UNIVERSIDADE FEDERAL DE PELOTAS
FACULDADE DE MEDICINA
DEPARTAMENTO DE MEDICINA SOCIAL
PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

TESE DE DOUTORADO

Ricardo Lanzetta Haack

Pelotas, 2013

Ricardo Lanzetta Haack

Cintura Hipertrigliceridêmica em adultos jovens pertencentes a uma coorte de nascimentos no sul do Brasil

Tese apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal de Pelotas, como requisito à obtenção do título de Doutor em Ciências (área do conhecimento: Epidemiologia)

Orientador: Bernardo Lessa Horta

Pelotas, dezembro de 2013.

Banca examinadora

Prof. Dr Bernardo Lessa Horta (Orientador)
Universidade Federal de Pelotas

Prof. Dr Juraci Almeida César
Universidade Federal do Rio Grande

Prof. Dra Maria Cecília Assunção
Universidade Federal de Pelotas

Prof. Dr Alexandre da Costa Pereira
Universidade de São Paulo - INCOR

“O entusiasmo é a maior força da alma. Conserva-o e nunca te faltará poder para conseguires o que desejas”

Napoleão Bonaparte

Agradecimentos

Aos meus pais, pelos exemplos, pela minha formação e por me dar, sempre, todas as condições para que eu buscasse os meus objetivos.

À minha esposa Liziane, que sempre me incentivou e compreendeu o esforço que dediquei a este Doutorado.

À minha filha Maria Clara, que está a caminho, mas que já é fonte inspiradora para que eu me torne uma pessoa melhor.

Ao meu orientador Bernardo, pelo convívio e amizade desde os tempos do mestrado. Sem dúvida nenhuma me conduziu na construção deste trabalho de forma tranquila e com muita competência.

A todos os professores e funcionários do Centro de Pesquisas Epidemiológicas da UFPel.

Resumo

Muitas doenças crônicas, entre elas doença cardiovascular (DCV) e câncer, têm origens comuns e estão relacionadas com sobrepeso e obesidade. A obesidade visceral pode ser considerada como um marcador de uma inabilidade do organismo em armazenar adequadamente o excesso de energia no tecido subcutâneo, criando depósitos ectópicos junto às vísceras. Esses depósitos não são identificados através da medida do Índice de Massa Corporal (IMC), existindo a necessidade de desenvolver um critério simples para identificar pacientes com obesidade visceral, que estão em risco metabólico.

A Cintura Hipertrigliceridêmica é definida pela presença simultânea de aumento na circunferência abdominal e níveis elevados de triglicerídeos, e sua presença seria um marcador de risco para o desenvolvimento de doenças crônicas não transmissíveis.

Evidências sugerem que exposições precoces (perinatais), como o peso ao nascer e amamentação, podem estar relacionadas com o desenvolvimento de doenças crônicas na vida adulta. Muitos estudos têm demonstrado que o baixo peso ao nascer (BPN) confere um aumento no risco de alterações metabólicas ou DCV na vida adulta e, possivelmente, aqueles que tiveram uma restrição no crescimento fetal, seguida por um período de rápida recuperação pós-natal, estão em maior risco. Estudo de metanálise demonstrou que a media de colesterol total é menor naqueles indivíduos que foram amamentados em comparação com quem recebeu leite artificial. Essa diferença parece ser ainda maior entre aqueles que receberam aleitamento materno exclusivo.

A Coorte de nascimentos de 1982 de Pelotas compreende, além do estudo perinatal, diversos acompanhamentos. No acompanhamento de 2004/5, quando foi encontrado cerca de 77% da coorte original, tornou-se possível medir a prevalência do fenótipo da cintura hipertrigliceridemica, uma vez que foram dosados os níveis séricos de

triglicerídeos e foi realizada a medida da circunferência da cintura. A medida deste fenótipo é importante, pois parece ser um método barato de identificação de indivíduos em risco de desenvolver DCV e diabete tipo II.

O objetivo desta tese foi determinar a prevalência de Cintura Hipertrigliceridêmica entre adultos jovens, pertencentes à Coorte de Nascimento de 1982, além de determinar os fatores associados com a ocorrência de Cintura Hipertrigliceridêmica nesta população, aos 23 anos de idade, e os fatores precoces (condições de nascimento e amamentação) associados com este fenótipo.

Este volume está estruturado em cinco partes, a saber:

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BPN – Baixo Peso ao Nascer

CC – Circunferência da Cintura

CH – Cintura Hipertrigliceridêmica

DAC – Doença Arterial Coronariana

DCNT – Doenças Crônicas Não Transmissíveis

DCV – Doença Cardiovascular

IARC – Agência Internacional de Pesquisa em Câncer

IMC – Índice de Massa Corporal

OMS – Organização Mundial da Saúde

PCR – Proteína C reativa

RCIU – Retardo de Crescimento Intrauterino

RO – Razão de odds

RR – Risco relativo

SM – Síndrome Metabólica

TG – Triglicerídeos

PARTE I. PROJETO DE PESQUISA

Universidade Federal de Pelotas
Faculdade de Medicina
Departamento de Medicina Social
Programa de Pós-Graduação em Epidemiologia

Projeto de Doutorado

Cintura Hipertrigliceridêmica em adultos jovens pertencentes a uma coorte de nascimentos no sul do Brasil

Aluno: Ricardo Lanzetta Haack
Orientador: Bernardo Lessa Horta

Maio/2011

Sumário:

Resumo:

Entre os mecanismos implicados na gênese de doenças crônicas destacam-se a presença de um processo inflamatório crônico e o desenvolvimento de resistência à insulina, os quais estão relacionados ao sobrepeso e obesidade.

A obesidade visceral (acúmulo de tecido adiposo, junto às vísceras abdominais e ao omento maior) pode ser considerada como um marcador da inabilidade do organismo em armazenar adequadamente o excesso de energia no tecido subcutâneo, criando depósitos ectópicos junto às vísceras abdominais, coração e músculo esquelético(Despres and Lemieux 2006).

Nesse contexto, evidências sugerem que a presença simultânea de um aumento na circunferência da cintura e uma concentração aumentada de um marcador metabólico simples (triglicerídeo plasmático), denominada de cintura hipertrigliceridêmica, estaria associada a uma constelação de anormalidades inflamatórias e pró-trombóticas, as quais resultam em um risco aumentado de desenvolver doença cardiovascular e diabetes tipo II(Despres, Arsenault et al. 2008).

O fenótipo da cintura hipertrigliceridêmica funciona como um algoritmo simples para a identificação na prática clínica de indivíduos em risco de desenvolver doença cardiovascular. Apesar disso, têm sido pouco estudados os fatores associados com o seu desenvolvimento.

O presente estudo será conduzido em uma coorte de adultos jovens que tem sido acompanhada prospectivamente desde o nascimento. Os principais objetivos do estudo são descrever a prevalência de cintura hipertrigliceridêmica e a sua associação com outros marcadores de risco cardiovascular (pressão arterial, glicemia, proteína C reativa e colesterol HDL); bem como identificar seus determinantes.

Os indivíduos pertencentes a coorte de 1982 têm sido acompanhados por inúmeras vezes desde o nascimento. Para o presente trabalho, serão utilizados os dados coletados no estudo perinatal, nas entrevistas dos primeiros anos de vida e na visita a coorte, ocorrida em 2004-5, quando foram entrevistados 77,4% dos indivíduos aos 23 anos de idade. Neste último acompanhamento, foi realizado exame antropométrico e coletado sangue venoso (Barros, Victora et al. 2008).

Nesse sentido, a cintura hipertrigliceridêmica será definida pela associação de uma circunferência da cintura maior ou igual a 90 cm e uma dosagem de triglicerídeos maior ou igual a 2,0mmol/l nos homens e circunferência da cintura maior ou igual a 85 cm e triglicerídeos maior ou igual a 1,5mmol/l nas mulheres.

A presente tese avaliará a associação das seguintes exposições com a ocorrência do fenótipo da cintura hipertrigliceridêmica:

- Exposições proximais: renda familiar, escolaridade do indivíduo, índice de massa corporal, pressão arterial, colesterol HDL, glicemia, proteína C reativa, consumo alimentar de gorduras e fibras e sedentarismo.
- Exposições distais: peso ao nascer, idade gestacional, crescimento intrauterino e duração da amamentação.

Artigos:

- Cintura Hipertrigliceridêmica em adultos jovens pertencentes a uma coorte de nascimentos no Sul do Brasil

- Determinantes precoces da Cintura Hipertrigliceridêmica: Efeito das condições de nascimento e duração da amamentação.

- Cintura Hipertrigliceridêmica e sua associação com fatores cardiometabólicos: revisão de literatura

Definição de termos e abreviaturas:

BPN – Baixo Peso ao Nascer

CC – Circunferência da Cintura

CH – Cintura Hipertrigliceridêmica

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TG – Triglicerídeos

Introdução:

De acordo com a Organização Mundial da Saúde (OMS), as doenças crônicas não transmissíveis (DCNT), como a doença cardiovascular (DCV), câncer e diabetes são as principais causas de óbito no mundo, sendo responsáveis por aproximadamente 60% das mortes(Murray C.L.J. and A.D. 1996; Blackburn, Lamarche et al. 2003; Esmaillzadeh, Mirmiran et al. 2006). Entre elas, a DCV figura como a mais importante(Murray and Lopez 1997; Mathers, Lopez et al. 2006).

As DCV englobam uma variedade de desordens, incluindo as miocardiopatias e as doenças do sistema vascular do coração, cérebro e outros órgãos vitais. A cardiopatia isquêmica, o acidente vascular cerebral e a insuficiência cardíaca congestiva são responsáveis por 80% destas doenças(Mathers, Lopez et al. 2006). A Associação Americana de Cardiologia estima que mais de um em cada três americanos adultos tenham uma ou mais DCV, sendo aproximadamente 50% destes menores de 60 anos(Roger, Go et al.).

As DCV são principal causa de óbito nos Estados Unidos, sendo responsáveis por 33,6% das mortes(Roger, Go et al.). Desde 1900, com exceção de 1918, as DCV foram responsáveis por mais mortes do que qualquer outra causa nos Estados Unidos, ficando a frente do câncer, doença pulmonar obstrutiva crônica e dos acidentes(Roger, Go et al.).

No Brasil, as DCV também são a principal causa de óbito(Ishitani, Franco Gda et al. 2006). Em 2003, elas foram responsáveis por 27,4% dos óbitos na faixa etária entre 35 e 64 anos (26% de homens e 30% de mulheres) e por 35,9%, na faixa de 65 anos ou mais (31% homens e 35% mulheres)(Azambuja, Foppa et al. 2008).

Algumas projeções indicam um aumento da importância das DCV nos países de baixa renda. A maior longevidade, devido à redução na mortalidade por doenças

infecciosas, associada à adoção de um estilo de vida mais favorável à exposição aos fatores de risco para as DCV, constitui as principais razões deste incremento(Ishitani, Franco Gda et al. 2006).

O termo câncer é usado genericamente para representar um conjunto de mais de 100 doenças, incluindo tumores malignos de diferentes localizações. Segundo a Agência Internacional de Pesquisa em Câncer (IARC), o impacto mundial desta doença mais que dobrou nos últimos 30 anos(Gomez-Huelgas, Bernal-Lopez et al. 2011) e o crescimento populacional, assim como o envelhecimento da população e a mudança em hábitos de vida contribuirão ainda mais para o aumento na sua incidência(Gomez-Huelgas, Bernal-Lopez et al. 2011).

O câncer e as DCV têm determinação multifatorial e compartilham alguns fatores de risco. Os fatores de risco comuns não-modificáveis são idade, sexo e raça, enquanto que os modificáveis incluem distribuição da gordura corporal (especialmente adiposidade central), sedentarismo, tabagismo, altos níveis de pressão arterial, níveis elevados de glicemia e colesterol elevado(Smith, Greenland et al. 2000). No tocante aos fatores de risco biológicos, a presença de dislipidemia aterogênica (níveis elevados de triglicerídeos, apo lipoproteína B e partículas pequenas de colesterol LDL e níveis baixos de colesterol HDL), hipertensão arterial e níveis elevados de glicemia plasmática(Grundy, Cleeman et al. 2005) aumentam o risco de ocorrência de DCV, enquanto que inúmeros estudos apontam para uma associação entre obesidade e risco de desenvolver câncer(Calle and Kaaks 2004).

Diversos mecanismos tentam explicar a relação entre excesso de peso e risco de câncer, entre eles os mais estudados são: o desenvolvimento de resistência à insulina, o processo inflamatório crônico relacionado ao excesso de peso, o excesso de hormônios sexuais e as adipocitocinas. A resistência à insulina e o processo inflamatório crônico

relacionado ao excesso de peso parecem estar associados ao risco de diversos tipos de neoplasias(Renehan, Roberts et al. 2008).

Cintura Hipertrigliceridêmica:

No ano de 2000, Lemieux e colegas propuseram que o aumento na circunferência abdominal, associado ao aumento nos níveis de triglicerídeos plasmáticos, seria preditivo da presença dos marcadores metabólicos de risco cardiovascular(Lemieux, Pascot et al. 2000) e chamaram esta associação de fenótipo da Cintura Hipertrigliceridêmica (CH). Neste estudo, mais de 80% dos indivíduos com aumento da circunferência abdominal e níveis elevados de triglicerídeos apresentavam níveis elevados de insulina, apo lipoproteína B e partículas pequenas de colesterol LDL, chamados pelos autores de ”tríade metabólica”(Lemieux, Pascot et al. 2000). Em um subgrupo de pacientes submetidos a cateterismo cardíaco, em que a presença de Doença Arterial Cardíaca (DAC) foi caracterizada pela existência de estenose em mais de 50% de uma das coronárias, a razão de odds para DAC foi 3,6 ($p < 0,003$) vezes maior entre os indivíduos com aumento da circunferência abdominal e níveis elevados de triglicerídeos, quando comparados com os indivíduos com circunferência abdominal e níveis de triglicerídeos dentro da normalidade(Lemieux, Pascot et al. 2000).

