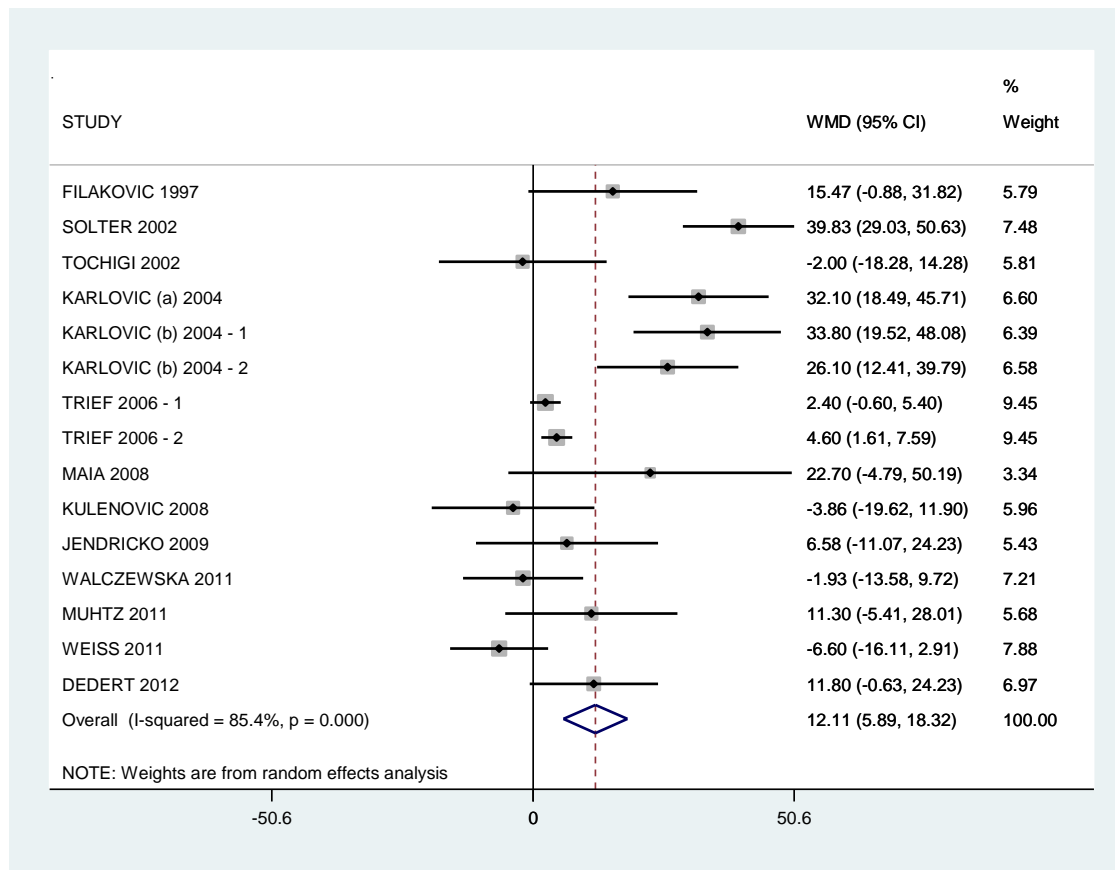


Figure 3: Forest Plot. Weighted mean difference (WMD) of low-density lipoprotein (LDL-C) - mg/dL - and respective 95% confidence interval (CI). PTSD vs non-PTSD populations. PTSD: posttraumatic stress disorder.

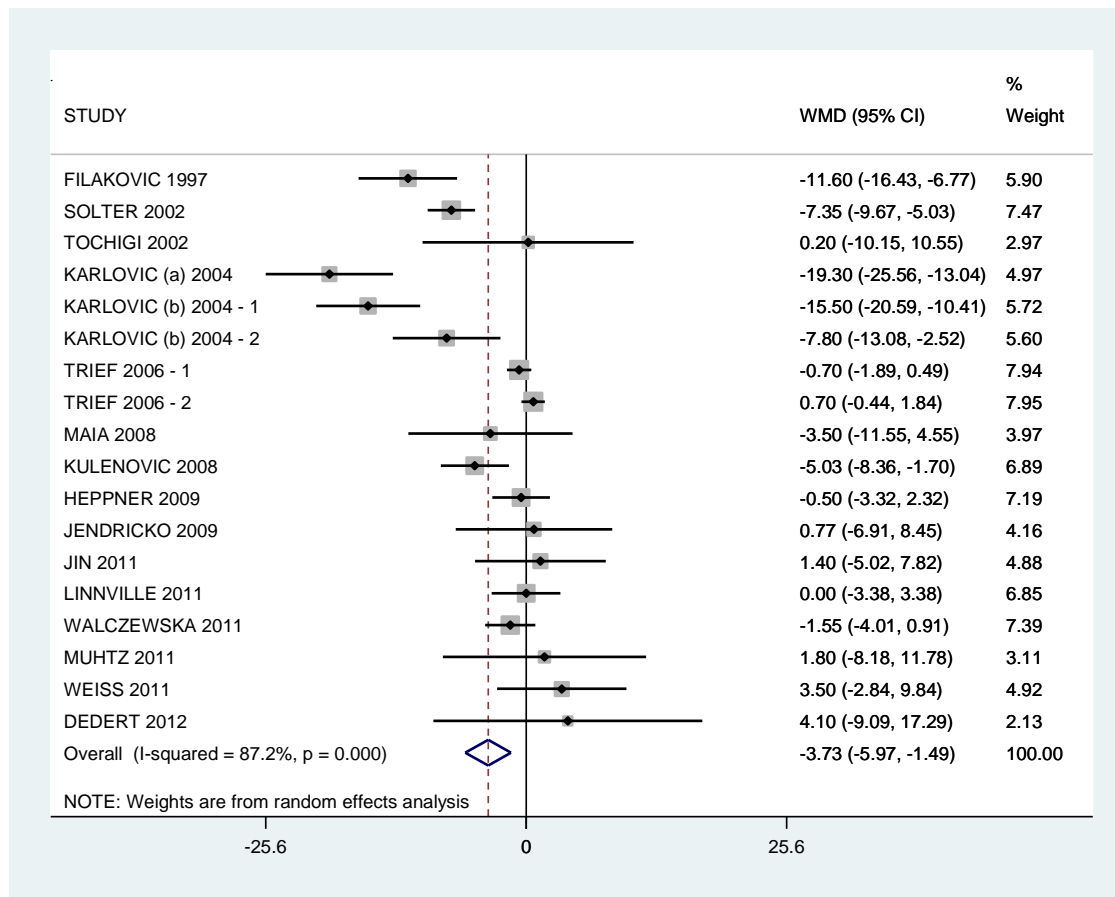


Figure 4: Forest-plot. Weighted mean difference (WMD) of high-density lipoprotein (HDL-C) - mg/dL - and respective 95% confidence interval (CI). PTSD vs non-PTSD populations. PTSD: posttraumatic stress disorder.

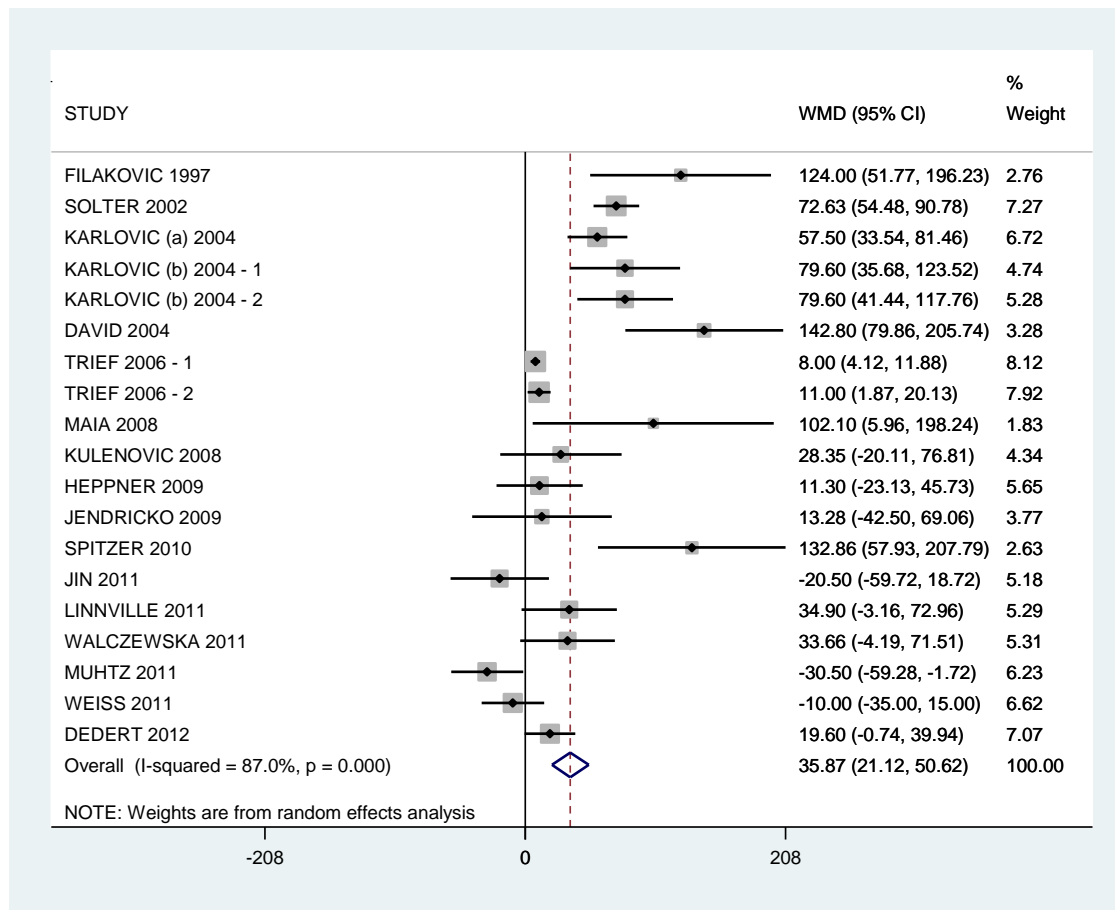


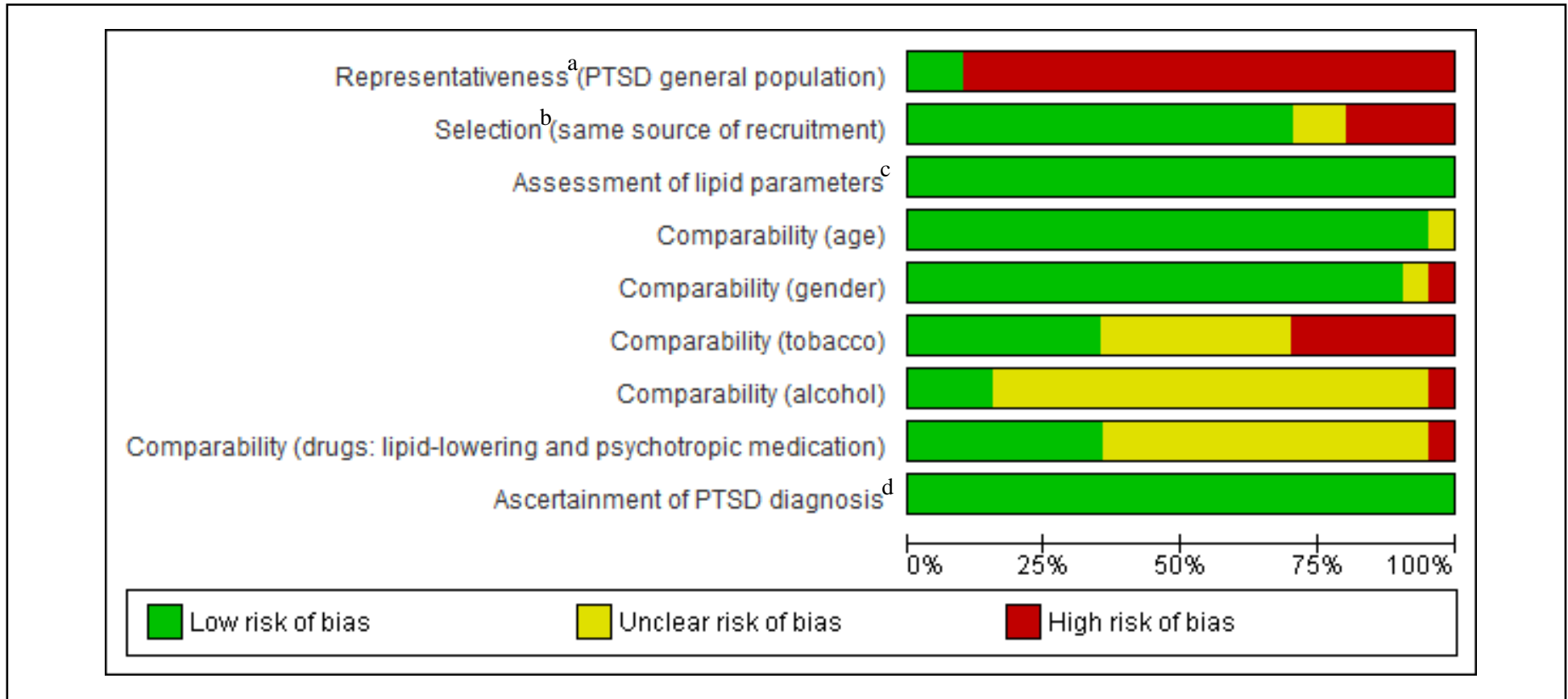
Figure 5: Forest-plot. Weighted mean difference (WMD) of triglycerides (TGs) - mg/dL - and respective 95% confidence interval (CI) of PTSD vs non-PTSD populations. PTSD: posttraumatic stress disorder.

Methodological quality of individual studies and sensitivity analysis

Figure 6 shows the assessment of methodological quality of the included papers. The fact that all studies were positively evaluated concerning the ascertainment of PTSD and the assessment of lipid parameters was due to exclusion criteria – self-reported measures were not accepted. Almost all studies were negatively assessed in the item representativeness as they investigated specific populations (e.g. veterans, soldiers) and their data cannot necessarily be representative of the lipid profile in general population. However, for the purpose of this review, internal validity (comparability) is more important than external validity (representativeness).

Concerning the domain comparability, we positively evaluated only the studies that presented balanced distribution for variables regarded as potential confounders, i.e. age, gender, use of tobacco, alcohol and drugs that have influence on serum lipid parameters. Information about the use of alcohol and medication between the groups was lacking for most of the studies. The fact that a study was negatively assessed in this domain does not mean that it did not apply any statistical tools for confounding control, but that the measures we had access to use in our meta-analysis were not adjusted for the concern variables. Only one study (Trief, et al., 2006) showed the adjusted mean values of serum lipid parameters controlling for age, substance use, other psychiatric disorders and the number of primary care encounters using propensity scores calculated from a multi-nomial logistic regression. We carried out sensitivity analyses to evaluate the impact of removing this study on the pooled measures. As no important changes were observed, we decided to keep the study in all analyses.

Figure 6. Quality assessment of included papers.



^aSample representative of general population with PTSD.

^bComparison sample without PTSD recruited from the same source population.

^cValidated diagnostic/screening tools for PTSD.

^dMeasured during the study or obtained through secure records.

*Additional analyses: Meta-regression**Bivariate analyses*

Meta-analysis regression models were fitted to explore the possible role of the following variables on the heterogeneity: age, gender, type of trauma (combat/war related *vs* others), PTSD group (veterans/soldiers *vs* others), PTSD psychiatric comorbidity (with *vs* without), type of control (with *vs* without psychiatric comorbidity), source of control (the same as the PTSD group *vs* different), method of adjustment (none, matching or restriction), diagnostic criteria (structured clinical interview, psychiatrist or self-report check-list), and human development index (HDI). Analyses per continent were not performed because the majority of the studies were concentrated in North America and Europe. Table 1 presents the regression coefficients for the variables with p-values ≤ 0.10 for at least one lipid parameter in bivariate analyses.

Table 2: Bivariate meta-regression analyses. HDI, human development index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TGs, triglycerides; I^2_{res} , I-squared residual; Adj R^2 , Adjusted R-squared.

Lipid Variable (mg/dL)	Age (years)	Gender (% of men)	HDI	Subgroup (veterans/soldiers vs others)	Type of trauma (war/combat vs others)
CT (n= 15)					*n=8
<i>Coef. (p-value)</i>	-91 (.03)	3.75 (.89)	-77.19 (.29)	-7.48 (.52)	-24.91 (.09)
$I^2; I^2_{res}$ (%)	87.2; 70.6	87.2; 87.7	87.2; 82.4	87.2; 88.0	87.2; 73.6
<i>Adj R² (%)</i>	39.23	-9.73	2.06	-5.52	36.35
LDL-C (n=15)					*n=9
<i>Coef. (p-value)</i>	-.64 (.04)	17.48 (.16)	-93.74 (.09)	-12.81 (.12)	-32.27 (<.01)
$I^2; I^2_{res}$ (%)	85.4; 76.1	85.4; 86.2	85.4; 77.9	85.4; 86.1	85.4; 30.1
<i>Adj R² (%)</i>	31.67	9.40	14.94	14.81	93.36
HDL-C (n=18)					*n=10
<i>Coef. (p-value)</i>	.29 (.01)	-11.23 (.05)	51.40 (<.01)	6.71 (.03)	11.99 (<.01)
$I^2; I^2_{res}$ (%)	87.2; 74.6	87.2; 87.8	87.2; 74.4	87.2; 87.8	87.2; 62.9
<i>Adj R² (%)</i>	46.27	17.61	46.15	22.61	80.39
TGs (n=19)					*n=10
<i>Coef. (p-value)</i>	-1.82 (.04)	41.59 (.23)	-284.09 (.06)	-30.54 (.18)	-58.22 (.05)
$I^2; I^2_{res}$ (%)	87.0; 75.1	87.0; 87.7	87.0; 72.5	87.0; 87.7	87.0; 70.0
<i>Adj R² (%)</i>	32.10	7.31	31.20	12.74	54.03

Age: The mean age of PTSD group was associated with the variance – *heterogeneity* – between individual studies for all lipid parameters. Figures 7 to 10 clearly show that the magnitude of the association of PTSD with worsened serum lipid profile is stronger in younger populations and loses strength with age increment.

Human development index: The higher the HDI, the lesser appears to be the negative effect of PTSD in serum concentrations of LDL-C, TGs and HDL-C (Figures 11 to 13). No statistically significant finding was observed for TC.

Type of trauma (war/combat related vs others): Although about half of the studies did not provide information about the type of trauma, we observed that a worsened serum lipid profile in PTSD group was more noticeable for those who experienced war/combat related trauma than for those who experienced other types of trauma (i.e. sarin poisoning, capture/imprisonment, deportation, flight and mixed) (Table 1).

Gender: The influence of gender on lipid levels was difficult to evaluate because most of the samples consisted mainly of men. Despite this limitation, we found that the larger was the proportion of men in the sample, the lower the levels of HDL-C in PTSD populations when compared to non-PTSD controls (Figure 14).