Estudos com pequenas diferenças nos pontos de corte adotados para identificar CH observaram resultados semelhantes(Lemieux, Pascot et al. 2000; Blackburn, Lamarche et al. 2003; LaMonte, Ainsworth et al. 2003; Solati, Ghanbarian et al. 2004; Gazi, Filippatos et al. 2006; St-Pierre, Lemieux et al. 2007; Sam, Haffner et al. 2009; Arsenault, Lemieux et al. 2010), mostrando que a CH seria, então, um marcador de utilidade clínica, para identificação de indivíduos em risco de desenvolver doença cardiovascular e diabetes.

A CH é definida pela presença simultânea de aumento na circunferência abdominal e níveis elevados de triglicerídeos plasmáticos(Lemieux, Pascot et al. 2000). A presença de circunferência abdominal aumentada e níveis séricos elevados de triglicerídeos seriam um marcador da relativa inabilidade do indivíduo em manejar e armazenar energia extra no tecido subcutâneo(Lemieux, Pascot et al. 2000) o que, segundo este modelo (Despres and Lemieux 2006), aumentaria o risco de DCV.

Os estudos de Lemieux e colaboradores sugerem que a presença de circunferência abdominal aumentada de forma isolada não é suficiente para identificar homens com a tríade metabólica e, quando se considera a hipertrigliceridemia (≥ 2.0mmol/l) em associação com a circunferência abdominal, aumenta-se o poder para identificar estes indivíduos(Lemieux, Pascot et al. 2000). Nestes trabalhos, mais de 80% dos homens com CH tinham a tríade metabólica, independentemente se o aumento na circunferência abdominal era moderado (entre 91 e 99 cm) ou substancial (≥ 100 cm)(Lemieux, Pascot et al. 2000).

Em outro estudo, a presença de CH esteve associada com maior risco cardiovascular entre homens e mulheres, mesmo após ajuste para os fatores de risco cardiovasculares tradicionais(Arsenault, Lemieux et al. 2010). Em estudos de base populacional com adultos, a prevalência de CH variou entre 11% e 19%(Lemieux, Almeras et al. 2002; LaMonte, Ainsworth et al. 2003; Rogowski, Shapira et al. 2009). Entre adolescentes de 10 a 19 anos, a prevalência de CH foi de 6,4% (IC 95% 5,5 – 7,2), sendo mais comum entre os meninos. Esta prevalência foi de 38,7% entre adolescentes com sobrepeso ou obesidade, contra 0,7% nos com peso normal(Esmaillzadeh, Mirmiran et al. 2006; Esmaillzadeh, Mirmiran et al. 2006).

Estudo de base populacional realizado no Canadá, com adultos do sexo masculino, encontrou prevalência de CH de 19% e este fenótipo esteve associado com uma maior

razão colesterol total : colesterol HDL(Lemieux, Almeras et al. 2002). Neste mesmo estudo, encontrou-se aumento na proporção de diabéticos entre os homens com CH (16,5%), comparados com homens com circunferência abdominal e triglicerídeos normais (1,6%)(Lemieux, Almeras et al. 2002). Por outro lado, homens não diabéticos com CH tinham peso, índice de massa corporal (IMC) e medida da circunferência abdominal similares aos de pacientes diabéticos e maiores níveis de colesterol LDL(Lemieux, Almeras et al. 2002).

Outro estudo, no Irã, também de base populacional e com homens entre 18 e 70 anos de idade, encontrou prevalência de CH de 19%(Solati, Ghanbarian et al. 2004) e este fenótipo esteve associado a maiores níveis de pressão arterial, colesterol total, colesterol LDL e glicemia e menor nível de colesterol HDL(Solati, Ghanbarian et al. 2004).

Estudo de base populacional com 4811 escolares, com média de idade de 12 anos, encontrou uma prevalência de CH de 8,5%, sem diferença entre os sexos(Alavian, Motlagh et al. 2008). A associação entre peso ao nascer e CH foi modificada pelo sexo, sendo um peso maior de 4.000g nos meninos (RO 1,4 IC 95% 1,10 – 2,05) e menor que 2.500g nas meninas (RO 1,2 IC 95% 1,09 – 1,70) associados com maior risco de CH(Alavian, Motlagh et al. 2008). Baixa escolaridade dos pais, história familiar de diabetes, obesidade ou DCV e baixo nível de atividade física estiveram associados positivamente com CH, em ambos os sexos(Alavian, Motlagh et al. 2008).

Diferentes pontos de corte para circunferência abdominal e triglicerídeos têm sido utilizados para definir a ocorrência do fenótipo da cintura hipertrigliceridêmica. Lemieux e colegas, trabalhando apenas com homens, realizaram análise de sensibilidade e especificidade para identificar os pontos de corte tanto de cintura quanto de níveis de triglicerídeos para indivíduos com risco de desenvolver DCV. Assim, utilizaram todos

os indivíduos não obesos incluídos no estudo (IMC<25Kg/m^2) e determinaram a mediana dos valores de insulina plasmática, apolipoproteína B e partículas pequenas de colesterol LDL. Consideraram, então, que apresentar valores das três medidas superiores a mediana da amostra, diagnóstico de portador da tríade metabólica. Entre estes não obesos, 21% foram caracterizados como portadores de tríade metabólica.

Para examinar a associação da circunferência da cintura com os componentes da tríade metabólica, a amostra estudada foi dividida em decis de circunferência da cintura, quando se percebeu que a concentração de apolipoproteína aumentava rapidamente até aproximadamente 100cm de circunferência da cintura, a partir de onde se mantinha razoavelmente estável. Já os níveis de insulina tinham um crescimento contínuo, na medida em que se aumentava a circunferência da cintura. Quanto ao colesterol LDL, a maior redução no diâmetro de suas partículas foi observada em um ponto entre 1.82 e 2.11mmol/l de triglicerídeos.

O ponto de corte para triglicerídeos de 1.9 a 2.0mmol/l, associado com circunferência da cintura entre 85 e 90cm, corresponde a valores com a melhor relação de sensibilidade (73% a 78%) e especificidade (78% a 81%)(Lemieux, Pascot et al. 2000) e, para simplificar o algoritmo na prática clínica, adotou o valor de 2.0mmol/l para triglicerídeos e 90cm para circunferência da cintura(Lemieux, Pascot et al. 2000).

Neste mesmo estudo, a razão de odds para doença coronariana foi, respectivamente, de 1,1 (IC 95% 0,41-2,98), para indivíduos com circunferência da cintura aumentada mas com triglicerídeos normais; 2,5 (IC 95% 0,65-9,67), para triglicerídeos aumentados porém com circunferência da cintura normal; e, de 3,6 (IC 95% 1,27-10,93), para aumento de triglicerídeos e circunferência da cintura(Lemieux, Pascot et al. 2000).

A Tabela 1 apresenta os pontos de corte utilizados pelos estudos de prevalência de CH, para definir a ocorrência do fenótipo.

Tabela 1. Principais trabalhos sobre Cintura Hipertrigliceridêmica e respectivos pontos de corte utilizados

Autor principal/ Ano	Circunferência Abdominal		Triglicerídeos	
	Homens	Mulheres	Homens	Mulheres
Lemieux/2000	≥ 90cm	--	≥2,0mmol/l	--
Blackburn/2003	≥90cm	--	≥2,0mmol/l	--
LaMonte/2003	--	≥88cm	--	≥1,7mmol/l
Solati/2004	≥ 95cm	--	≥1,8mmol/l	--
Gazi/2006	≥90cm	≥88cm	≥2,0mmol/l	≥1,7mmol/l
Esmaillzadeh/2006	≥ ao percentil 90 para sexo e idade	≥ ao percentil 90 para sexo e idade	≥1,2mmol/l	≥1,2mmol/l
St-Pierre/2007	≥ 90cm	≥ 85cm	≥2,0mmol/l	≥2,0mmol/l
Rogowski/2009	≥90cm	≥ 85cm	≥2,0mmol/l	≥1,5mmol/l
Sam/2009	≥90cm	≥ 85cm	≥2,0mmol/l	≥2,0mmol/l
Arsenault/2010	≥90cm	≥85cm	≥2,0mmol/l	≥1,5mmol/l

Justificativa:

Muitas doenças crônicas, entre elas doença cardiovascular e câncer, têm origens comuns e estão relacionadas com sobrepeso e obesidade. Entre os mecanismos implicados na gênese de doenças crônicas destacam-se a presença de um processo inflamatório crônico e o desenvolvimento de resistência à insulina. As DCV permanecem como a principal causa de óbito nos países industrializados e apresentam um crescimento alarmante em países em desenvolvimento(Myerburg, Kessler et al. 1993).

As doenças crônicas, em geral, têm um longo período de latência pré-clínico, quando o indivíduo fica exposto aos fatores de risco, que geralmente são modificáveis

através de alterações em hábitos de vida, pela adoção de medidas de prevenção primária. Uma tríade de marcadores de risco metabólico, definida pela presença simultânea de níveis elevados de insulina, apo lipoproteína B e partículas pequenas de colesterol LDL, demonstrou-se fortemente associada com aumento de risco coronariano em adultos assintomáticos(Lamarche, Tchernof et al. 1998). A medida da cintura, associada com a medida dos triglicerídeos séricos, parece ser uma boa aproximação desta tríade uma vez que mais de 80% dos homens adultos com cintura maior ou igual a 90 cm e medida de triglicerídeos maior ou igual a 2,0mmol/l, de acordo com Lemieux, eram portadores desta tríade metabólica, o mesmo ocorrendo com apenas 10% daqueles com cintura menor que 90 cm e nível plasmático de triglicerídeos menor que 2,0mmol/l(Lemieux, Pascot et al. 2000).

Atualmente, sabe-se que a CH está associada positivamente com obesidade(Alavian, Motlagh et al. 2008), maior IMC(Arsenault, Lemieux et al. 2010) e pior perfil lipídico(Lemieux, Almeras et al. 2002). Também se relaciona positivamente com a presença de marcadores de inflamação sistêmica(Rosolova, Petrlova et al. 2008; Esmaillzadeh and Azadbakht 2010), maior prevalência de síndrome metabólica(Gazi, Filippatos et al. 2006) e diabetes(Gazi, Filippatos et al. 2006; St-Pierre, Lemieux et al. 2007). Todos estes fatores são importantes na gênese das doenças crônicas, não só das DCV, mas também de algumas neoplasias como câncer de cólon e de mama. Além disso, CH por si só é um marcador de risco importante, uma vez que os indivíduos com cintura hipertrigliceridêmica tendem a ter eventos cardíacos mais precocemente(St-Pierre, Lemieux et al. 2007) e maior mortalidade(Arsenault, Lemieux et al. 2010), com maior risco de morrer por todas as causas e por DCV(Tanko, Bagger et al. 2005).

Estudos longitudinais têm demonstrado que fatores precoces, incluindo aqueles relacionados à gestação e crescimento, podem programar o desenvolvimento de doenças

crônicas(Horta, Barros et al. 2003; Singhal and Lucas 2004). O estudo dos nascidos em Pelotas em 1982, com dados desde a gestação até a vida adulta, tornam possível a investigação da prevalência de CH e dos fatores precoces e tardios a ela associados. O presente estudo será conduzido com adultos jovens, em uma faixa etária na qual a maioria dos hábitos de vida já estão estabelecidos, mas quando as doenças crônicas em geral ainda não se manifestaram. Além disso, existem pouquíssimos estudos sobre os determinantes, tanto precoces quanto contemporâneos, da CH. Logo, conhecer a prevalência deste fenótipo, assim como investigar os fatores precoces (distais), que estão relacionados com a sua programação e, ao mesmo tempo, identificar os fatores proximais, no início da vida adulta, podem auxiliar no desenvolvimento de estratégias para prevenção de doenças crônicas.

Revisão de literatura:

Com o objetivo de obter uma ampla revisão da literatura, foram utilizadas as seguintes estratégias:

a) Primeiro, na base de dados pubmed/medline, identificaram-se artigos que apresentassem as palavras chave (mesh terms) “lipids” e “waist circumference” (lipids AND waist circumference). Esta pesquisa foi realizada sem limitação de tempo e apenas para artigos escritos em inglês ou português. Com esta estratégia, foram localizados 521 trabalhos, dos quais, 5 foram selecionados para leitura na integra após análise dos títulos.

b) A segunda pesquisa no pubmed/medline utilizou as palavras chave “waist circumference” e “hypertriglyceridemia”, também sem limitação de tempo, sendo localizados 34 artigos, dos quais 9 foram selecionados para leitura na íntegra.

c) Na terceira e última pesquisa no pubmed/medline, procuraram-se todos os trabalhos que contivessem o termo "hypertriglyceridemic waist phenotype" no título, sem limitação de tempo, sendo encontrados 15 artigos, os quais foram selecionados para leitura na íntegra.

d) A quarta estratégia foi a pesquisa, na base de dados Web of Science, de artigos que citaram os principais trabalhos já localizados anteriormente. Com esta estratégia, foram localizados 29 artigos para leitura na íntegra.

e) Na base de dados SciELO (Scientific Eletronic Library on Line), procuraram-se trabalhos com o termo "Cintura Hipertrigliceridêmica", sendo encontrados 3 artigos e selecionado 1 para leitura.

f) Ainda na base de dados SciELO, utilizaram-se os termos "Hipertrigliceridemic Waist Phenotype" e "Hipertriglyceridemia AND Waist circunference" ambas sem resultado.

g) Por fim, utilizaram-se os termos "hipertrigliceridemia AND circunferência da cintura" na base de dados SciELO, sendo localizado 7 trabalhos, porém, após análise dos títulos, nenhum foi selecionado para leitura na íntegra.

Esta revisão localizou ao todo 59 artigos, sendo excluídos 28, por serem duplicatas, cinco por incluírem apenas populações específicas, como diabéticos, pacientes internados ou de clínicas de tratamento de dislipidemia e um por se tratar de editorial. Restaram, assim, 25 trabalhos para a revisão de literatura.

A Tabela 2 apresenta os artigos selecionados e seus principais resultados.