PTSD group (veterans/soldiers vs others): Samples consisted of veterans/soldiers showed a worse HDL-C profile for PTSD groups when compared to other populations (Figure 15).

Bivariate analysis did not show any statistically significant associations for type of control, source of control, method of adjustment, adjusted variables, PTSD psychiatric comorbidity and diagnostic criteria. Nevertheless, the results from the latter two were not conclusive because PTSD psychiatric comorbidity was difficult to categorize - several studies did not provide useable data - and because more than 70% of studies applied structured clinical interviews for PTSD assessment.

Multiple meta-regression analyses

Initially multiple meta-regression models were fitted including the mean age of the PTSD group. Overall, the magnitude of the meta-regression coefficients for the mean age of the PTSD group reduced when HDI was added to the model. This was probably because the

samples of the studies conducted in countries with higher HDI tended to be older (Spearman's $\rho = .58$; $p < .01$). The variables proportion of men and PTSD subgroups (veterans/soldiers vs others) lost their statistical significance when added, one by one, to the model already including age. Findings from the analyses including age and type of trauma were not reliable as only about half of the studies could be used.

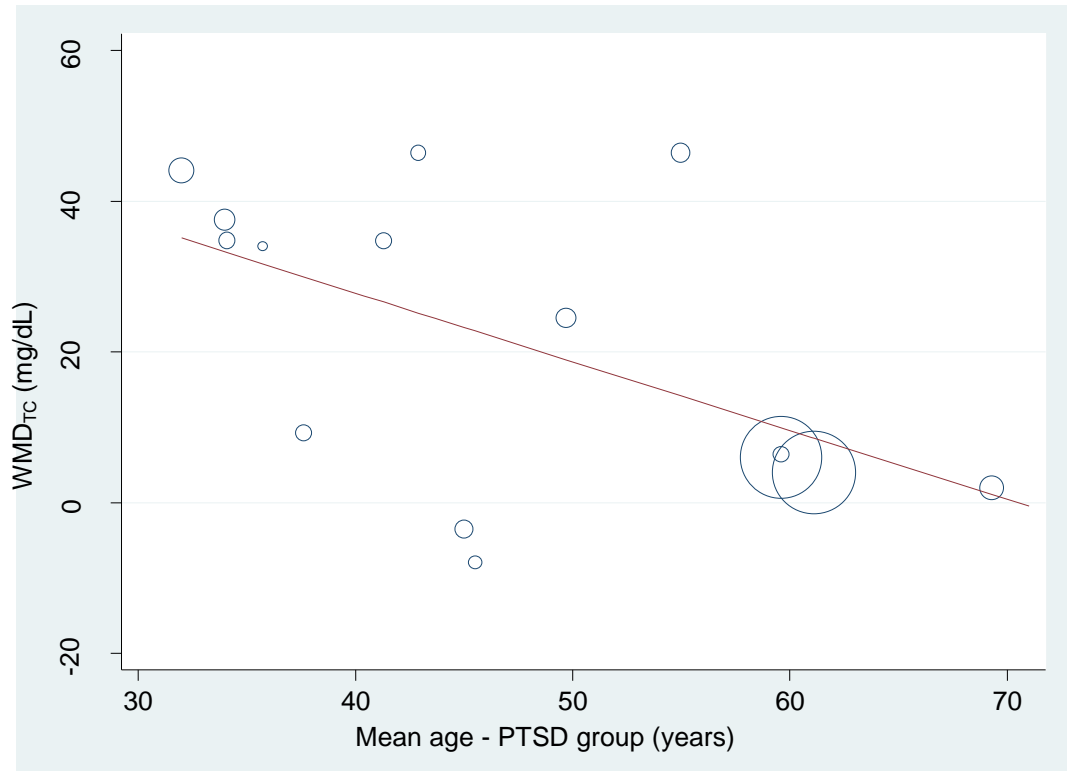


Figure 7: The impact of age in the reported mean differences of total cholesterol (TC). PTSD vs non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

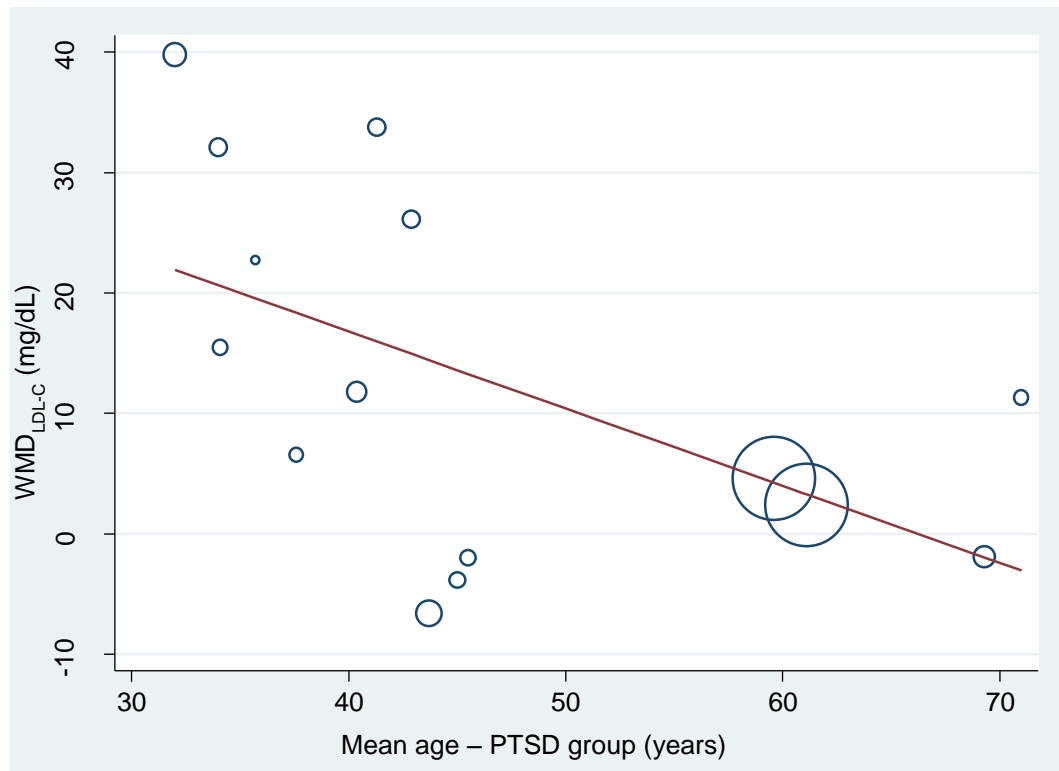


Figure 8: The impact of age in the reported mean differences of low-density lipoprotein cholesterol (LDL-C). PTSD vs non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

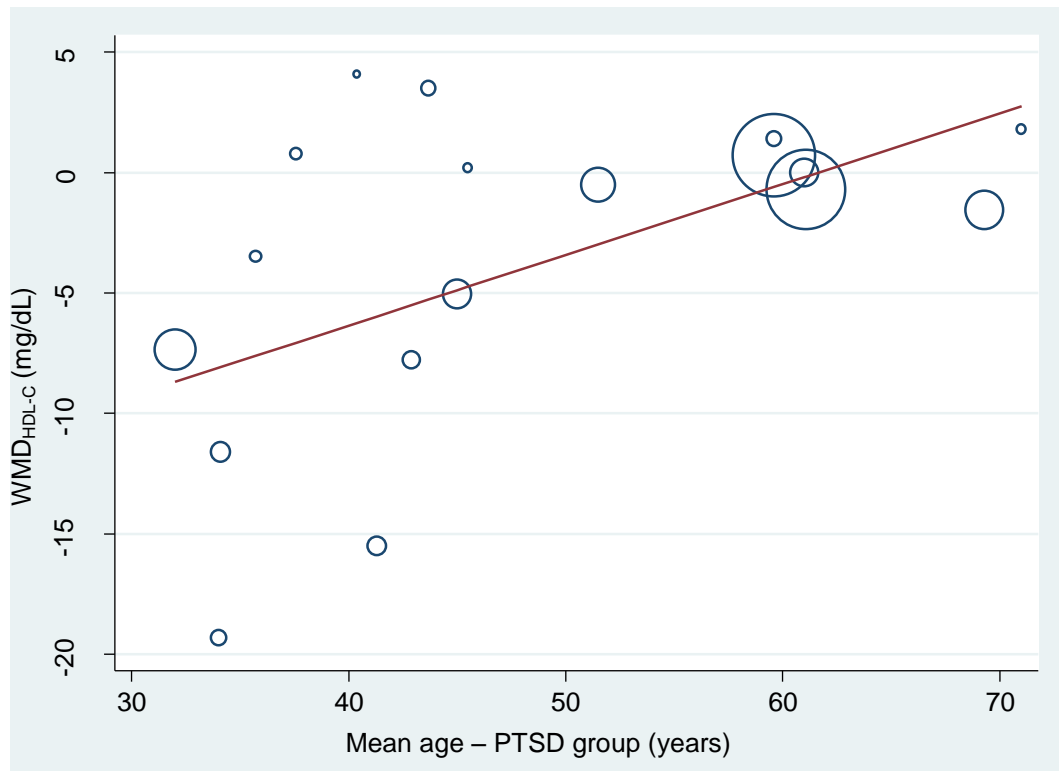


Figure 9: The impact of age in the reported mean differences of high-density lipoprotein cholesterol (HDL-C). PTSD vs non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

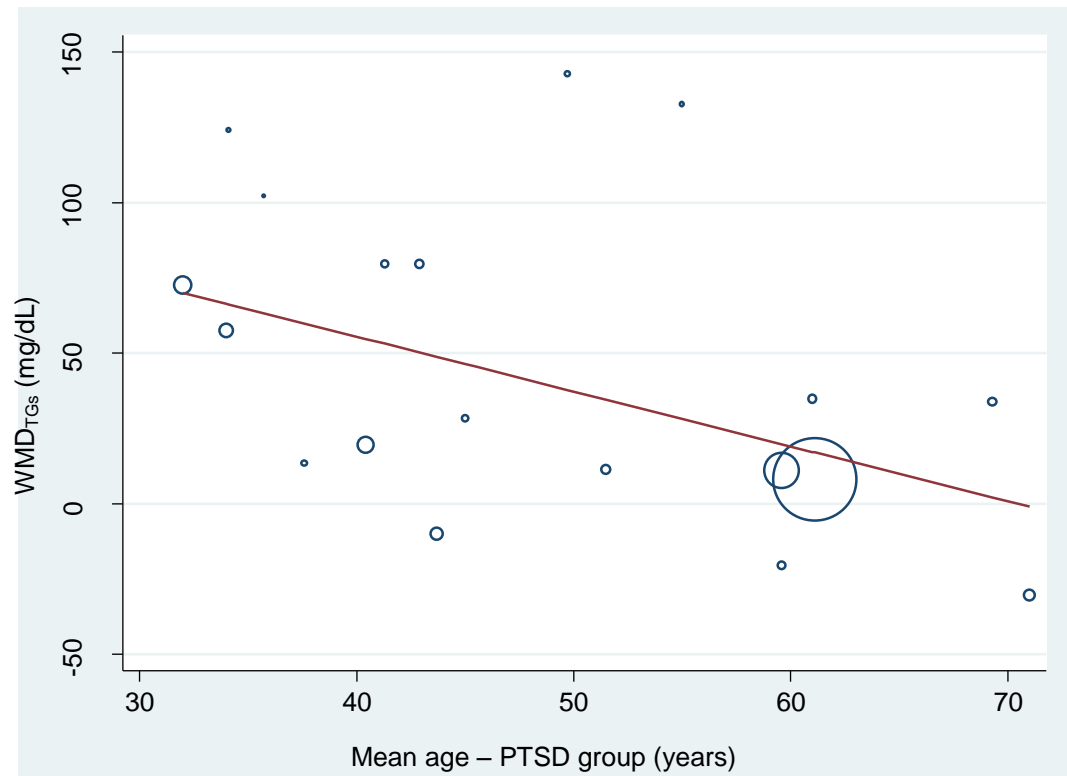


Figure 10: The impact of age in the reported mean differences of triglycerides (TGs). PTSD vs non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

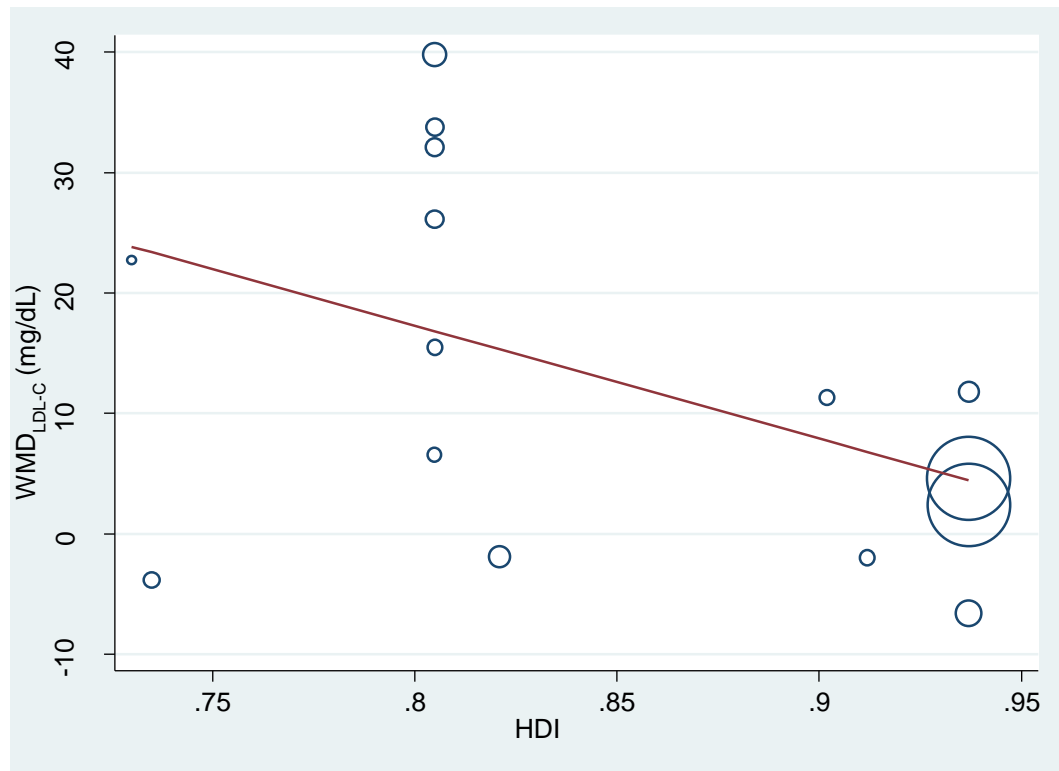


Figure 11: The impact of human development index (HDI) in the reported mean differences of low-density lipoprotein cholesterol (LDL-C). PTSD vs non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

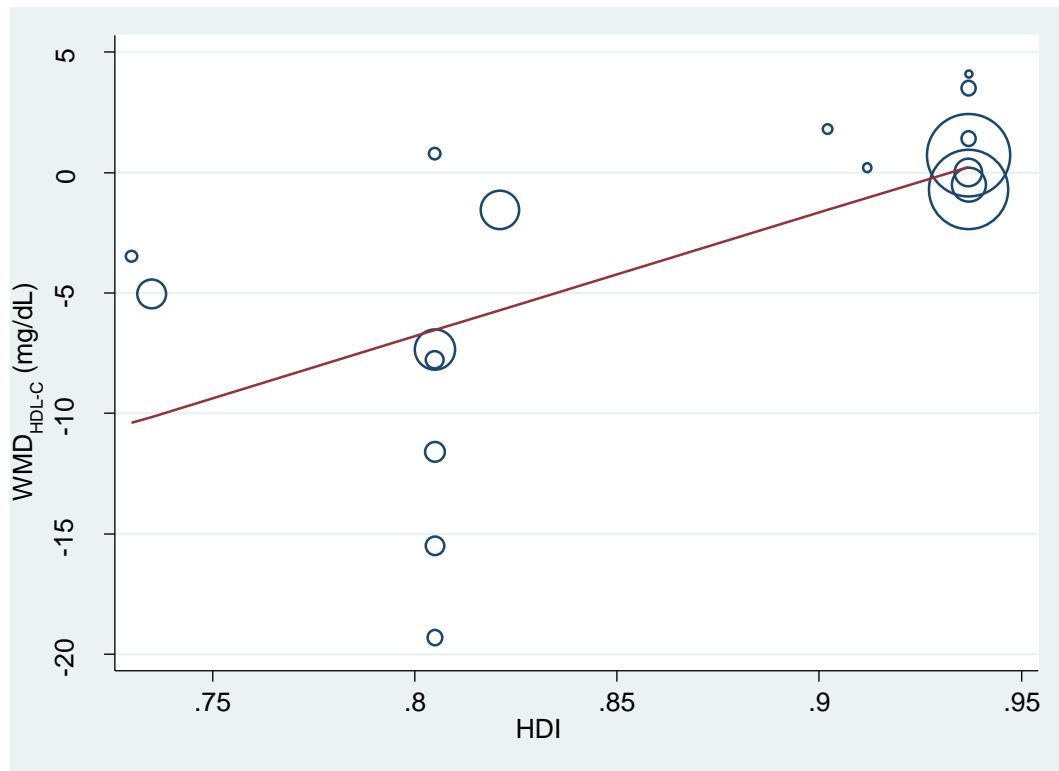


Figure 12: The impact of human development index (HDI) in the reported mean differences of high-density lipoprotein cholesterol (HDL-C). PTSD vs non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

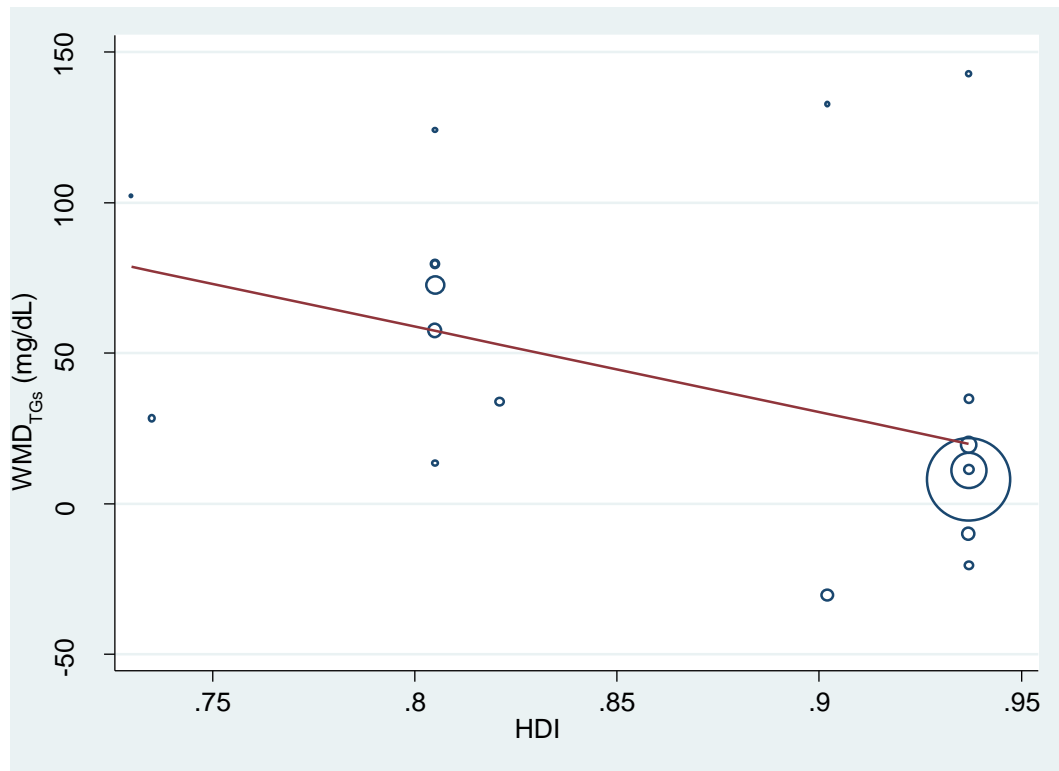


Figure 13: The impact of human development index (HDI) in the reported mean differences of triglycerides (TGs). PTSD *vs* non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