Resultados da revisão de literatura:

Estudos de prevalência de cintura hipertrigliceridêmica (CH):

Ao todo, 14 estudos de base populacional avaliaram a prevalência de CH, cujos resultados tiveram uma variação muito grande, em decorrência das diferentes populações amostradas e pontos de corte utilizados para definir a ocorrência do desfecho. Desse modo, foram excluídos estudos que trabalharam com populações selecionadas, como, por exemplo, pacientes de centros de tratamento para dislipidemia e grupos de pacientes diabéticos(Gazi, Filippatos et al. 2006; Blackburn, Lemieux et al. 2009; de Graaf, Schuijf et al. 2010). Entre os estudos que trabalharam com adultos de ambos os sexos, a prevalência variou entre 12,7% e 36,5%(Kahn and Valdez 2003; Gazi, Filippatos et al. 2006; Rogowski, Shapira et al. 2009; de Graaf, Schuijf et al. 2010; Yu, Huang et al. 2010; Amini, Esmaillzadeh et al. 2011; Gomez-Huelgas, Bernal-Lopez et al. 2011).

Kahn, em 2003, trabalhando com uma amostra nacional de adultos, com idade entre 18 e 90 anos, nos Estados Unidos, encontrou uma prevalência de 24,8%, sendo a mais baixa de 6,2%, na faixa etária de 18 a 24 anos. A prevalência aumentou até a faixa de 55 a 64 anos, quando atingiu 43,7%, e diminuiu, sucessivamente, atingindo 42,1%, entre 65 e 74 anos, e 36,4%, entre 75 e 90 anos(Kahn and Valdez 2003).

Entre adultos sadios em Israel, Holanda e Espanha, a prevalência foi respectivamente, 12,7%, 31% e 14,5%(Rogowski, Shapira et al. 2009; de Graaf, Schuijf et al. 2010; Gomez-Huelgas, Bernal-Lopez et al. 2011).

Em 2010, Yu, na China, avaliou 14770 adultos entre 35 e 74 anos e encontrou prevalências altas de CH, sendo 35,4% entre os homens e 33,6% entre as mulheres(Yu, Huang et al. 2010). Já no Irã, com 1323 adultos com idade entre 30 e 55 anos, a prevalência encontrada foi 9,6% entre os homens e 23,6% entre as mulheres(Amini, Esmaillzadeh et al. 2011).

Lemieux - no Canadá -, e Solati - no Irã- avaliaram apenas homens e observaram uma prevalência de 19%(Lemieux, Almeras et al. 2002; Solati, Ghanbarian et al. 2004). Já na França, a prevalência encontrada por Czernichow foi de 12,1%(Czernichow, Bruckert et al. 2007).

Já em relação às mulheres, foram identificados apenas três estudos, sendo as prevalências encontradas geralmente um pouco mais baixas que entre os homens. LaMonte, nos Estados Unidos, encontrou prevalência de 10,9%(LaMonte, Ainsworth et al. 2003), enquanto que Tanko, na Suíça, avaliou mulheres na pós-menopausa e encontrou 15,8%(Tanko, Bagger et al. 2005). Em outro estudo, somente com mulheres, na Grécia, utilizaram-se quatro diferentes pontos de corte para determinar CH, a prevalência variou entre 12 e 22% na pré-menopausa e, entre 26 e 52%, na pós-menopausa(Gazi, Milionis et al. 2008), dependendo do ponto de corte utilizado.

Dois estudos trabalharam com escolares e adolescentes, ambos no Irã, Esmaillzadeh, em 2006, realizou estudo com 3036 adolescentes entre 10 e 19 anos e encontrou uma prevalência de CH de 6,4%(Esmaillzadeh, Mirmiran et al. 2006). Já Alavian, em 2008, estudando 4811 escolares com média de idade de 12 anos, encontrou CH em 8,5%(Alavian, Motlagh et al. 2008).

Fatores de risco para cintura hipertrigliceridêmica (CH):

Fatores precoces:

Foi identificado apenas um estudo que investigou a associação entre exposições precoces e o desenvolvimento de CH. Neste trabalho, com 4811 escolares com média de idade de 12 anos, em uma análise de regressão logística ajustada para idade, o efeito do peso ao nascer foi modificado pelo sexo. A razão de odds para CH

foi maior nos meninos com peso ao nascer maior que 4.000g (RO 1,4; IC 95% 1,10 – 2,05) e, nas meninas, com peso ao nascer menor que 2.500g (RO 1,2; IC 95% 1,09 – 1,70)(Alavian, Motlagh et al. 2008).

Fatores contemporâneos:

Apenas dois estudos incluíram, em suas análises, nível socioeconômico e escolaridade, sendo que menor escolaridade do sujeito da pesquisa(Gomez-Huelgas, Bernal-Lopez et al. 2011) e de seus pais(Alavian, Motlagh et al. 2008) estiveram associadas com maior prevalência de CH.

O sedentarismo aumenta a prevalência de CH tanto na adolescência(Alavian, Motlagh et al. 2008)como na vida adulta(Esmaillzadeh and Azadbakht 2010; Gomez-Huelgas, Bernal-Lopez et al. 2011).

A CH também mostrou-se associada com obesidade(Alavian, Motlagh et al. 2008) e maior IMC(Arsenault, Lemieux et al. 2010). Em um estudo transversal, com 3036 adolescentes, CH estava presente em 38,7% dos adolescentes com sobrepeso, 7,7% daqueles em risco de sobrepeso e em 0,7% dos com peso normal ($p=0,001$)(Esmaillzadeh, Mirmiran et al. 2006).

Estudo transversal conduzido no Irã, com 861 adultos entre 18 e 74 anos, avaliou a relação de CH com o consumo de grãos. Indivíduos no quartil de maior consumo de grãos tiveram menor prevalência de CH (29%), quando comparados com o quartil de menor consumo (44%)($p<0,05$). Por outro lado, indivíduos no quartil de maior consumo de grãos refinados tiveram a maior prevalência de CH (45%), quando comparados com o quartil de menor consumo (27%) ($p<0,05$)(Esmaillzadeh, Mirmiran et al. 2005).

No estudo realizado com escolares de 12 anos de idade, no Irã, história familiar de diabete, de obesidade ou de DCV precoce estavam associadas com CH, assim como sedentarismo(Alavian, Motlagh et al. 2008).

Tabela 2. Artigos selecionados para revisão de literatura

Autor ano/local	Desenho	Definição de CH	Principais resultados
Lemieux, I. 2000 / Canadá	Estudo I- transversal com 185 homens sedentários. Realizada coleta de sangue para dosagem de colesterol, triglicerídeos, insulina e apoB Excluídos os diabéticos Estudo II- transversal com 287 homens submetidos a cateterismo cardíaco para investigação de dor retroesternal. Realizada coleta de sangue para dosagem de colesterol, triglicerídeos, insulina e apoB	CC ≥ 90cm TG ≥ 2,0mmol/l	Determinou os pontos de corte para CH com melhor relação entre sensibilidade e especificidade. Mostrou que é necessária a associação de aumento na circunferência da cintura com triglicerídeos elevados para identificar indivíduos com a tríade metabólica. Razão de Odds de 3,6 (1,17-10,93) para doença coronariana entre aqueles com CH.
Lemieux, I. 2002 / Canadá	Transversal com 907 homens que participaram do estudo e para os quais havia dados completos de risco cardiovascular. Foi realizada dosagem sanguínea e medidas antropométricas.	CC ≥ 90cm TG ≥ 2,0mmol/l	Prevalência de CH de 19%. CH associada à maior razão colesterol total/colesterol HDL. Razão de odds de 7,0 (2,7-18,4) para diabetes entre aqueles com CH. Pessoas com CH tinham perfil metabólico tão deteriorado quanto aqueles com diabete.
St-Pierre, J. 2002/ Canadá	Transversal aninhado a uma coorte. 569 homens (18 – 69 anos) submetidos a cateterismo cardíaco por dor retroesternal, sendo incluídos somente aqueles com doença coronariana comprovada. Uma segunda amostra com 250 homens sem história de doença coronariana usado como grupo controle. Foram excluídos os diabéticos e realizados exames laboratoriais e medidas antropométricas.	CC ≥ 90cm TG ≥ 2,0mmol/l	Razão colesterol total/colesterol HDL aumentada em indivíduos com CH independente da glicemia. CH aumenta o odds para doença coronariana enquanto que a glicemia de jejum não tem impacto.
Hiura, Y. 2003/ Australia	Transversal com 80 mulheres indígenas. Realizadas medidas antropométricas e dosagens laboratoriais.	CC > 95 cm TG > 2,0mmol/l	CH associada com maior razão colesterol total/colesterol HDL, menores níveis de HDL e maiores níveis de LDL.
LaMonte, M. J. 2003/ Estados Unidos	Transversal com 135 mulheres americanas. Realizado exames laboratoriais e medidas antropométricas.	CC ≥ 88 cm TG ≥ 150mg/dl	Prevalência de CH 10,9%. Prevalência da tríade metabólica maior nas mulheres com CH.
Kahn, H. S. 2003/ Estados Unidos	Transversal com 9183 adultos de 18 a 90 anos	Homens CC ≥ 95cm TG≥1,45 mmol/l Mulheres CC ≥88cm TG≥1,45mmol/l	Prevalência de CH 24,8% 6,2% (18 -24 anos) 43,7% (55-64 anos) 42,1% (65-74 anos) 36,4% (75-90 anos) CH associada com pior perfil lipídico e fatores de risco DCV

Tabela 2. Continuação

Autor ano/local	Desenho	Definição de CH	Principais resultados
Solati, M. 2004/ Irã	Transversal com 4169 homens de 18 a 70 anos.	CC ≥ 95 cm TG ≥ 1,8mmol/l	Prevalência de CH 19%. CH esteve associada com maiores níveis de colesterol total, triglicerídeos, colesterol LDL e glicose e menores níveis de colesterol HDL. No grupo de indivíduos com CH, 75% tinham 4 ou mais fatores de risco para DCV.
Tanko, L. B. 2005/ Suiça	Longitudinal com 686 mulheres na pós-menopausa acompanhadas por 8,5 anos. Medidas antropométricas e sanguíneas no início do estudo. Desfecho era mortalidade por todas as causas e por DCV.	CC ≥ 88 cm TG ≥ 1,45mmol/l	Prevalência de CH 15,8% Mulheres com CH o risco relativo para morte por todas as causas foi 2,2 (1,3-3,6) e para morte por DCV foi 4,7 (2,2-9,8). WC ≥ 95 cm TG ≥ 1,8mmol/l
Esmaillzadeh, A. 2005/Irã	Transversal com 861 adultos entre 18 e 74 anos. Excluídas pessoas com diabetes, doença cardiovascular e acidente vascular cerebral. Excluídas pessoas com consumo energético diário menor de 800kcal/d ou maior que 4200kcal/d.	Homens CC ≥ 80 cm Tg≥150mg/dl Mulheres CC ≥ 79 cm Tg≥150mg/dl	Indivíduos no quartil de maior consumo de grãos tiveram significativamente menor prevalência de CH (29%) quando comparados com o quartil de maior consumo (44%) p<0,05. Indivíduos no quartil de maior consumo de grãos refinados tiveram a maior prevalência de CH (45%) quando comparados com o quartil de menor consumo (27%) p<0,05.
Esmaillzadeh, A. 2006/ Irã	Transversal com 3036 adolescentes de 10 a 19 anos. Realizadas medidas antropométricas e exames laboratoriais.	CC > percentil 90 para sexo e idade TG ≥ 110mg/dl	Prevalência de CH 6,4% Mais comum em meninos. CH presente em 38,7% dos com sobrepeso, 7,7% dos em risco de sobrepeso e 0,7% dos com peso normal (p=0,001).
Esmaillzadeh, A. 2006/ Irã	Transversal com 3036 adolescentes de 10 a 19 anos. Realizadas medidas antropométricas e exames laboratoriais.	CC > percentil 90 para sexo e idade TG ≥ 110mg/dl	CH associada significativamente com maiores prevalências de todos os fatores de risco metabólicos exceto glicemia. Após controlar idade, sexo e atividade física, CH associada com maior PA (RR2,1; 1,7-2,7), maior LDL (RR3,3; 2,5-4,4), menor HDL (RR 2,1;1,7-2,5), maior colesterol total (RR5,1;3,9-6,7) e maior HAS (RR 2,8; 2,0-3,8). Após controlar para IMC a associação com PA e HAS sumiu. Glicemia não esteve associada em nenhum modelo.

Tabela 2. Continuação

Autor ano/local	Desenho	Definição de CH	Principais resultados
Gazi, I. F. 2006/ Grécia	Transversal com 260 adultos. Excluídos da amostra pacientes com DCV, diabete, doença hepática ou renal e hipotireoidismo.	Homens CC ≥90cm Tg ≥180mg/dl Mulheres CC≥88cm Tg≥150mg/dl	CH presente em 66,2% dos indivíduos com diagnóstico de SM e em 5,5% dos sem SM. CH associado a maior PA sistólica e diastólica, maior nível de glicose, insulina e índice de HOMA. CH associada ao maior nível de colesterol total, triglicerídeos, colesterol não HDL, apoB e VLDL. E associada a menor taxa de HDL. CH associada ao menor tamanho de partículas do LDL. 66,7% dos indivíduos com CH tinham a tríade metabólica.
Czernichow, S. 2007/ França	Prospectivo com 3430 homens e um seguimento de 7,5 anos.	CC ≥ 90cm TG ≥ 2mmol/l	Prevalência de CH 12,1%. Risco de DCV 2,13 (1,21-3,76)
St-Pierre, J. 2007/ Canadá	Transversal 1190 adultos, excluídos diabéticos. DCV considerada quando presente IAM documentado ou diagnostico por cateterismo.	CC ≥ 90cm TG ≥ 2mmol/l	CH perfil lipídico mais deteriorado e maior PA. Teste de tolerância oral a glicose alterado em pacientes com CH mesmo com glicemia de jejum normal. Evento cardíaco tende a ser mais cedo do que nos sem CH.
Alavian, S. M. 2008/ Irã	Transversal com 4811 escolares com média de idade de 12 anos.	Definidos pontos de corte através de curva ROC	Prevalência de CH 8,5%. CH associado com peso ao nascer maior que 4000g nos meninos (RR1,4;1,1-2,05) e menor que 2500g nas meninas (RR1,2;1,09-1,7). História familiar de DM, obesidade ou DCV prematura e baixo nível educacional associado com maior prevalência de CH. Sedentarismo aumenta prevalência de CH (meninos RR1,4;1,2-2,5 e meninas RR1,3;1,1-1,9).