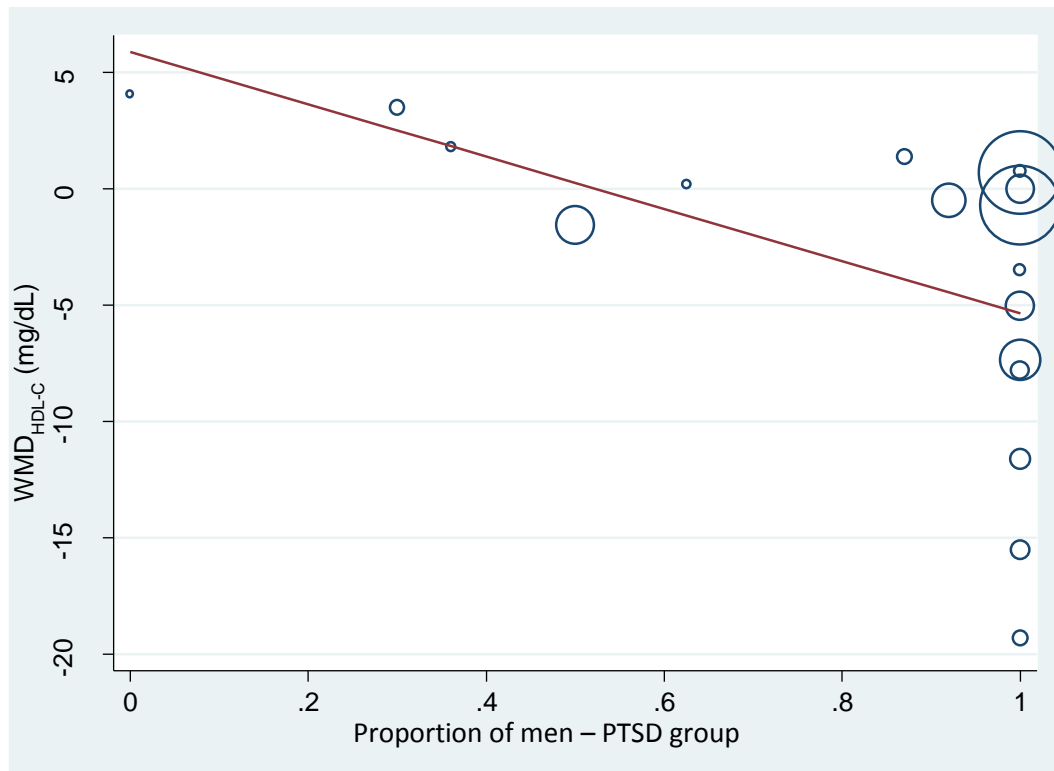


Figure 14: The impact of gender - proportion of men - in the reported mean differences of high-density lipoprotein cholesterol (HDL-C). PTSD vs non-PTSD populations. WMD, weighted mean difference; PTSD, posttraumatic stress disorder.

Discussion

Summary of evidence

Despite the high heterogeneity, pooled measures showed that PTSD was associated with a worsened serum lipid profile - higher levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and lower levels of high-density lipoprotein cholesterol (HDL-C). Some mechanisms that can plausibly explain why PTSD populations are at greater risk of having worsened serum lipid profile have been proposed. Mostly, they involve hypothalamic-pituitary-adrenal (HPA) axis dysregulation, abnormal sympathetic activation, immune dysfunction and behavioral risk factors. (Kario, et al., 2003; Wentworth, et al., 2013)

As a result from HPA axis dysfunction, low levels of plasma cortisol and a heightened inflammation state are commonly observed in PTSD. (Wentworth, et al., 2013) Both of these consequences are known to deregulate lipid metabolism. (Black, 2003; Fries, 2008) In parallel, it has been shown that chronic activation of HPA axis is associated with overeating and obesity. (Dallman, et al., 2004; Nishitani & Sakakibara, 2006) The enhanced sympathetic activation with increased levels of catecholamines may directly impact serum lipid concentrations because: (i) norepinephrine inhibit lipoprotein lipase activity, leading to reduced TGs clearance, decrease in HDL-C levels and increase in LDL-C levels in bloodstream (Stoney, 2007); (ii) norepinephrine reduces the activity of hepatic triglyceride lipase, which promotes high serum concentrations of lipoproteins rich in TGs (Stoney, 2007); (iii) catecholamines directly stimulate the release of free fatty acid and glycerol from fat depots in the bloodstream. (Stoney, 2007)

Sleeping disturbances, an important dimension of PTSD, may also contribute to this worsened lipid profile by the: (i) resulting decreased leptin and increased ghrelin levels, which enhance hunger and appetite (Spiegel, et al., 2004; Pejovic, et al., 2010); (ii) raised hydrocortisone levels - when chronically elevated, it favors fat deposition on blood vessels and abdomen. (McEwen, 2002)

Last but not least, behavioral risk factors related to PTSD e.g. smoking, alcohol/substance abuse, diminished physical activity, poor diet and low self-care (Keane, et al., 2006; Dedert, et al., 2010; Wentworth, et al., 2013) may also contribute to negatively impact serum lipid concentrations.

A recent meta-analysis showed a higher rate of metabolic syndrome in people suffering from PTSD (OR=1.37, IC 95% 1.03-1.82) when compared to controls without psychiatric morbidities. (Bartoli, et al., 2013) Our results appear to be consistent with this finding as lipid profile is an important dimension of metabolic syndrome.

Although our data showed a worsened serum lipid profile in PTSD populations, studies were pretty heterogeneous concerning the observed magnitude of this association, indicating that differences between subgroups might be present. Age, human development index (HDI), type of trauma and sex explained, in part, the inconsistency of the results found from the individual studies.

The impact of age in the reported mean differences of all lipid parameters is plausible, as aging is associated with an impairment of blood lipids. (Arnarson, et al., 2013) Thus, it is expected that the differences between the groups tend to reduce as the average age of the samples increases. Accordingly, we observed a reduction of the magnitude of PTSD association with worsened serum lipid profile in older samples.

Studies conducted in countries with higher HDI tended to show smaller differences of LDL-C, HDL-C and TGs concentrations between the groups, suggesting that the more developed the country, the lesser the impact of PTSD in such lipid parameters. We can speculate that this association could be due to the better health care access/assistance and an overall better quality of life in more developed countries. However, when the variables age and HDI were fitted together, the magnitude of the coefficient for HDI reduced and lost its statistical significance, suggesting that age might have acted as a confounder in this relationship. In fact, these variables were positively correlated i.e. studies conducted in countries with higher HDI assessed older people.

The worsened serum lipid profile in PTSD groups was more pronounced in studies investigating combat/war related trauma. As the mean age of PTSD group was much lower for war/combat related trauma than for other types of trauma (36.9 vs 57.6), we attempted to control for this potential confounder. However, we must be cautious concerning these results as only a small number of studies reported the type of trauma. Also, the impact of proportion of men on the magnitude of the differences in HDL-C between PTSD and non-PTSD groups was precluded as most of the studies consisted only of men.

Strengths and limitations

As far as we know, this is the first meta-analysis that systematically synthesizes data from studies comparing the mean differences of serum lipid concentrations between groups with and without PTSD. We attempt to minimize the risk of bias searching the studies in five databases, with no restriction regarding to language, year of publication or publication status. Additionally, we screened the reference lists of all included articles. A quality analysis of the individual studies was carried out to provide a comprehensive view of the positive and negative methodological aspects of included data in our review/meta-analysis.

Some limitations of our study must be addressed. First, serum lipid concentrations are known to be highly influenced by numerous of environmental and psychosocial factors, which makes this sort of analysis challenging. Most of the studies were conducted with specific populations – e.g. veterans – which may compromise the inference of our results to the general population. Another limitation was the impossibility to use adjusted mean values of lipid parameters for potential confounders. Mostly, we only had access to the crude measures of serum lipid concentrations and some of the individual results might have been biased if confounders were unbalanced between the groups. Also only cross-sectional data were available and therefore, causal inferences were compromised. Nevertheless, reverse causality – worsened lipid profile causing PTSD – is not expected in most of the included studies. Ultimately, we were not able to investigate the risk of publication bias due to the high heterogeneity of results from the individual studies. So, we cannot rule out that some contrary or uncertain results may remain unpublished, which could have resulted in an overestimation of the observed associations between worsened lipid profile and PTSD.

Conclusions

Our results show that PTSD is associated with a worsened serum lipid profile – higher levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and lower levels of high-density lipoprotein cholesterol (HDL-C). The magnitude of this association, however, varied widely across studies. Among the explored variables, age appears to be an important effect modifier of this relationship: the impact of PTSD on lipid levels was more noticeable in younger groups.

Considering implications for practice, our findings highlight the importance of an ongoing cardiometabolic monitoring of PTSD patients, even if they are young. We suggest that clinicians should implement a routine map of lipid profile in people suffering from PTSD

aiming to reduce the risk of atherosclerosis and the consequent morbidity and mortality by cardiovascular diseases in PTSD patients.

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6 ARTIGO 2: PTSD SYMPTOM CLUSTERS AND DYSLIPIDEMIA: A STRONG DOSE-RESPONSE RELATION WITH HYPERAROUSAL SYMPTOMS

Resumo

Introdução: O transtorno do estresse pós-traumático (TEPT) é um fator de risco independente para diversos problemas físicos de saúde, especialmente doenças cardiovasculares. Sugere-se que a desregulação lipídica atue como mediadora da relação entre TEPT e doenças cardiovasculares.

Objetivo: Investigar a relação entre os parâmetros séricos de lipídeos e os grupos de sintomas do TEPT - *revivescência, esquiva e entorpecimento emocional e hiperestimulação autonômica* - em uma amostra urbana de policiais com e sem TEPT.

Métodos: Este estudo transversal foi realizado com 118 policiais da ativa do sexo masculino. As concentrações séricas de colesterol total (CT), lipoproteína de baixa densidade (LDL), lipoproteína de alta densidade (HDL) e triglicerídeos (TG) foram determinados enzimaticamente. Os coeficientes de correlação de Spearman foram estimados para os parâmetros lipídicos e grupos de sintomas do TEPT.

Resultados: Uma forte correlação positiva estatisticamente significativa foi observada entre os níveis de CT e LDL com o grupo de sintomas de *hiperestimulação autonômica*, somente no grupo TEPT: $\rho = 0,89$ ($p < 0,01$) e $\rho = 0,92$ ($p < 0,01$), respectivamente.

Conclusões: A forte correlação positiva entre os níveis de CT e LDL com os sintomas de *hiperestimulação autonômica* pode ajudar a estabelecer um acompanhamento clínico mais adequado em pacientes com TEPT sob maior risco de doenças cardiovasculares.

Palavras-chave: TEPT; Colesterol; LDL; Triglicerídeos; Lipídeos; Hiperestimulação Autonômica.

Abstract

Background: Posttraumatic Stress Disorder (PTSD) is an independent risk factor for several physical health problems, especially cardiovascular diseases. It has been suggested that lipid dysregulation is one of the factors that mediates the relationship between PTSD and cardiovascular diseases.

Purpose: To investigate the relationship between serum lipid parameters and PTSD symptom clusters - *re-experiencing, avoidance and hyperarousal* - in a civilian sample of urban police officers with full and non-PTSD symptoms.

Methods: This cross-sectional survey was conducted with 118 active duty male police officers. Serum concentrations for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) were enzymatically determined. Spearman correlation coefficients were estimated for lipid parameters and PTSD symptom clusters.

Results: A significant and strong positive correlation was observed between TC and LDL-C with hyperarousal symptom cluster, but only in the full PTSD group: $\rho = 0.89$ ($p < .01$) and $\rho = 0.92$ ($p < .01$), respectively.

Conclusions: The strong positive correlation between the levels of TC and LDL-C with hyperarousal may help to establish a more appropriate medical monitoring of PTSD patients at high risk for cardiovascular diseases.

Keywords: PTSD; Cholesterol; LDL-C; HDL-C; Triglycerides; Lipids; Hyperarousal.

Introduction

Posttraumatic Stress Disorder (PTSD) is a well-established risk factor for several negative physical health outcomes, especially cardiovascular diseases (CVD). (Boscarino, 2004; Dedert, et al., 2010; Boscarino, 2011; Jordan, et al., 2011; Boscarino, 2012) This disorder has been associated with incident CVD and/or mortality in some large prospective observational studies. (Kubzansky, et al., 2007; Boscarino, 2008; Scherrer, et al., 2010; Ahmadi, et al., 2011; Coughlin, 2011; Jordan, et al., 2011) For instance, Jordan et al. (Jordan, et al., 2011) examined the associations between September 11, 2001 World Trade Center (WTC) disaster-related exposures, PTSD and subsequent development of heart disease on a

longitudinal study of 39,324 WTC Health Registry participants. They found that PTSD was associated with an elevated risk of heart disease, and that risk had a dose–response relationship with PTSD symptoms. In another recent study, Ahmadi et al. reported that PTSD was associated with presence and severity of coronary atherosclerosis and predicted mortality independent of age, gender, and conventional risk factors.(Ahmadi, et al., 2011)

The knowledge about mechanisms that could explain the association between PTSD and CVD has been growing. Several researches have consistently shown higher serum lipid profile in both veterans and civilian PTSD populations (Kagan, et al., 1999; Karlovic, et al., 2004a; Karlovic, et al., 2004b; Trief, et al., 2006; Maia, et al., 2008; Heppner, et al., 2009; Jin, et al., 2009; Von Kanel, et al., 2010; Linnville, et al., 2011; Walczewska, et al., 2011). Inasmuch as dyslipidemia is associated with greater risk of atherosclerosis and consequently to vascular incidents (Wentworth, et al., 2013), PTSD patients might be at risk of a numerous somatic complications, especially cerebro/cardiovascular diseases due to worsened serum lipid profile. (Karlovic, et al., 2004a; Wentworth, et al., 2013)

PTSD is a highly heterogeneous disorder and separating out the different clinical subgroups might be a proficuous research strategy for a better understanding of the relationship between PTSD, dyslipidemia and CVD. Thus, it is reasonable to consider that each PTSD symptom cluster - *re-experiencing, avoidance and hyperarousal* - may involve separate pathophysiological mechanisms in this process. Nevertheless, studies designed to investigate these associations are scarce and have yielded mixed results. (Tochigi, et al.; Kimerling, et al., 2000; Steptoe & Brydon, 2005)

We only have found a few reports that concerns about the association of PTSD symptom clusters and an objective laboratory measure (Tochigi, et al.; Wang, et al., 1995; Karlovic, et al., 2004b). Serum lipid concentrations are one of these parameters particularly noteworthy because of their relationship with CVD. In the only study we found that explored the relationship between serum lipid concentrations and PTSD symptom clusters, Karlovic et al. observed a strong and positive correlation between total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) with hyperarousal symptoms in male war veterans with PTSD. (Karlovic, et al., 2004b)

The purpose of this paper is to investigate the relationship between serum lipid profile and PTSD symptom clusters in a civilian sample of urban police officers regularly exposed to critical incidents.

Material and Methods

Study population

This cross-sectional survey is part of a larger study (Maia, et al., 2008) conducted in 2004 with 157 active duty male police officers of an elite unit of the Police Force of the State of Goiás-Brazil. This unit is physically well-trained and deployed only in critical situations. Only officers on vacation or on leave (including those on sick leave) were not assessed. The study was approved by the Internal Review Board of the Institute of Psychiatry of the Federal University of Rio de Janeiro and all subjects provided written informed consent. Ultimately, thirty nine (25%) participants were excluded from the study — 2 respondents who failed to fill out the questionnaires and 37 whose blood samples were not collected for various reasons.

Measures

We used a Portuguese version of the PTSD Checklist —Civilian Version (PCL-C) (Berger, et al., 2004) to screen for Post-Traumatic Stress Disorder (PTSD), a validated screening tool for PTSD. (Blanchard, et al., 1996) The full PTSD group was determined according to the DSM-IV criteria: scores equal or higher than three (“somewhat”) on at least one symptom of *reexperiencing* (cluster B), at least three *avoidance and numbing* symptoms (cluster C), and at least two *hyperarousal* symptoms (cluster D). (REF). On the first day of assessment, a nutritionist interviewed the volunteers about their dietary habits, tobacco and alcohol consumption before any nutritional orientation. They were also asked to collect blood samples after a 12-hour overnight fasting.

Statistical Analysis

Statistical significance was tested for differences between the groups regarding to socio-demographic variables and alcohol and tobacco consumption. Chi-square and Fisher exact tests were used for categorical variables and t-Student and Kruskal-Wallis tests were carried out for the continuous ones. Spearman’s correlation coefficients were estimated between lipid parameters and PTSD symptom clusters: *re-experiencing*, *avoidance and hyperarousal*. Correlations were considered statistically significant when $p \leq .05$ and borderline when $.05 \leq p \leq .10$.

Results

There was no significant difference between the full PTSD and non-PTSD groups regarding to age (mean 34.7 vs 32.7; $p=.40$), education – complete high school (71% vs 77%; $p=.74$), body mass index (BMI) (mean 27.1 vs 25.4; $p=.07$), alcohol consumption (62% vs 55%; $p=.64$) and tobacco use (8% vs 18%, $p=.35$). Only four individuals were using beta-blockers (two in each group) and three were using anti-depressant (one in the full PTSD group). No participant was on statins or anti-psychotic medication.

Table 1 presents Spearman's correlation coefficients between serum lipid parameters and PTSD symptom clusters – *re-experiencing*, *avoidance and hyperarousal* – in full PTSD ($n=10$) and non-PTSD ($n=107$) groups. One participant showed outliers results for lipid variables and was excluded from subsequent analyses. A strong positive and statistically significant correlation was observed between levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) with hyperarousal symptoms, only in the full PTSD group.