Tabela 2. Continuação

Autor ano/local	Desenho	Definição de CH	Principais resultados
Gazi, I. F. 2008/ Grécia	Transversal com 228 mulheres. Excluídos da amostra pacientes com DCV, diabete, doença hepática ou renal e hipotireoidismo.	1. HTGW-L: TG ≥1.7 mmol/L e CC ≥88 cm 2. HTGW-T: TG ≥1.45 mmol/L e CC ≥88 cm 3. HTGW-H: TG ≥2.0 mmol/L e CC ≥80 cm 4. HTGW-P: TG ≥2.0 mmol/L e CC ≥90 cm	De acordo com o critério adotado, a prevalência de CH variou de 12% a 22% na pré-menopausa e 26% a 52% na pós-menopausa.
Rosolova, H. 2008/ Repúplica Checa	Transversal com 381 pacientes com DM tipo II entre 50 e 80 anos.		CH principal fator associado com níveis elevados de proteína c reativa.
Blackburn, P. 2009/ Canadá	Transversal com 272 homens entre 25 e 63 anos. Tomografia realizada para determinar adiposidade abdominal.	CC ≥ 90cm TG ≥ 2mmol/l	Prevalência de CH 51,1% CH menores níveis de HDL, maiores de triglicerídeos, glicose e maior taxa colesterol total/colesterol HDL
Rogowski, O. 2009/ Israel	Estudo transversal com 9842 adultos com média de idade de 44 anos.	Homens CC ≥90 cm TG ≥177mg/dl Mulheres CC≥ 85 cm TG ≥133mg/dl	Prevalência de CH 12,7% CH associada com níveis elevados de proteína c reativa.
Sam, S. 2009/ Estados Unidos	Prospectivo com 375 indivíduos diabéticos. Realizado tomografia para evidenciar obesidade visceral.	Homens CC >90 cm TG ≥177mg/dl Mulheres CC>85cm TG ≥177mg/dl	CH associada com maiores níveis de colesterol total, colesterol não HDL, Apo B, adiposidade visceral e hemoglobina glicosilada e menor nível de colesterol HDL.

Tabela 2. Continuação

Autor ano/local	Desenho	Definição de CH	Principais resultados
Arsenault, B. J. 2010/ Inglaterra	Estudo longitudinal com 25668 adultos entre 45 e 79 anos com acompanhamento médio de 9,8 anos. Estudo de caso e controle aninhado a coorte com 2840 participantes.	Homens CC ≥90cm TG≥ 2,0mmol/l Mulheres CC≥ 85cm TG≥ 1,5mmol/l	Homens e mulheres com CH são mais velhos, têm IMC maior, maior PA, maior nível de colesterol total, colesterol LDL, proteína c reativa e ApoB, menores níveis de HDL e menor tamanho de partículas de LDL. CH tem risco relativo de 1,28(1,07-1,54) para DCV entre homens e 1,67(1,35-2,06) entre as mulheres. Maior mortalidade entre aqueles com CH.
de Graaf, F. R. 2010/ Holanda	Transversal com 202 indivíduos adultos diabéticos com média de idade de 54 anos. Realizadas medidas antropométricas e exames de sangue. Realizada angiotomografia para detectar doença arterial coronariana.	Homens CC>102cm TG≥1,7mmol/l Mulheres CC>88cm TG≥1,7mmol/l	Prevalência de CH 31%. CH maior nível de colesterol total, LDL, ApoB, proteína c reativa e PA. CH menor nível de colesterol HDL. Razão de odds para doença coronariana 3,3(1,31-8,13) e para doença coronariana obstrutiva 2,9(1,16-7,28).
Esmaillzadeh, A. 2010/ Irã	Transversal com 507 mulheres entre 40 e 60 anos.	CC≥89cm TG≥150mg/dl	Mulheres com CH eram mais velhas e menos ativas. CH com maiores níveis de proteína c reativa, fator de necrose tumoral alfa, interleucina 6 e seletina E.
Yu, D. 2010/ China	Transversal com 14770 chineses entre 35 e 74 anos. Realizadas medidas antropométricas e exames laboratoriais.	CC≥75cm TG≥110mg/dl	Prevalência de CH de 35,4% entre homens e 33,6% entre as mulheres.
Amini, M. 2011/ Irã	Transversal com 1323 adultos entre 30 e 55 anos e com parentes de primeiro grau com Dm tipo II	Homens CC≥102cm TG≥150mg/dl Mulheres CC≥88cm TG≥150mg/dl	Prevalência de CH de 9,6% entre os homens e 23,6% entre as mulheres. Maior prevalência de Dm entre os portadores de CH.
Gomez-Huelgas, R. 2011/ Espanha	Estudo transversal com 2270 adultos entre 18 e 80 anos.	Homens CC≥94cm TG≥1,71mmol/l Mulheres CC≥80cm TG≥1,71mmol/l	Prevalência de CH 14,5% (18,2% entre homens e 10,8% mulheres). Pessoas com CH eram mais velhas, menor nível educacional, mais em homens e mais sedentários. CH associada com maior nível de colesterol total, colesterol LDL, PA e acido úrico. CH associada com menor nível de HDL. Razão de odds para DM 3,61(2,6-5,01) Razão de odds para DCV 2,63(1,66-4,16)

Marco teórico:

O aumento no consumo energético, o decréscimo no gasto de energia, ou a combinação de ambos, leva a um balanço energético positivo e a um aumento no peso. Nesse sentido, diversos trabalhos indicam que a epidemia da obesidade é um problema de saúde pública mundial. Nos Estados Unidos, aproximadamente 65% da população adulta apresenta sobrepeso ou obesidade(Stein and Colditz 2004). No início dos anos 1960, a prevalência de obesidade entre adultos americanos (20 a 74 anos) era 11% entre os homens e 16% entre as mulheres. Já entre 2003 e 2004, esta prevalência subiu para 31,7% e 34%, respectivamente(Ogden, Yanovski et al. 2007). Entre as crianças e adolescentes, a tendência de aumento da obesidade foi similar ao encontrado nos adultos(Ogden, Yanovski et al. 2007).

Assim como nos Estados Unidos, o aumento na prevalência de obesidade também tem sido observado em outros países(Luo and Hu 2002; Padez, Fernandes et al. 2004; Deepa, Farooq et al. 2009). O Brasil, desde a década de 70, vem enfrentando uma transição nutricional. A prevalência da obesidade praticamente triplicou entre homens e mulheres maiores de vinte anos, no Nordeste, e entre homens, no Sudeste(Batista Filho and Rissin 2003). Estudo realizado em 2006, nas capitais brasileiras, com adultos maiores de 18 anos, encontrou uma prevalência de sobrepeso de 47,3% e obesidade de 11,3%, entre os homens; e, 38,8% e 11,5%, respectivamente para sobrepeso e obesidade, entre as mulheres(Gigante, Moura et al. 2009). Na cidade de Pelotas, Rio Grande do Sul, a prevalência de obesidade e sobrepeso é, respectivamente, de 19,4% e 33,7%, em adultos entre 20 e 69 anos(Gigante, Dias-da-Costa et al. 2006) e de 5% e 20,9%, entre adolescentes de 15 a 18 anos(Terres, Pinheiro et al. 2006). Um dos principais efeitos da obesidade na infância e

adolescência é a sua persistência até a vida adulta e o desenvolvimento de todas as suas consequências(Biro and Wien), entre elas o desenvolvimento de DCV.

Mais recentemente, investigadores do *European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk)* relataram a relação entre circunferência da cintura e circunferência do quadril na incidência de doença coronariana. A circunferência da cintura aumentada está associada com risco aumentado de DCV, enquanto que, após ajuste para IMC, idade, pressão arterial sistólica, colesterolemia, tabagismo, atividade física e uso de álcool, a circunferência do quadril aumentada protege contra DCV (Canoy, Boekholdt et al. 2007). Este achado, de que a circunferência da cintura é fator de risco para DCV, é compatível com resultados de outros estudos(Rexrode, Carey et al. 1998; Lakka, Lakka et al. 2002; Balkau, Deanfield et al. 2007). Canoy e colaboradores descreveram que a diminuição em 5 cm na circunferência da cintura é capaz de reduzir o risco de DCV em 11% nos homens e em 15% nas mulheres(Canoy, Boekholdt et al. 2007). O risco cardiovascular resultante de uma circunferência da cintura elevada é consequência do excesso de gordura visceral, que é preditivo de resistência a insulina e de um estado pró-inflamatório e pró-trombótico(Hotamisligil 2000; Lemieux, Pascot et al. 2001). O crescimento acelerado do tecido adiposo visceral faz com que a angiogênese não seja suficiente para prevenir a hipóxia do tecido, o que causa sua inflamação (Halberg, Wernstedt-Asterholm et al. 2008). Além disso, este tecido torna-se um grande órgão endócrino, com produção e liberação de citoquinas, o que contribui ainda mais para a resistência a insulina e o aumento do risco de DCV(Hotamisligil 2000). A obesidade visceral pode ser, então, considerada como um marcador de uma inabilidade do organismo em armazenar adequadamente o excesso de energia no tecido subcutâneo, criando, assim, depósitos ectópicos junto às vísceras abdominais, coração e músculos esqueléticos(Despres and Lemieux 2006).

Devido a estes depósitos ectópicos não poderem ser identificados através da medida do IMC, existe a necessidade de se desenvolver um critério simples, para identificar indivíduos com obesidade visceral, que estão em risco metabólico. Diante disso, foi proposto que a presença simultânea de uma circunferência da cintura elevada e uma concentração aumentada de triglicerídeos, um fenótipo denominado de CH, poderia ser útil para identificar as pessoas em risco aumentado de desenvolver DCV e diabetes tipo II(Despres, Arsenault et al. 2008).

Existem poucos estudos que avaliaram fatores associados com CH. Porém, os que o fizeram relataram associação de CH com fatores de risco clássicos para desenvolvimento de DCV(Kahn and Valdez 2003), como sedentarismo(Alavian, Motlagh et al. 2008; Esmaillzadeh and Azadbakht 2010; Gomez-Huelgas, Bernal-Lopez et al. 2011), menor nível educacional(Alavian, Motlagh et al. 2008; Gomez-Huelgas, Bernal-Lopez et al. 2011), maior IMC(Arsenault, Lemieux et al. 2010) e sexo masculino(Gomez-Huelgas, Bernal-Lopez et al. 2011). Várias hipóteses tentam explicar a associação de exposições precoces (perinatais) com doenças crônicas na vida adulta, entre elas a hipótese da origem fetal, proposta por Barker(Barker 1990), e a hipótese do fenótipo econômico(Hales, Barker et al. 1991). A associação entre peso ao nascer e Síndrome Metabólica (SM) na vida adulta ainda não tem um mecanismo explicativo, acreditando-se que a interação entre mecanismos genéticos, os quais influenciam o peso ao nascer, e fatores ambientais determine as alterações que culminam em SM e no consequente risco cardiovascular na vida adulta(Hadjinikolaou, Klimatsidas et al. 2010). Fatores socioeconômicos, como escolaridade e renda familiar, estão inversamente associados com DCV(Kaplan and Keil 1993) e, consequentemente, deverão estar associados da mesma maneira com CH. A associação inversa entre nível socioeconômico e DCV, em países de alta

renda, é o resultado da elevada prevalência e efeitos combinados de vários fatores de risco comportamentais e psicossociais entre indivíduos de nível socioeconômico baixo. No entanto, evidências sugerem que fatores do início da vida e as desigualdades na atenção nos serviços de saúde também contribuem para a elevação de risco para DCV em pessoas de baixo nível socioeconômico, que vivem em países de alta renda(Clark, DesMeules et al. 2009). Estudos sobre os efeito do nível socioeconômico no risco de DCV em países em desenvolvimento são escassos, mas evidências sugerem que o aumento da riqueza desses países está conduzindo à replicação dos padrões observados em países desenvolvidos(Clark, DesMeules et al. 2009). De modo a facilitar e melhor orientar o processo de determinação do desfecho, criou-se, para este estudo, um modelo teórico de análise. O modelo empregado propõe que até a ocorrência do desfecho (CH) exista uma cadeia de determinantes hierarquizados, os quais são importantes fatores envolvidos na sua ocorrência (Figura 1).

1	**FATORES DEMOGRÁFICOS E SÓCIOECONOMICOS** Renda familiar ao nascer Escolaridade da mãe em 1982 Cor da pele Sexo

2	**FATORES PERINATAIS** Crescimento intrauterino Idade gestacional

3	**FATORES DA INFÂNCIA** Duração da amamentação

4	**FATORES DA VIDA ADULTA (2004)** Renda familiar aos 23 anos Escolaridade do indivíduo Índice de massa corporal Pressão arterial Colesterol HDL Glicemia Proteína c reativa Sedentarismo Tabagismo Consumo de gordura Consumo de fibras

CINTURA HIPERTRIGLICERIDÊMICA

Figura 1. Modelo Teórico de Análise

Objetivos:

- Determinar a prevalência de Cintura Hipertrigliceridêmica entre adultos jovens, pertencentes à Coorte de Nascimento de 1982.
- Determinar os fatores associados com a ocorrência de Cintura Hipertrigliceridêmica nesta população, aos 23 anos de idade.
- Determinar os fatores precoces (condições de nascimento e amamentação) associados com a ocorrência da Cintura Hipertrigliceridêmica.

Hipóteses:

A prevalência de cintura hipertrigliceridêmica será baixa, em torno de 10%, por se tratar de adultos jovens.