We conjectured that this correlation *only* observed in the full PTSD group could be due to its higher levels of hyperarousal symptoms when compared to the non-PTSD group, as if there was a threshold for this effect to be manifested. Therefore, we replicated the analysis in the non-PTSD group including only those scoring at least 14 points in hyperarousal scale of symptoms, the minimum value in the full PTSD group. However, the magnitude of the correlations dropped substantially, losing its statistical significance in the case of TC ($-.37$; $p=.15$) and reaching a borderline value for LDL-C ($-.43$; $p=.09$). Therefore, hyperarousal symptoms alone were not correlated with TC and LDL-C; only when the other two PTSD symptom clusters were present the positive correlation between hyperarousal with TC and LDL-C was observed.

Table 1. Correlation coefficients between serum lipid parameters and PTSD symptom clusters in police officers with full PTSD (n=10) and non-PTSD symptoms (n=107), according to PCL-C. PTSD, posttraumatic stress disorder.

Serum lipid parameters (mg/dL)	Full PTSD (n = 10)			Non-PTSD (n = 107)		
	<i>Re-experiencing</i>	<i>Avoidance</i>	<i>Hyperarousal</i>	<i>Re-experiencing</i>	<i>Avoidance</i>	<i>Hyperarousal</i>
	<i>rho (p-value)</i>	<i>rho (p-value)</i>	<i>rho (p-value)</i>	<i>rho (p-value)</i>	<i>rho (p-value)</i>	<i>rho (p-value)</i>
Total Cholesterol	0.03 (.95)	0.14 (.70)	0.89 (< .01)	0.01 (.88)	0.11 (.24)	0.09 (.38)
LDL-C	0.06 (.87)	0.24 (.50)	0.92 (< .01)	-0.04 (.70)	0.12 (.21)	0.08 (.39)
HDL-C	0.24 (.49)	0.42 (.22)	0.20 (.58)	0.09 (.36)	-0.04 (.66)	0.09 (.36)
Triglycerides	-0.26 (.50)	-0.46 (.22)	0.16 (.69)	-0.06 (.51)	0.11 (.26)	0.03 (.75)

Discussion

We found a strong correlation between hyperarousal symptoms and two serum lipid parameters – total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) – in officers with full PTSD. This result is consistent with Karlovic et al.' findings in a sample of Croatian veterans. (Karlovic, et al., 2004b)

The non-PTSD group did not show this correlation and even when restricted to subjects scoring similarly to those in the full PTSD group in hyperarousal scale of symptoms (≥ 14), the correlation of hyperarousal with TC and LDL-C was weak and failed to reach statistical significance. This finding suggests that not only high levels of hyperarousal are correlated to increased TC and LDL-C, but also that re-experiencing and avoidance symptom clusters should be present for this relation to occur.

This observation raises some interesting etiopathogenic speculations regarding the concept of *allostatic load* (Karatoreos & McEwen, 2013) and the role of hyperarousal and PTSD on negative physical health outcomes, especially dyslipidemia and CVD.

Allostasis is a process by which our brain activates mediators that allow our organism to adapt to environmental changes on the short term. However, the overuse and dysregulation of this process – *allostatic load* or *allostatic overload* – may lead to pathophysiological consequences like CVD. (Kario, et al., 2003; Cohen, et al., 2007; McEwen & Gianaros, 2011) Most of the allostatic responses involve the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis (Kario, et al., 2003). Both of these systems are often dysregulated in PTSD (Wentworth, et al., 2013), and there are good evidence to consider that these imbalances play an important role on the development of dyslipidemia.

As a result from HPA axis dysregulation, low levels of plasma cortisol and a heightened inflammation state are commonly observed in PTSD. (Wentworth, et al., 2013) Decreased cortisol can result in an enhanced immune state and in dysregulation of lipid metabolism. (Fries, 2008) Cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)- α have shown to be higher in individuals with PTSD, (von Kanel, et al., 2007; Gill, et al., 2009) and both of these inflammatory parameters contribute to increase triglyceride levels. (Black, 2003) In parallel, it has been shown that chronic activation of HPA axis is associated with overeating and obesity (Dallman, et al., 2004; Nishitani & Sakakibara, 2006), a recognized *allostatic overload* sign (McEwen, 2002).

With a closer relationship to hyperarousal symptom cluster, the abnormal sympathetic activation with higher levels of catecholamines probably contributes to a worsened serum lipid profile in PTSD populations by different means. It is known that norepinephrine inhibit lipoprotein lipase activity, leading to reduced triglyceride clearance, decrease in high-density lipoprotein cholesterol (HDL-C) levels and increase in very-low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol (IDL-C), and low-density lipoprotein cholesterol (LDL-C) levels in bloodstream. (Stoney, 2007) This stress hormone also reduces the activity of hepatic triglyceride lipase, which promotes high serum concentrations of lipoproteins rich in triglycerides. (Stoney, 2007) Also, catecholamines directly stimulate the release of free fatty acid and glycerol from fat depots in the bloodstream. (Stoney, 2007)

Another plausible path between PTSD and dyslipidemia is through sleeping disturbances, a relatively common complain among individuals with PTSD, that have been related to hyperarousal. (Palagini, et al., 2013) For instance, it has been shown that sleep loss induces decreased leptin and increased ghrelin levels, resulting in enhanced hunger and appetite (Spiegel, et al., 2004; Pejovic, et al., 2010). Thus, changes in food ingestion must be considered and it may negatively influence serum lipid concentrations. In addition, sleep

deprivation raises levels of hydrocortisone, and when chronically elevated, it favors fat deposition on blood vessels and abdomen.(McEwen, 2002)

We cannot neglect that serum lipid concentrations are highly influenced by multiple environmental and psychosocial variables. Among risk factors for dyslipidemia, we can name some that are admittedly related to PTSD: smoking, alcohol/substance abuse, diminished physical activity, poor diet and even decreased socioeconomic status due to emotional and physical impairments inherent to the disorder. (Keane, et al., 2006; Wentworth, et al., 2013) Nevertheless, as presented in the results section, we found no important differences between full PTSD and non-PTSD groups regarding to these variables, except for tobacco use that was less prevalent in the full PTSD group - although not statistically significant.

The present study has some limitations: i. we used a self-report instrument as a diagnostic tool for PTSD; ii. the small sample size reduced statistical power; iii. the cross-sectional design compromised causal inferences. Despite these limitations, our finding of a strong correlation between a psychometric variable (hyperarousal symptom cluster) and biological parameters (TC and LDL-C) is extremely unusual in such a small sample. This finding, if corroborated by future studies, may have important clinical implications and help to establish a more appropriate medical monitoring of PTSD patients. A thorough cardiovascular screening, especially for those with high levels of hyperarousal symptoms, could be a useful tool to reduce the morbidity and mortality due to CVD among these patients. Also, the use of antiadrenergic medication e.g. prazosin, propranolol might be particularly beneficial for PTSD patients with increased arousal. (Berger, et al., 2009) Future randomized clinical trials with this drug class could help to establish if it has a role beyond PTSD treatment - preventing cardiovascular complications.

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CONSIDERAÇÕES FINAIS

Conforme apresentado nas seções introdutórias, essa dissertação enfoca dois tópicos de grande relevância no âmbito da saúde pública: o transtorno do estresse pós-traumático (TEPT) e alterações lipídicas. Além da alta prevalência na vida do TEPT, um pior perfil lipídico é fator de risco bem estabelecido para doenças cardiovasculares (DCV), principal causa de óbito no Brasil. Além disso, as inconsistências existentes nessa área de estudo - possivelmente pelo fato de o TEPT ser um transtorno bastante heterogêneo, frequentemente associado a outras morbidades psiquiátricas e de concentrações séricas de lipídeos serem altamente influenciadas por inúmeros fatores ambientais e psicossociais - tornaram a pesquisa necessária.

Tendo como referência as pesquisas realizadas, a hipótese de que o TEPT está associado a um pior perfil lipídico foi corroborada pelos resultados de nossa metanálise. Adicionalmente, a observação de que alterações lipídicas em indivíduos com TEPT possam ser mais pronunciadas entre aqueles com níveis de hiperestimulação autônoma mais elevados, pode ser mais um passo na busca de um melhor entendimento da aparente complexa relação entre o transtorno e um pior perfil lipídico. Esse dado merece ser investigado de forma mais aprofundada através de estudos especificamente delineados para abordar essa questão.

Considerando-se implicações para a prática clínica, esses resultados destacam a importância de um monitoramento cardiometabólico contínuo nos pacientes com TEPT, com atenção redobrada para aqueles mais jovens e com níveis de hiperestimulação autônoma mais elevados. A implementação de uma rotina de mapeamento do perfil lipídico em pacientes com TEPT, associada a medidas preventivas, podem ajudar a reduzir o risco de aterosclerose e suas consequências em indivíduos acometidos pelo transtorno.

No âmbito da pesquisa científica, os achados dessa dissertação destacam a importância do avanço de pelo menos três linhas de pesquisa relacionadas ao tema, incluindo estudos (i) direcionados para identificar as variáveis que impactam na relação entre o TEPT e um pior perfil lipídico (ii) desenhados para explorar mais profundamente os mecanismos biológicos envolvidos nessa relação (iii) voltados para o uso de medicações antiadrenérgicas no manejo do TEPT. Essas duas primeiras linhas podem auxiliar na identificação de indivíduos sob maior risco de DCV e assim, possibilitar ações mais direcionadas e eficientes. Adicionalmente, futuros ensaios clínicos randomizados com bloqueadores adrenérgicos

podem ajudar a determinar se um possível efeito protetor no desenvolvimento de DCV pode ser alcançado no TEPT.

Por fim, espera-se que os resultados dessa dissertação ofereçam subsídios adicionais para a melhoria da saúde e o aumento da expectativa de vida dos indivíduos acometidos pelo TEPT, particularmente com a redução de doenças cardiovasculares devido a alterações lipídicas.