O fenótipo da cintura hipertrigliceridêmica estará associado positivamente com os seguintes fatores contemporâneos:

- sexo masculino;
- sedentarismo na vida adulta;
- maiores níveis de glicemia;
- maiores níveis de pressão arterial;
- maiores níveis de proteína C reativa;
- maior IMC;
- menores níveis de colesterol HDL;
- menor escolaridade;
- menor nível econômico;
- maior consumo de gorduras;
- menor consumo de fibras;

O fenótipo da cintura hipertrigliceridêmica estará associado positivamente com os seguintes fatores precoces:

- baixo peso ao nascer;
- retardo de crescimento intrauterino;
- menor duração do aleitamento materno.

Metodologia:

1.1 Delineamento:

Estudo longitudinal de coorte de nascidos vivos na cidade de Pelotas no ano de 1982.

1.2 População em estudo:

Todos os nascidos vivos, em hospitais, de mães residentes na zona urbana de Pelotas, RS, em 1982.

1.3 Critérios de inclusão:

Participantes da coorte de Pelotas de 1982, para os quais se disponha de informações completas para a circunferência da cintura e níveis de triglicerídeos plasmáticos na visita de 2004-5.

1.4 Critérios de exclusão:

Foram excluídas da análise as grávidas e as mulheres com ≤ 6 meses pós-parto, por poder alterar a medida da circunferência abdominal utilizada no desfecho.

1.5 Cálculo do tamanho da amostra e poder:

Uma vez que este estudo utilizará os dados coletados na visita de acompanhamento da coorte, realizada em 2004-5, quando foram localizados 4851 indivíduos, apresentam-

se estimativas do poder estatístico do estudo para identificar algumas associações. Para a variável renda, na comparação entre o tercil de maior renda e o de menor, considerando-se um risco relativo de 2,0 e um α de 0,05, o poder do estudo será de 99%.

A Tabela 3 apresenta os cálculos de poder estatístico do estudo.

Tabela 3: Cálculos de poder do estudo

Variável	N	RR	α	Poder
Renda	3682	2,0	0,05	99%
	3682	1,5	0,05	71%
BPN	3682	2,0	0,05	90%
	3682	1,5	0,05	46%
RCIU	3129	2,0	0,05	94%
	3129	1,5	0,05	52%
Sexo	3682	2,0	0,05	99%
	3682	1,5	0,05	69%
Cor da pele	3682	2,0	0,05	99%
	3682	1,5	0,05	73%
IMC	3682	2,0	0,05	99%
	3682	1,5	0,05	99%

RR – risco relativo
BPN – baixo peso ao nascer
RCIU – retardo de crescimento intrauterino
IMC – índice de massa corporal

1.6 Principais variáveis a serem coletadas:

1.6.1 Operacionalização do desfecho:

O desfecho CH utiliza uma medida da circunferência da cintura associada a uma medida de triglicerídeos séricos. Para o presente estudo, serão utilizados os seguintes pontos de corte:

- Homens: circunferência da cintura ≥ 90 cm e triglicerídeos ≥ 2,0 mmol/l

- Mulheres: circunferência da cintura ≥ 85 cm e triglicerídeos ≥ 1,5 mmol/l

Estes valores, segundo diversos autores, são os pontos de corte correspondentes a maior sensibilidade e especificidade para diagnóstico da tríade metabólica(Lemieux, Pascot et al. 2000; Lemieux, Almeras et al. 2002; Arsenault, Lemieux et al. 2010).

A circunferência da cintura foi medida com fita métrica inextensível (Cardiomed), a meio caminho entre a espinha ilíaca anterossuperior e o último arco costal. Para os exames laboratoriais, foram coletados 10ml de sangue, por punção venosa periférica do braço de cada indivíduo, sendo 5 ml de sangue coletados com anticoagulante (EDTA 25 mM), para a extração de DNA, e 5 ml sem anticoagulante, para o banco de soro. No momento da coleta, foram realizados dois exames: medida da glicose, a partir de sangue da polpa digital, com Glicosímetro (Advantage), e a tipagem sanguínea. Os triglicerídeos foram dosados em mg/dL e posteriormente expressos em mmol/l multiplicando-se o seu resultado em mg/dL por 0,0113.

1.6.2 Operacionalização das variáveis de exposição (ano de coleta da informação):

- Cor da pele, branca ou não branca, auto-referida (2004-05)
- Peso ao nascer, em gramas, contínuo e dicotômico (BPN <2500g) (1982).
- Crescimento intrauterino – Retardo de Crescimento Intrauterino (RCIU) foi considerado um peso ao nascer abaixo do percentil 10 para idade gestacional e sexo da população de referência de Willians(1982).
- Duração da amamentação foi coletada nas visitas realizadas na infância (1983, 1984 e 1986). Esta variável foi agrupada em: ≤ 1; 1-2,9; 3-5,9; 6-8,9; 9-11,9; ≥12 meses. A idade do desmame foi considerada como sendo a idade em que aconteceu a interrupção total do aleitamento.
- Escolaridade da mãe (1982) e escolaridade do indivíduo (2004-05).

- Renda familiar, em salários mínimos. Classificada em categorias e tercis (1982 e 2004-05).
- Índice de massa corporal (peso dividido pela altura ao quadrado), em kg/m^2 contínuo e agrupado segundo critérios da OMS: < 18,5, baixo peso; 18,5-24,9, peso adequado; 25-29,9, sobrepeso e ≥ 30 obesidade. (2004-05)
- Mudança de renda familiar, em 1982 e 2004, os indivíduos no primeiro tercil (mais pobres) serão considerados "pobres" e os demais como "não pobres", sendo assim criados quatro categorias (sempre pobres, pobre-não pobre, não pobre-pobre e nunca pobre) na comparação entre 1982 e 2004.
- Sexo dos indivíduos, masculino ou feminino
- Proteína C reativa (PCR), em mg/l contínuo (2004-05), dosado em equipamento IMMULITE para testes de PCR-as(Diagnostic Products Corporations, Los Angeles, EUA), ensaio imunométrico por quimiluminescência em fase sólida. Sensibilidade até 0,01mg/l.
- Colesterol HDL em mg/dl (2004-05)
- Glicemia ao acaso em mg/dl (2004-05), dosada a partir de sangue da polpa digital com Glicosímetro (Advantage).
- Pressão Arterial em mmHg, contínuo (2004-5), foi medido com esfigmomanômetro da marca Omron modelo HEM 629, digital. Foram realizadas duas medidas, uma logo após a apresentação da entrevistadora, antes da aplicação do questionário, e outra medida, logo após a aplicação do questionário, sendo utilizada a média das duas medidas.
- Sedentarismo total e no lazer: a versão longa do Questionário Internacional de Atividade Física (IPAQ) foi utilizada. Escores de atividade física semanal foram estimados pela soma de tempo caminhando, em atividade física

moderada ou em atividade física vigorosa, multiplicado por dois. Aqueles indivíduos que não atingiram 150 minutos nos momentos de lazer foram classificados como sedentários no lazer.

- Consumo alimentar de gorduras e de fibras: foi utilizado o questionário proposto por Block(Sam, Haffner et al. 2009) apesar de não validado para esta população, para avaliar a frequência alimentar. Esse questionário é dividido em duas partes. A primeira parte, composta de 15 itens alimentares, visa avaliar a frequência de consumo de alimentos ricos em gordura. A segunda parte, composta de nove itens, avalia a ingestão de alimentos ricos em fibras. Block et al.(Sam, Haffner et al. 2009) atribuiram determinado número de pontos a cada frequência de consumo, os quais são usados para estimar um escore para classificação dos teores de fibra e gordura na dieta. Segundo Block et al.(Sam, Haffner et al. 2009), indivíduos com pontuação superior a 27 pontos no primeiro bloco são classificados como tendo dieta rica em gordura; e, aqueles com menos de 20 pontos no segundo bloco são classificados como tendo dieta pobre em fibra.
- Tabagismo do indivíduo, atual (fuma todos os dias), ex-fumante (alguma vez na vida já fumou todos os dias) ou se nunca fumou (2004-05).

A Tabela 4 resume as variáveis a serem estudadas.

Tabela 4: Descrição e tipo de variáveis estudadas

Variável	Descrição (categorias)	Tipo
Variáveis precoces		
Sexo	Masculino e feminino	Dicotômica
Cor da pele	Branca e não branca	Dicotômica
Escolaridade da mãe	Anos completos	Numérica discreta
Peso ao nascer e BPN	Gramas	Numérica contínua e dicotômica
RCIU	Abaixo do percentil 10 para sexo e idade	Dicotômica
Amamentação	Meses agrupados	Categórica ordinal
Renda familiar ao nascer	Agrupada em tercis	Categórica ordinal
Variáveis contemporâneas		
Renda familiar aos 23 anos	Agrupada em tercis	Categórica ordinal
Escolaridade	Anos completos	Numérica discreta
IMC	Agrupada segundo OMS	Categórica ordinal
Mudança de renda familiar	Sempre pobre Pobre – não pobre Não pobre – pobre Nunca pobre	Categórica nominal
Colesterol HDL	mg/dl	Numérica continua
Glicemia	mg/dl	Numérica continua
PCR	mg/l	Numérica continua
Pressão arterial	mmHg	Numérica continua
Sedentarismo total e no lazer	Escore IPAQ	Dicotômica
Consumo de gorduras	Escore Block	Dicotômica
Consumo de fibras	Escore Block	Dicotômica
Tabagismo	Atual, passado ou nunca	Categórica nominal

BPN – baixo peso ao nascer
RCIU – retardo de crescimento intrauterino
IMC – índice de massa corporal
PCR – proteína c reativa

1.7 Logística:

Informações sobre seleção e treinamento de entrevistadores, logística do trabalho de campo, coleta de dados, entrevistas e controle de qualidade estão disponíveis no anexo I deste projeto (Relatório do Trabalho de Campo).

1.8 Digitação e análise de dados:

Os dados foram duplamente digitados, por diferentes digitadores, com o intuito de identificar possíveis erros, no programa Epi-Info versão 6 (CDC, EUA, www.cdc.gov/epiinfo).

A análise de dados será realizada no pacote estatístico Stata 11.1(StataCorp. 2009). Em um primeiro momento, será realizada uma análise univariada de todos os dados coletados, com cálculo das medidas de tendência central e dispersão para as variáveis contínuas, e de proporções, para as categóricas. A seguir, será realizada a análise bivariada, quando será utilizado teste qui-quadrado para tabelas de contingência(2xk). Por fim, será realizada análise mulivariável, através de regressão do Poisson, levando em consideração o modelo hierárquico previamente estabelecido (Figura 1). Neste modelo, a significância estatística de cada variável será avaliada através do teste de Wald. Inicialmente, cada bloco de variáveis de um determinado nível será incluído na análise, sendo mantidas no modelo todas aquelas variáveis com valor de $p \leq 0,20$. Neste modelo, as variáveis situadas em um nível hierarquicamente superior ao da variável em questão serão consideradas como potenciais fatores de confusão na relação com o desfecho em estudo, enquanto que as variáveis situadas em níveis inferiores, serão consideradas como potenciais mediadores da associação. As variáveis selecionadas em um determinado nível, permanecem no modelo, sendo consideradas como fatores de risco para a CH, mesmo que com a inclusão de variáveis hierarquicamente inferiores, tenham perdido sua significância(Victora, Huttly et al. 1997).

1.9 Aspectos éticos:

Este estudo foi aprovado pelo Comitê de Ética da Faculdade de Medicina da Universidade Federal de Pelotas. Todos os participantes assinaram termo de consentimento para participação na pesquisa e outro para coleta de sangue e sua posterior análise.

Alguns participantes da coorte ou familiares, durante a realização da entrevista, solicitavam atendimento médico com especialista por algum problema de saúde. Os pesquisadores eram comunicados e os casos eram encaminhados ao ambulatório da Faculdade de Medicina da UFPel ou Secretaria da Saúde, em casos específicos.

1.10 Cronograma:

ATIVIDADES	2010		2011		2012		2013	
	Semestre							
	1°	2°	1°	2°	1°	2°	1°	2°
Proficiência em inglês								
Definição do tema								
Revisão de literatura								
Submissão do plano de trabalho								
Elaboração do projeto								
Defesa do projeto								
Exame de qualificação								
Redação do primeiro artigo								
Submissão do primeiro artigo								
Redação do segundo e terceiro artigo								
Finalização da tese								
Defesa da tese								

1.11 Divulgação dos resultados:

Os resultados desta pesquisa serão divulgados na forma de artigos científicos publicados em revistas indexadas com revisão por pares.

1.12 Orçamento/financiamento:

Este estudo é atualmente financiado pela Wellcome Trust Major Awards for Latin America on Health Consequences of Population Change. Fases anteriores do estudo foram financiadas pelo International Development Research Center, pela Organização Mundial da Saúde, pelo Overseas Development Administration, pela União Européia, pelo Programa Nacional de Núcleos de Excelência (PRONEX) e pelo Conselho Nacional de Pesquisa (CNPq) e Ministério da Saúde.

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PARTE II. MODIFICAÇÕES DO PROJETO

As modificações realizadas na versão final do projeto de pesquisa referem-se aos artigos sugeridos:

- O artigo proposto, "Cintura Hipertrigliceridêmica e sua associação com fatores cardiometabólicos: Revisão da literatura" seria produzida através de uma extensa revisão sistemática da literatura e possível meta-análise sobre a associação do fenótipo com fatores de risco já conhecidos para DCV. Entretanto, como estas associações já foram exaustivamente discutidas na literatura, tornou-se mais interessante investigar a associação de fatores precoces com o desenvolvimento de CH. Os fatores precoces escolhidos foram peso ao nascer e amamentação. Devido à inexistência de artigos relacionando estes fatores com o desenvolvimento de CH, optou-se por investigar peso ao nascer e amamentação com cada um dos componentes da CH (triglicerídeos e circunferência da cintura).

- O artigo proposto "Determinantes precoces da cintura hipertrigliceridêmica: Efeito das condições de nascimento e duração da amamentação" deveria ser baseado em uma análise longitudinal do peso ao nascer e da amamentação com CH aos 23 anos, porém tornou-se mais interessante à investigação avaliar o efeito do ganho de peso durante diferentes períodos na infância, para com isto tentar esclarecer o dilema do crescimento acelerado na infância. Este artigo, então, passou a ser intitulado "Fenótipo da Cintura Hipertrigliceridêmica: Efeito do peso ao nascer e do ganho de peso na infância".

Todas as alterações realizadas após a avaliação do projeto ocorreram de forma a enriquecer o trabalho. A proposta inicial da pesquisa não foi prejudicada e seus objetivos principais foram mantidos e respeitados.

PARTE III: ARTIGOS RESULTANTES DA PESQUISA

ARTIGO 1

“Hypertriglyceridemic waist phenotype in young adults from South Brazil”

Publicado na revista “Cadernos de Saude Pública”- *Cad. Saúde Pública*, May 2013, vol.29, no.5, p.999-1007. ISSN 0102-311X

Hypertriglyceridemic waist phenotype in young adults from South Brazil

Ricardo Lanzetta Haack*

Bernardo Lessa Horta

Denise Petrucci Gigante

Fernando C. Barros

Isabel Oliveira

Vera M. Silveira

* ricardohaack@yahoo.com.br

RESUMO

Introdução: O presente estudo teve como objetivo determinar a prevalência do fenótipo da cintura hipertrigliceridêmica(HWP) e seus fatores associados entre indivíduos que foram seguidos desde o nascimento. Métodos e Resultados: Em 1982, as maternidades de Pelotas, sul do Brasil, foram visitadas e todos os nascimentos foram identificados. Em 2004-2005, buscou-se acompanhar toda a coorte. A presença de HWP foi definida como circunferência da cintura ≥ 90 cm e triglicerideos ≥ 177mg/dl para o sexo masculino e circunferência da cintura ≥ 85 cm e triglicerideos ≥ 133mg/dl para as mulheres. Prevalência HWP foi de 5,9% e 4,5% entre os homens e mulheres, respectivamente. Para os homens, o sedentarismo no lazer, tabagismo e obesidade esteve associado com HWP. Por outro lado, entre as mulheres, HWP foi positivamente associado com a cor da pele, renda familiar, obesidade e consumo de gordura.

ABSTRACT

Background: The present study was aimed to access the prevalence of Hipertriglyceridemic Waist Phenotype(HWP) and its associated factors among subjects that have been followed since birth. Methods and Results: In 1982, the maternity hospitals in Pelotas, southern Brazil, were visited and all births were identified. Those livebirths whose family lived in the urban area of the city were studied prospectively. In 2004–2005, we attempted to follow the whole cohort. The presence of HWP was defined as waist circumference ≥ 90 cm and triglycerides ≥ 177mg/dl for males and waist circumference ≥ 85 cm and triglycerides ≥ 133mg/dl for females. HWP prevalence was 5.9% and 4.5% among men and women, respectively. For

males, sedentary lifestyle at leisure time, smoking and obesity was associated to HWP. On the other hand, among females, HWP was positively associated with skin color, family income, obesity and fat intake.

Introduction

Chronic non-communicable diseases, such as cardiovascular disease (CVD), cancer and diabetes are the main causes of death worldwide, accounting for approximately 60% of deaths [1, 2]. In the United States, The American Cardiology Association estimates that more than one in three adults have CVD[3].

In 2000, Lemieux and colleagues reported that adults with increased abdominal circumference and high plasma triglyceride levels presented more frequently other metabolic markers of cardiovascular risk[4] and called this association Hypertriglyceridemic Waist Phenotype (HWP). Several studies have reported that HWP is associated with cardiometabolic risk profile (higher levels of insulin, Apolipoprotein B, C-reactive protein and small dense LDL cholesterol) as well an increased risk of coronary artery disease[4-10]. In spite of this marked association with metabolic risk factors of cardiovascular disease, few studies have evaluated the risk factors for HWP, especially in young adults. Some studies have identified the following factors related to the presence of HWP: sedentary lifestyle;[11-13], obesity[9, 11, 14]; lower schooling[11, 13]; and low intake of grains.[15].

This study was aimed at assessing the prevalence of HWP and its association with skin color, family income, smoking, sedentary lifestyle, fat consumption and fiber intake among 23 years old subjects that have been followed since birth, in a southern Brazilian city.

Methods

In 1982, all maternity hospitals in Pelotas, a southern Brazilian city, were visited daily, and 7392 births were identified. Those live births whose parents lived in the urban area of Pelotas (N = 5914) were examined and the mothers interviewed. These individuals have been followed on several opportunities and further details on the study methodology have been published elsewhere[16].

From October 2004 to August 2005, we tried to follow all subjects belonging to the cohort when they were aged 22-23 years, and those found answered a questionnaire, were examined and invited to donate a blood sample, collected by venous puncture.

The presence of hypertriglyceridemic waist phenotype was defined as waist circumference ≥ 90 cm and triglycerides ≥ 177mg/dl for males and waist circumference ≥ 85 cm and triglycerides ≥ 133mg/dl for females[4, 17, 18]. Waist circumference was measured using a fiberglass tape (Cardiomed), halfway between the iliac crest and last costal arch. Pregnant women and those who had had children in the last six months were excluded. Triglyceride was assessed with a colorimetric enzymatic method.

The following metabolic cardiovascular risk factors were measured:

- Blood pressure was measured at the beginning and at the end of the interview, using a digital wrist sphygmomanometer (Omron HEM-629) calibrated, in the left arm. Before each measurement the individual should sit at rest for at least five minutes. The mean values were used in the analyses. The mean arterial pressure was estimated as 2/3 mean diastolic blood pressure + 1/3 mean systolic blood pressure.
- Random blood glucose was assessed from fingertip blood, at the time of collecting the blood samples, using a portable glucose meter (Accu-Check

Advantage – Roche). Because glucose levels were related to fasting time, glucose estimates were corrected for the time elapsed since the last meal[19].

- HDL cholesterol was measured using an ultrasensitive direct method, with a Selectra 2 analyzer (Merck).
- High-sensitivity C-reactive protein (hs-CRP) was measured using an Immulite chemiluminescent immunoassay (Siemens). Because the lower detection limit was 0.1 mg/L, measures below that value were converted to 0.05mg/L. Subjects with hs-CRP >10mg/L were excluded from the analyses involving hs-CRP, as well as pregnant women and those using oral contraceptives.

  The following socioeconomic, demographic and behavioral characteristics were also assessed as possible risk factors:

- Skin color self-reported
- Family income in adulthood
- Leisure-time physical activity: the long version of the International Physical Activity Questionnaire (IPAQ)[20], previously validated[21] was used to assess physical activity, and weekly score of physical activity was estimated by the sum of time of walking and moderate physical activity and time spent on vigorous activities was multiplied by two. Those subjects whose scores at leisure time were lower than 150 minutes were classified as sedentary.
- Tobacco smoking: those subjects who smoked at least one cigarette per day were considered as smokers.
- High fat and low fiber diet: in the 2004/05 visit, the dietary pattern in the last 12 months was evaluated using the Block questionnaire, which included 24 items evaluated by using a scoring format. From the information of weekly consumption of each food was given a score and individuals whose score was less than 20

points were considered as having a low dietary fiber intake and individuals with 25 points or more are considered high dietary intake of fat[22].

Triglycerides and hs-CRP values were asymmetrically distributed, and these variables were natural log-transformed. Therefore, all results of hs-CRP and triglycerides concentrations are expressed as back-transformed and the geometric means are presented.

Statistical analysis was performed using the software Stata 12.0 and was stratified by sex. Chi-square test with Yates correction for 2 x 2 tables was used for comparisons between proportions, and means were compared using analysis of variance. For multivariate analysis, we use the Poisson regression with robust adjustment of the variance, based on the hierarchical model shown in Figure 1.

In order to assess whether the presence of enlarged waist and hypertriglyceridemia was related to higher values of cardiovascular risk factors, an interaction term was included in the analysis on the association of waist circumference and triglycerides with cardiovascular risk factors.

The study was approved by the Ethical Review Board of the Faculty of Medicine of the Federal University of Pelotas, and written informed consent was obtained from participating subjects.

Results:

In the 2004/2005 visit, 4297 subjects were interviewed, that added to 282 deaths identified, represented a follow-up rate of 77.4%.

Table 1 shows that about 75% of the population studied is white. At 23 years, the prevalence of overweight and obesity was 23.1% and 7.5% among men and 17.9% and 9.1% among women, respectively. Table 1 also shows the mean values of triglycerides, HDL cholesterol, non-fasting blood glucose, high- sensitivity C - reactive protein and blood pressure for men and women. HWP prevalence was 5.9% and 4.5% among men and women, respectively. Furthermore, 69.9% of men and 68.6% of women had a diet low in fiber and 54.8% of men and 45.4% of women were considered to have a high fat diet. Around a quarter of the sample studied is smoker and 80% of women and 50% of men are sedentary at leisure time.

Table 2 shows that those subjects with normal waist circumference and triglycerides presented higher mean values of HDL cholesterol and lower blood pressure, non-fasting blood glucose and body mass index. The presence of hypertriglyceridemia or enlarged waist circumference was related to slight changes in the metabolic cardiovascular risk factors. In addition, those subjects with enlarged waist and hypertriglyceridemia presented lower HDL cholesterol and higher blood pressure and hs-CRP. Test for interaction between hypertriglyceridemia and waist circumference, for each of the cardiovascular metabolic risk factors was statistically significant suggesting that the presence of the phenotype increases the values of the metabolic cardiovascular risk factors more than would be expected by adding the risk factors.

Table 3 and 4 presents the prevalence, prevalence ratio and adjusted prevalence ratio of hypertriglyceridemic waist phenotype according to sample characteristics for males and females, respectively. For males, sedentary lifestyle at leisure time, smoking and obesity was associated to HWP. On the other hand, among females, HWP was positively associated with skin color, family income, fat consumption and BMI.

Discussion

The present study was a cross-sectional analysis, because we only analyzed data gathered in the 2004/2005 follow-up visit of 1982 Pelotas birth cohort.

Among the study limitations, we would like to mention the extent of food consumption that represents a big challenge. The instrument used is not validated for the Brazilian population, however more complex methods of measuring food frequency were tested, with similar results to the BLOCK questionnaire[22].

Another important limitation is the reverse causality that can affect all cross-sectional study, and even when we are working with a nested cohort where we have better information on confounders still suffers with reverse causality.

Recent studies indicate that the process of atherosclerosis starts at an early age, and is already linked to obesity and other components of the metabolic syndrome in childhood[23]. The identification of asymptomatic individuals at high risk of coronary heart disease and diabetes has important public health implications for prevention of cardiovascular diseases, given the increased incidence of these diseases[24]. The prevalence of HWP was 5.9% among males and 4.5% among females, and the presence of the phenotype was related to a higher level of metabolic cardiovascular risk factors. Lemieux[4, 5], Hiura[7] and many others[8-10, 14, 25-29] also reported such association, demonstrating that HWP is an important marker of cardiovascular risk.

Regarding the prevalence of phenotype, studies with adults of both sexes, the prevalence ranged from 12.7% to 36.5%[10, 13, 29, 30]. Kahn, in 2003, working with a sample of adults, aged 18 to 90 years in the United States, observed a prevalence of 24.8%, the lowest being 6.2% in the age group of 18 to 24 years[25]. Among healthy

adults in Israel, the Netherlands and Spain, the prevalence was respectively 12.7%, 31% and 14.5%[13, 29, 30]. In 2010 in China, Yu, evaluated 14770 adults between 35 and 74 years and reported that 35.4% of the men and 33.6% of the women[31] presented HWP. On the other hand, in Iran, among adults aged between 30 and 55 years, the prevalence was 9.6% among men and 23.6% among women[32].

Studies with young people are rare, however in Iran two studies were conducted, one in 2006 with adolescents aged 10 to 19 years reported a prevalence of 6.4%[36] and other in 2008, with adolescents with a mean age of 12 years the prevalence of HWP was 8.5%[11].

In the present study individuals with HWP had lower HDL cholesterol and higher mean blood pressure, non fasting blood glucose and hs-CRP than those subjects with normal waist circumference and triglycerides levels. Similar findings have been reported in another studies[5-10, 12-14, 25-30, 37, 38], suggesting that the presence of an enlarged waist and increased triglycerides is related to metabolic cardiovascular risk factors. Therefore, the presence of HWP should be considered as marker for presence of risk factors of cardiovascular disease.

With respect to factors associated with HWP, we found that for males, sedentary lifestyle at leisure time, smoking and obesity were associated to the presence of the phenotype. For females, sedentary lifestyle in the leisure time also increased the prevalence but the association was not statistically significant. Three other studies have also reported that sedentary lifestyle increases the prevalence of HWP[11-13]. In our study, the protective effect of physical activity was observed even among obese subjects. For women, white skin color, low-income family, low fat intake in the diet and obesity were also associated with the presence of HWP.

Studies with adults over 45 to 79 years of age have reported that obesity is related to the

presence of HWP[9, 11, 14, 36]. We also observed that body mass index was positively related to the prevalence of HWP, and about four of every ten obese subjects presented the phenotype. This indicates hat even among young adults, obesity is related to a higher risk of presenting a phenotype that is strongly related to the presence of atherogenic risk factors, reinforcing the relevance of preventing obesity in young ages.

Other studies have reported that low socioeconomic status is related to a higher risk of presenting HWP [11, 13]. In the present study, we observed that the prevalence of the HWP tended to be positively related to income among males and negatively associated to income among females. A hypothesis raised in a previous study[39] is that poorer women have more children, and therefore a larger waist circumference, but even after controlling for parity socioeconomic status was still associated with the phenotype among women. Therefore, parity is not mediating this association. On the other hand, the association vanished after controlling for obesity and overweight. Therefore, the association between low socioeconomic status and HWP is being mediated by overweight/obesity.

Given the findings from Esmaillzadeh[15], who reported that a higher consumption of refined grains was associated with higher prevalence of HWP, and from Alavian[11] where the risk of HWP increased with the consumption of solid hydrogenated fat as well as white-flour bread, we would expect an association in the opposite direction. One possible explanation would be that our analysis is cross-sectional, and therefore susceptible to reverse causality bias. Among girls, the lowest consumption of fat in the diet is also positively associated with overweight and obesity. Probably these girls, because they present overweight and obesity, have a diet with less fat and are also more exposed to dieting practices. On the other hand, in a longitudinal analysis with a subset of girls evaluated at 19 years of age, the risk of developing HWP was independent of fat

consumption based on scoring format ($p = 0.57$).