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APÊNDICE A – Formulário de extração de dados**FORMULÁRIO DE EXTRAÇÃO DE DADOS****TRANSTORNO DO ESTRESSE PÓS-TRAUMÁTICO COMO FATOR DE RISCO PARA
ALTERAÇÕES LIPÍDICAS: REVISÃO SISTEMÁTICA E METANÁLISE****1. INFORMAÇÕES GERAIS:****a. REFERÊNCIA BIBLIOGRÁFICA:**

--

b. ANO DO ESTUDO (COLETA DE DADOS):**c. LOCAL DO ESTUDO:****d. TIPO DE PUBLICAÇÃO:**

- () Artigo na íntegra.
() Resumo.
() Estudo não-publicado.
() Dissertação/tese.
() Outro. Especifique:

AUTOR CONTACTADO?

- () Sim. AUTOR RESPONDEU? () Sim. () Não.
() Não.

2. MÉTODOS:**a. DESENHO DE ESTUDO:**

- () Coorte.
() Seccional.
() Caso-controle; Fonte dos Controles:

b. PERFIL DOS PARTICIPANTES:**• Grupo TEPT:**

- () População Geral.
() Outro. Especifique:

- Grupo Não-TEPT:
 - () População Geral.
 - () Outro. Especifique:

- c. TAMANHO AMOSTRAL
 - Grupo TEPT:
 - () N TOTAL () N MASC () N FEM
 - Grupo Não-TEPT:
 - () N TOTAL () N MASC () N FEM

- d. Fonte dos Controles
 - () A mesma dos casos
 - () Diferente dos casos

- e. IDADE:
 - Grupo TEPT:
 - () FAIXA ETÁRIA (medida de dispersão)
 - Grupo Não-TEPT:
 - () FAIXA ETÁRIA (medida de dispersão)

- f. INSTRUMENTO DIAGNÓSTICO PARA TEPT:
 - () Entrevista estruturada. Especifique:
 - () Escala auto preenchida. Especifique:
 - () Médico psiquiatra.

- g. COMORBIDADE PSIQUIÁTRICA:
 - Grupo TEPT:
 - () Sim. Especifique (N):
 - () Não.
 - Grupo Não-TEPT:
 - () Sim. Especifique (N):
 - () Não.

h. CARACTERÍSTICAS DO TRAUMA:

- Misto.
 Específico. Especifique:

i. VARIÁVEIS DE AJUSTE:

- Raça/etnia.
 Sexo.
 Idade.
 Status marital.
 Escolaridade.
 Status socioeconômico/Renda familiar
 Ocupação.
 Local de moradia.
 IMC.
 Presença de comorbidades. Especifique:
 Prática de atividades físicas.
 Uso de álcool.
 Uso de tabaco.
 Uso de drogas de abuso.
 Uso de medicações hipolipemiantes.
 Uso de medicações antiadrenérgicas.
 Uso de outras medicações. Especifique:
 Dieta.
 Outros; Especifique:

j. MÉTODO DE AJUSTE:

- Restrição. Especifique:
 Pareamento.
 Estratificação.
 Modelagem.

3. RESULTADOS :

Média (medida de dispersão)	TEPT	Não TEPT
LDL		
HDL		
Colesterol Total		
Triglicerídeo		

a. **PERDAS:**

- Grupo TEPT: () N () %
- Grupo Não-TEPT: () N () %

4. CONFLITO DE INTERESSE:

() Declarado. Especifique:

() Não declarado.

APÊNDICE B – Adaptação da nos de estudos de coorte para estudos seccionais

Newcastle–Ottawa Scale adapted for cross-sectional studies data abstraction form				
Bias	Cross-Sectional Study	Low risk of bias (+)	High risk of bias (-)	Unclear risk of bias (?)
Selection (max 3*)	Representativeness of exposed sample (PTSD participants)	<input type="checkbox"/> Truly representative of the general population <input type="checkbox"/> Somewhat representative of general population	<input type="checkbox"/> Selected group: particular disease group, particular occupation eg MDD, veterans	<input type="checkbox"/> No description of derivation of sample
	Selection of non-exposed sample (absence of PTSD)	<input type="checkbox"/> Drawn from the same community as the exposed sample	<input type="checkbox"/> Drawn from a different source	<input type="checkbox"/> No description of derivation of non-exposed sample
	Ascertainment of exposure (PTSD diagnosis)	<input type="checkbox"/> Structured interview <input type="checkbox"/> Secure record (diagnosed by a psychiatrist) <input type="checkbox"/> Self-report checklist	<input type="checkbox"/> Written self-report (N/A)	<input type="checkbox"/> No description
Comparability (max 2*)	Comparability of samples on basis of design or analysis	<input type="checkbox"/> Study controls for chronic diseases or other important factor (age)	<input type="checkbox"/> No control for any important factors	
		<input type="checkbox"/> Study controls for any additional factor (medication – lipid lowering and psychotropic drugs/ alcohol/ smoke status/ gender)		
Outcome (max 1*)	Assessment of outcome (lipid profile)	<input type="checkbox"/> Independent blind assessment <input type="checkbox"/> Record linkage	<input type="checkbox"/> Self-report (N/A)	<input type="checkbox"/> No description

ANEXO A – Termo de consentimento livre e esclarecido

Descrição e propósito do estudo

O Senhor (a) está sendo convidado (a) a participar de um estudo para avaliar a presença de sintomas emocionais e comportamentais associados a sua atividade de trabalho.

Para isso, o senhor (a) irá responder alguns questionários, os quais são amplamente aceitos em todo o mundo, sendo utilizados em estudos de vários Transtornos mentais. Os questionários serão aplicados em uma sala, e as respostas serão fornecidas de forma verbal e escrita.

Nenhum exame complementar será necessário neste estudo.

Se o senhor (a) concordar em participar deste estudo, será entrevistado (a) por um psicólogo, o qual aplicará os seguintes questionários: PCL-C, GHQ 12, MBI, AUDIT, THQ, PDEQ, PDI, CIHQ, SM, FA, PANAS e Questionário para coleta de dados clínicos e sócio-demográficos.

Participação e término

Sua participação neste estudo é voluntária. O senhor (a) pode recusar-se a participar do estudo. Se decidir participar, pode mudar de idéia a qualquer momento e retirar-se.

Riscos e benefícios

Este estudo não envolve a administração de qualquer substância, apenas os questionários já citados, portanto não oferece riscos para a sua saúde.

Custos

Não haverá custos para participar deste estudo.

Confidencialidade

Sua identidade neste estudo será tratada de forma estritamente confidencial.

Eu li o texto acima e entendi completamente a natureza e o propósito do estudo ao qual fui convidado (a). Eu concordo em participar deste estudo.

RG do participante

Assinatura do participante

Nome do pesquisador

Assinatura do pesquisador

Goiânia, ___/___/___.

ANEXO B - PCL-C

Instruções:

- Abaixo, há uma lista de problemas e de queixas que policiais às vezes apresentam como uma reação a incidentes críticos. Por favor, indique o quanto você foi incomodado por estes problemas **durante o último mês**, em resposta ao **incidente crítico que você selecionou anteriormente**.
- Por favor, marque 1 para “nada”, 2 para “um pouco”, 3 para “médio”, 4 para “bastante” e 5 para “muito”.

	Nada	Um Pouco	Médio	Bastante	Muito
1. <i>Memória, pensamentos e imagens</i> repetitivos e perturbadores referentes ao incidente crítico que você selecionou?	1	2	3	4	5
2. <i>Sonhos</i> repetitivos e perturbadores referentes ao incidente crítico que você selecionou?	1	2	3	4	5
3. De repente, <i>agir</i> ou <i>sentir</i> como se o incidente crítico que você selecionou estivesse acontecendo de novo (como se você o estivesse revivendo)?	1	2	3	4	5
4. Sentir-se <i> muito chateado</i> ou <i>preocupado</i> quando alguma coisa lembra você o incidente crítico que você selecionou?	1	2	3	4	5
5. Sentir <i>sintomas físicos</i> (por exemplo, coração batendo forte, dificuldade de respirar, suores) quando alguma coisa lembra você o incidente crítico que você selecionou?	1	2	3	4	5
6. Evitar <i>pensar</i> ou <i>falar sobre</i> o incidente crítico que você selecionou?	1	2	3	4	5
7. Evitar <i>atividades</i> ou <i>situações</i> porque <i>elas lembram</i> o incidente crítico que você selecionou?	1	2	3	4	5
8. Dificuldades para <i>lembrar-se de partes importantes</i> do incidente crítico que você selecionou?	1	2	3	4	5
9. <i>Perda de interesse</i> nas atividades que você antes costumava gostar?	1	2	3	4	5

10. Sentir-se <i>distante</i> ou <i>afastado</i> das outras pessoas?	1	2	3	4	5
11. Sentir-se <i>emocionalmente entorpecido</i> ou <i>incapaz</i> de ter sentimentos amorosos pelas pessoas que lhe são próximas?	1	2	3	4	5
12. Sentir como se <i> você não tivesse expectativas para o futuro</i> ?	1	2	3	4	5
13. Ter problemas para <i>pegar no sono</i> ou para <i>continuar dormindo</i> ?	1	2	3	4	5
14. Sentir-se <i>irritável</i> ou ter <i>explosões de raiva</i> ?	1	2	3	4	5
15. Ter dificuldades para se concentrar?	1	2	3	4	5
16. Estar <i>“superalerta”</i> , <i>vigilante</i> ou <i>“em guarda”</i> ?	1	2	3	4	5
17. Sentir-se <i>tenso</i> ou facilmente <i>sobressaltado</i> ?	1	2	3	4	5