Smoking is a well-known cardiovascular risk factor and its association with other factors remains under investigation. In our study, among men, smoking was associated inversely with the outcome HWP, with a prevalence of 6.5% among smokers versus 4.3% in nonsmokers ($p = 0.06$). In this study, male smokers had a 18.2% of overweight and 5.9% of obesity, which is lower than the values found in non-smokers, 25.0% of overweight and 8.2% of obesity respectively ($p < 0.05$). Smokers showed no increased or lower rates of triglycerides when compared with nonsmokers.

In conclusion the prevalence of HWP among young adults is strongly associated with cardiovascular risk factors. The association of the measure the circumference of the waist with a dosage of triglycerides seems to be a good method, little invasive and inexpensive for screening individuals at risk of developing cardiovascular disease.

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Figure 1. Hierarchical model for hypertriglyceridemic waist phenotype

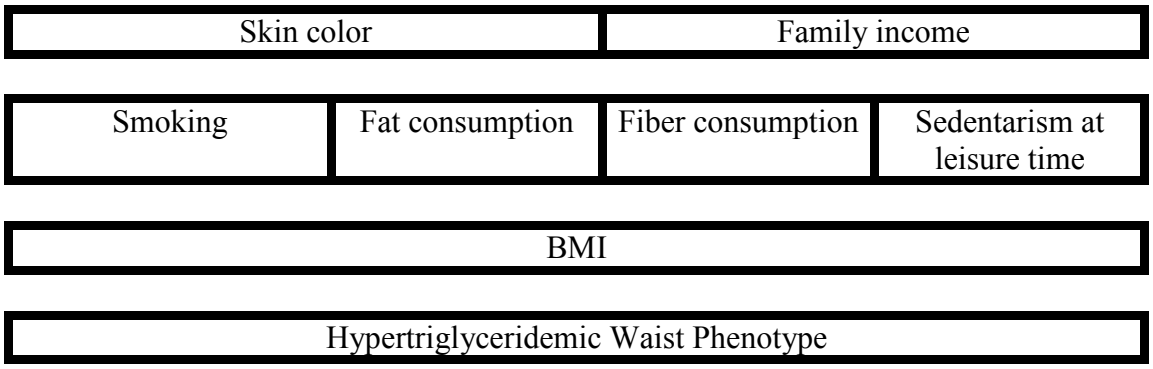

Table 1. Distribution of sample studied, according to key characteristics.

Sample characteristics	Male	Female
Skin color N (%)		
White	1658(74.9)	1580(75.9)
Non white	555(25.1)	503(24.2)
Family income (tertiles) mean R$ (SD)		
1st tertile	463.2(171.2)	443.8(179.8)
2nd tertile	1054.3(206.3)	1046.1(205.6)
3rd tertile	3170.8(2696.4)	3189.6(2518.4)
Body mass index(kg/m^2) N(%)		
< 18,5	107(4.9)	150(7.2)
18,5 to 24,9	1,424(64.6)	1,370(65.8)
25,0 to 29,9	509(23.1)	372(17.9)
≥ 30	166(7.5)	190(9.1)
Sedentarism at leisure time N(%)	1091(49.3)	1676(80.5)
Smoking N (%)	611(27.6)	492(23.6)
Triglycerides (mmol/l) geometric mean (SD)	1,00(1.78)	1,03(1.62)
Waist circunference (cm) mean(SD)	80,9(10.1)	75,6(11.1)
HDL cholesterol (mg/dL) mean(SD)	51,6(11.2)	59,4(13.5)
Non-fasting glucose (mg/dL) mean(SD)	99,8(15.6)	94,8(14.1)
Hs-CRP (mg/dL) geometric mean (SD)	0,78(3.17)	1,31(3.33)
Mean arterial blood presure (mmHg) mean(SD)	91,6(11.9)	84,6(11.1)
Hypertrygliceridemic waist phenotype N (%)	113(5.9)	80(4.5)

Table 2. Biological cardiovascular risk factors according to hypertriglyceridemic waist phenotype. Mean (CI 95%)

	Hypertriglyceridemic waist phenotype				
	No	Only hypertriglyceridemia	Only enlarged waist	Hypertriglyceridemic waist phenotype	p value of interaction
HDL cholesterol (mg/dL)	56.0(55.5;56.5)	55.2(53.7;56.6)	53.0(51.7;54.3)	48.9(47.3;50.6)	0.02
Non-fasting blood glucose (mg/dL)	96.8(96.3;97.4)	98.5 (97.0;100.1)	98.9(97.3;100.5)	101.5(99.6;103.5)	0.50
Mean blood pressure (mmHg)	87.1(86.7;87.5)	88.6(87.5;89.8)	91.9(90.6;93.3)	97.9(96.2;99.5)	<0.00
Hs-CRP(mg/dL)	0.82(0.78;0.86)	1.26(1.17;1.42)	1.72(1.52;1.93)	2.03(1.79;2.34)	0.06
BMI (kg/m^2)	22.2(22.1;22.3)	23.2(22.9;23.4)	30.5(30.0;30.9)	31.7(31.1;32.3)	<0.00
Total N (%)	2745(74.6)	376(10.2)	368(10.0)	193(5.2)	

Table 3. Prevalence, prevalence ratio and adjusted prevalence ratio of hypertriglyceridemic waist phenotype according sample caracteristics for males.

Characteristic	N	P (%)	PR(95% CI)	PR*(95% CI)
Skin color		p=0.13	p=0.13	p=0.21
White	1425	6.4	1	1
Non-white	489	4.5	0.70(0.45;1.11)	0.74(0.45;1.18)
Family income		p=0.23	p=0.23	p=0.35
1st tertile	605	5.0	0.70(0.45;1.08)	0.80(0.53;1.23)
2nd tertile	650	5.5	0.78(0.51;1.18)	0.73(0.46;1.15)
3rd tertile	659	7.1	1	1
Smoking		p=0.06	p=0.07	p=0.05
No	1378	6.5	1	1
Yes	536	4.3	0.66(0.42;1.03)	0.65(0.41;1.01)
Sedentary lifestyle at leisure time		p=0.05	p=0.05	p=0.03
No	967	4.9	1	1
Yes	947	7.0	1.43(1.00;2.06)	1.49(1.03;2.14)
Fat score(g)		p=0.50	p=0.50	p=0.51
< 25	48	5.5	1	1
≥ 25	65	6.2	1.13(0.79;1.63)	1.14(0.78;1.69)
Fiber score(g)		p=0.55	p=0.55	p=0.49
<20	1335	5.7	1	1
≥20-29	579	6.4	1.12(0.77;1.64)	1.15(0.78;1.69)
BMI (kg/m^2)		p< 0.00	p<0.00	p<0.00
<25	3	0.2	1	1
25 – 29.9	40	9.0	39.9(12.4;128.5)	39.91(12.32;129.32)
≥ 30	70	48.6	215.0(68.6;674.4)	209.53(66.58;659.38)

* adjusted for variables of the same level and upper level

Table 4. Prevalence, prevalence ratio and adjusted prevalence ratio of hypertriglyceridemic waist phenotype according sample caracteristics for females.

Characteristic	N	P (%)	PR(95% CI)	PR*(95% CI)
Skin color		p=0.04	p=0.05	P=0.01
white	1333	5.1	1	1
Non-white	435	2.8	0.54(0.30;0.99)	0.45(0.25;0.82)
Family income		p=0.00	p=0.00	p<0.00
1st tertile	642	6.5	2.73(1.48;5.03)	1.92(0.99;3.73)
2nd tertile	584	4.3	1.78(0.92;3.45)	3.11(1.69;5.74)
3rd tertile	542	2.4	1	1
Smoking		p=0.78	p=0.78	p=0.88
No	1349	4.5	1	1
Yes	419	4.8	1.07(0.65;1.76)	0.96(0.59;1.58)
Sedentarism at leisure time		p=0.24	p=0.24	p=0.51
No	357	3.4	1	1
Yes	1411	4.8	1.43(0.78;2.61)	1.23(0.67;2.24)
Fat score (g)		p=0.00	p=0.00	p=0.01
< 25	57	5.9	1	1
≥ 25	23	2.8	0.48(0.30;0.77)	0.52(0.32;0.85)
Fiber score (g)		p=0.47	p=0.47	p=0.24
<20	1214	4.3	1	1
≥20-29	554	5.1	1.18(0.75;1.85)	1.31(0.84;2.05)
BMI (kg/m^2)		p<0.00	p<0.00	p<0.00
<25	5	0.4	1	1
25 – 29.9	23	7.5	19.5(7.5;50.9)	20.18(7.67;53.08)
≥ 30	52	33.8	88.2(35.8;217.5)	87.74(34.69;221.92)

* adjusted for variables of the same level and upper level

ARTIGO 2

“Early determinants of Hipertriglyceridemic Waist Phenotype: effect of birth weight and breastfeeding. A systematic review and meta-analysis”

Submetido ao *Journal of Developmental Origins of Health and Disease*, Cambridge UK

Requisitos para a publicação do artigo intitulado "Early determinants of Hipertriglyceridemic Waist Phenotype: effect of birth weight and breastfeeding. A systematic review and meta-analysis" no periódico *Journal of Developmental Origins of Health and Disease".*

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References

References should be numbered consecutively (in superscript) as they appear in the text. Type the reference list with double-spacing on a separate sheet. References (using Index Medicus abbreviations) should appear in the style as demonstrated below. Please note that if six authors or more, the first three authors should be listed and then 'et al.'. Examples:

1. Burdge GC, Slater-Jefferies J, Torrens C, et al. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. *Br J Nutr.* 2007; 97, 435-439.

2. Gilbert JS, Nijland MJ. Sex differences in the developmental origins of hypertension and cardiorenal disease. *Am J Physiol Regul Integr Comp Physiol.* 2008; 295, 1941-1952.

3. Mitchell M, Schulz SL, Armstrong DT, Lane M. Metabolic and Mitochondrial Dysfunction in Early Mouse Embryos Following Maternal Dietary Protein Intervention. *Biol Reprod.* 2009 [Epub ahead of print].

4. Gluckman PD, Hanson MA. The developmental origins of health and disease: an overview. In *Developmental Origins of Health and Disease* (eds. Gluckman P, Hanson M), 2006; pp. 1-5. Cambridge University Press, Cambridge.

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12th February 2013

Early determinants of Hipertriglyceridemic Waist Phenotype: effect of birth weight and breastfeeding. A systematic review and meta-analysis

Ricardo Lanzetta Haack*

Bernardo Lessa Horta

*ricardohaack@yahoo.com.br

Abstract

Objectives: To analyze the evidence from literature of the effects of birth weight and breastfeeding on each components of the hypertriglyceridemic waist Phenotype (HWP). **Methods**: A search in the databases Pubmed and Lilacs was carried out without time limit. We combined the following terms for the exposures: birth weight (birth weight; birthweight) and breastfeeding (breastfeeding; breast feeding; infant feeding; human milk; lactation) with the following terms for the outcomes: waist circumference (waist circumference; waist girth) and triglycerides (triglycerides; lipids). 172 articles were examined and 29 studies reporting the associations of interest were included. **Results**: Birth weight was positively associated with waist circumference with the pooled effect using a random-effects model of 0.44 (95% CI: 0.22-0.66), conversely birth weight was inversely related to triglycerides levels with the pooled effect -0.04(95% CI: -0.05; -0.03) mmol/L. Subjects who had been breastfed had lower waist circumference, the pooled effect was -0.53 cm (95% CI: -0.82, -0.23) and there was no heterogeneity among studies (p=0.22). On the other hand, breastfeeding was not associated with triglycerides in adulthood [pooled effect -0.01 (95% CI: -0.06,0.03)]. **Conclusions:** Birth weight was positively associated with waist circumference and inversely related to triglycerides levels, moreover breastfed was not associated with triglycerides and inversaly to waist circumference. So the results presented suggest that birth weight and breastfeeding are not associated with HWP.

Introduction

In 2000, Lemieux and colleagues proposed that the hypertriglyceridemic waist phenotype (HWP) a combination of increased waist circumference with increased levels of triglycerides would be associated with the presence of metabolic risk factors for cardiovascular disease.[1] In this study over 80% of individuals with HWP presented elevated insulin levels, apolipoprotein B and small LDL particles[1]. Other studies have also reported similar findings.[2-8] Because waist circumference alone does not discriminate between subcutaneous and visceral obesity, it has been suggested that the presence of high levels of triglycerides could be used as a marker of an "dysfunctional" adipose tissue and visceral obesity in people with enlarged waist circumference.[1, 7, 9] It has also been reported that the HWP phenotype increases the risk of cardiovascular disease and that non-diabetic men with HWP had weight; body mass index (BMI) and waist circumference similar to diabetic patients.[10]

With respect to the factors related to the presence of the phenotype, several studies have reported that HWP is positively associated with metabolic cardiovascular risk factors in adulthood.[1, 5, 11-15] On the other hand, little is known about early factors that may be associated to the development of this phenotype.

According to our knowledge, only one study evaluated the association between early life exposures and the hypertriglyceridemic waist phenotype. Alavian et al[16] observed that among school children with a mean age of 12 years, the odds ratio for HWP, was higher among those boys whose birth weight was > 4000g (OR 1.4, 95% CI 1.10 to 2.05) and among girls whose birth weight was <2,500 g (OR 1.2, 95% CI 1.09 to 1.70). On the other hand, several studies have evaluated whether birth weight and

breastfeeding are associated with components of HWP (enlarged waist or higher triglycerides) [17-28], and it has been suggested that early exposures, during pregnancy or the first years of life, may program the development of chronic diseases.[29, 30,31]

Given the scarcity of studies assessing the programming effect of birth weight and breastfeeding on HWP, we decided to carry out a systematic review on the association of birth weight and breastfeeding with each one of the components of hypertriglyceridemic waist phenotype.

Methodology

Literature search

We systematically searched for studies reporting on the association of breastfeeding and birth weight with waist circumference and triglycerides. We combined the following terms for the exposures: birth weight (birth weight; birthweight) and breastfeeding (breastfeeding; breast feeding; infant feeding; human milk; lactation) with the following terms for the outcomes: waist circumference (waist circumference; waist girth) and triglycerides (triglycerides; lipids). Every breastfeeding and birth weight term was combined with each of the outcomes terms, using the Boolean operator AND. MEDLINE and LILACS databases were searched and the final list of references of included articles was checked. There was no time limit on revision and we excluded those studies that evaluated subjects < 12 years of age.

All studies were independently reviewed by two authors (RLH and BLH), and any disagreement was solved by consensus. The following variables were extracted from each manuscript: author's name, year of publication, gender of participants, number of participants, mean age of participants, type of study, comparison groups, mean difference between the groups and control for confounding factors.

Stata 12.0 was used in the analysis. Q test was used to check for heterogeneity between studies[32] and, in case of heterogeneity, studies were pooled using a random effects-model[33]. We also stratified the analysis according to studies characteristics, in order to identify possible effect modifiers. Publication bias was evaluated using the Egger's and Begg's tests and funnel plot[34].

Results

Figure 1 shows the flow chart of studies selection. Initially, 8423 articles were identified and 3772 duplicates were excluded. We examined the title of the 4651 manuscripts and 4479 were excluded after reading the abstracts. Thereafter, 172 articles were examined and 29 studies reporting the associations of interest were included. Having checked the references of the selected studies, none new article was included in the meta-analysis. Some articles showed the results stratified by gender and were included separately. The main reasons for exclusion of manuscripts were not reporting the association of interest, analysis restricted to children up to 12 years and fail to report the effect of birth weight as a continuous variable.

Table 1 shows, the main characteristics of the studies that assessed the association of birth weight with waist circumference and triglycerides. Only cohort studies reported on the programing effect of birth weight on triglycerides, whereas for waist circumference a cross-sectional study was identified. Figure 2 shows the results of the 8 studies that assessed the effect of birth weight on waist circumference, there was marked heterogeneity among the studies and the test of heterogeneity was statistically significant ($p < 0.001$). Seven studies reported that birth weight was positively associated with waist circumference whereas three reported an association in the opposite direction, and for two studies the regression coefficients were close to the null

value. The pooled effect using a random-effects model was 0.44 (95% CI: 0.22-0.66), i.e., waist circumference increased 0.44 cm for every increase of 1 kg in birth weight.

Conversely to what was observed for waist circumference, the 8 studies that assessed the relationship between birth weight and triglycerides were homogeneous, the test for heterogeneity was not statistically significant (p = 0.11). And the pooled effect using a fixed effect model was -0.04(95% CI: -0.05; -0.03) mmol/L (Figure 3), suggesting, that birth weight was inversely related to triglycerides levels.

Table 2 shows that for breastfeeding, most of the studies were also cohort. Figure 4 shows that only four studies reported on the association between breastfeeding and waist circumference and that all studies reported that those subjects who had been breastfed had lower waist circumference and the confidence interval did not included the reference (0) in three of these studies. The pooled effect was -0.53 cm (95% CI: -0.82, -0.23) and there was no heterogeneity among studies (p=0.22). On the other hand, Figure 5 shows that breastfeeding was not associated with triglycerides in adulthood [pooled effect -0.01 (95% CI: -0.06,0.03)].

Discussion

In this review birth weight was positively associated with waist circumference and negatively associated with triglycerides in adulthood whereas breastfeeding showed a negative association with waist circumference and was not related to triglycerides in adulthood. These evidences suggest that birth weight and breastfeeding may not be related to the occurrence of HWP because the associations with the components of the HWP were in opposite directions.

The hypertriglyceridemic waist phenotype is composed for a combination of two measures (waist circumference and triglycerides), and aims to identify those subjects with visceral obesity that would be in higher risk of developing cardiovascular disease.[1]

In the pooled analyses, an increase of 1 kg in birth weight lead to an increase of 0.44cm in waist circumference, in adulthood, whereas breastfeeding decreased waist circumference in 0.53 cm. Some studies also compared the waist circumference across different categories of birth weight, and the pooled effect was 0.49(95% CI: 0.28-0.71) comparing the lowest category with the highest of birth weight.

Waist circumference has been used as an indirect measure of visceral obesity, however recent study demonstrated that high birth weight is associated with lean mass and height and not with increased adiposity in adulthood.[35] Only two studies included in this review controlled the association between birth weight and waist circumference to height[22, 36]. Both studies showed a positive association between birth weight and waist circumference, and after controlling for height remained positive but with a very marked fall in the measure of effect, suggesting the presence of residual confusion. It has been suggested that the ratio between waist circumference and height would be the best predictor of cardiovascular risk[37, 38] because taller individuals would also have large waist circumference. Therefore, we cannot exclude that most of the observed association between birth weight and waist circumference is due to residual confounding by height.

The inverse association of breastfeeding with waist circumference may imply a possible protective effect of breastfeeding on measures of central obesity, this protective effect was small, but it is remarkable that this relationship still exists at adulthood. On the other hand, given the small number of studies reporting on such association, we cannot rule out that the observed association was due to publication bias. Furthermore, this

association could be due to confounding by socioeconomic status because breastfeeding duration and obesity are distributed differently between social classes. But studies from high-income countries provided estimates that were adjusted for socioeconomic variables. On the other hand, in a study that evaluated data from five birth cohorts from developing countries, the authors found no evidence that breastfeeding or prolonged breastfeeding would be protective against overweight or obesity in adulthood[39].

With respect to triglycerides, we observed that birth weight was inversely related, and that for each increase of 1 kg in birth weight, there was a decrease of 0.04mmol/L. Studies that evaluated the risk of hypertriglyceridemia also reported that low birth weight subjects were at increased risk[18, 40], on the other hand, breastfeeding was not related to triglycerides. Other studies have also failed to observe a long-term effect of breastfeeding on total cholesterol[19].

The results of this review show that birth weight is positively associated with waist circumference and negatively with triglycerides levels in adulthood, however there may be residual confounding in this association. And breastfeeding had negative correlation with waist circumference and shows no association with triglyceride levels in adulthood. Because the hypertriglyceridemic waist phenotype is a combination of waist circumference with triglycerides, very likely, birth weight and breastfeeding are not associated with it.

The main limitation of this meta-analysis is the fact that it was performed with the components of the phenotype (waist circumference and triglycerides) and not on the phenotype itself, although the results presented suggest that birth weight and breastfeeding are not associated with HWP, would be of great importance new studies with phenotype not with its components to confirm these findings.

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Flow diagram of study selection

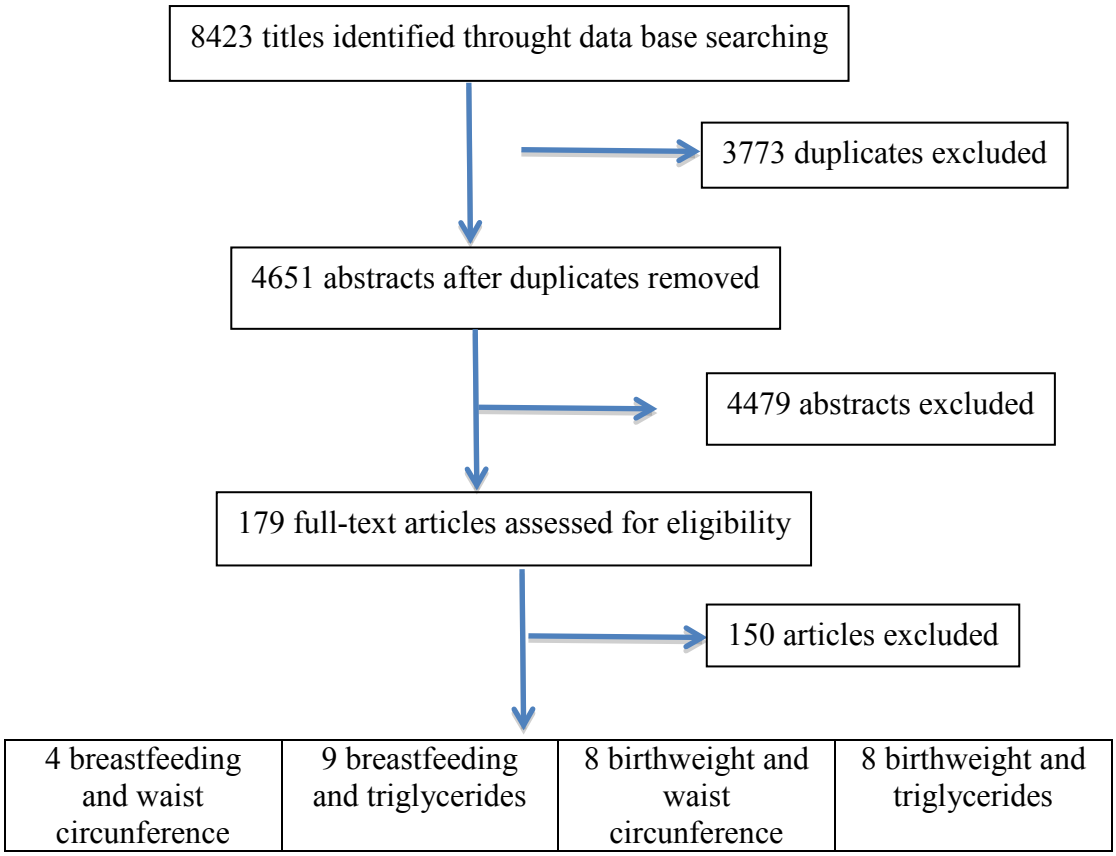

Figure 1. Flow diagram of studies selection

Table 1. Overview of studies included in the systematic review of Birth Weight with Triglycerides (n=8) and Waist Circunference (n=8)

Author, Publication year	Mean Age	Design	Comparison groups	Gender	Sample Size	Mean difference (SE)	Adjustments
Studies on Birth weight and triglycerides							
Mzayek, 2003	13	Cohort	birthweight continous	A	1155	-.06(.03)	age, gender, ethnicity, BMI
Lawlor, 2005	12	Cohort	birthweight continous	A	219	-.01(.02)	sex, age, pubertal stage, BMI, height, SES, maternal smoking, paternal smoking, maternal BMI, paternal BMI
Daly, 2005	15.5	Cohort	birthweight continous	A	855	-.03(.03)	age, sex, ethnicity
Ramadhani, 2006	28.5	Cohort	birthweight continous	A	745	-.032(.01)	gender, adulthood BMI, participant's education
Ruiz, 2008	15.4	Cohort	birthweight continous	M	260	-.017(0.81)	--
				F	242	-.06(0.98)	--
Cooper, 2008	45	Cohort	birthweight continous	A	7186	-.07(.01)	sex
Sayers, 2009	11.4	Cohort	birthweight continous	A	280	.017(.06)	sex, puberty status, gestational age, chronological age
Pinto Pereira, 2012	45	Cohort	birthweight continous	F	3897	-.04(.01)	--
				M	3897	-.03(.01)	--
Studies on birthweight and waist circunference							
Kahn, 2000	19.5	cohort	birthweight continous	M	192	3.9(1.2)	race, height
Kuh, 2002	43	cohort	birthweight continous	M	1589	.64(.24)	BMI
				F	1585	-.32(.3)	--
Te Velde, 2003	31.5	cohort	birthweight continous	F	192	-1.449(.7)	adult body mass
				M	137	-.814(.56)	--
Ramadhani, 2006	28.5	cohort	birthweight continous	A	719	.913(.75)	gender, education
Yliharsila, 2007	63	cohort	birthweight continous	M	928	.002(.33)	age, adult BMI
				F	1075	.005(.41)	--
McCarthy, 2007	25	cohort	birthweight z score continous	A	679	.42(.41)	age, sex
Eriksson, 2008	15	cohort	birthweight z score continous	M	1255	1.32(.33)	current age, lenght z-score, SES
				F	1198	.82(.3)	--
Labayen, 2008	15.8	cs	birthweight z score continous	A	1223	1.42(.496)	age, pubertal status, SES, gestational age, physical activity, height

CS – cross sectional
BMI – body mass index
SES – socioeconomic level

Table 2. Overview of studies included in the systematic review of Breastfed with Triglycerides (n=09) and Waist Circunference (n=4)

Author, Publication year	Mean Age	Design	Comparison groups	Gender	Sample Size	Mean difference (SE)	Adjustments
Studies on breastfed and triglycerides							
Fall, 1992	65	cohort	exclusively breastfed vs. formula fed	M	485	.1(.07)	--
Hromadova, 1997	13	cohort	breastfed vs. formula fed	A	76	-.05(.07)	--
Ravelli, 2000	50	cohort	exclusively breastfed vs. bottle fed during hospital stay	M	625	-.06(.07)	sex, prenatal exposure to famine, maternal age, length of hospital stay
Singhal, 2004	14	rct	allocated to bank breastmilk vs. allocated to preterm formula	A	198	-.1(.13)	--
Lawlor, 2005	15	cohort	ever breastfed vs. never breastfed	A	2192	-.01(.03)	age, sex, country, pubertal age, BMI, SES, height
Martin, 2005	52	cohort	breastfed vs. bottle fed	A	362	-.02(.14)	sex, age
Victora, 2006	18	cohort	ever breastfed vs. never breastfed	M	2250	.16(.39)	SES, cor da pele, peso ao nascer, maternal smoking, BMI, behavioural variables
Rudnicka, 2007	44	cohort	breastfed > 1 month vs. never breastfed	A	8172	-.15(1.59)	SES, gender, smoking, BMI, maternal body size, ...
Parikh, 2009	41	cohort	breastfed vs. not breastfed	A	962	-.45(.37)	age, sex, lipid treatment, smoking status, SES, physical activity
Studies on breastfed and waist circunference							
Rudnicka, 2007	45	cohort	breastfed > 1 month vs. never breastfed	A	8172	-.81(.34)	SES, gender, birthweigth, smoking, bmi, ...
Grjibovski, 2008	15	cohort	breastfed < 2 month vs. breastfed > 6 month	A	394	-3.2(1.53)	age, gender, pubertal maturation, birth weight, maternal education, maternal and paternal BMI
De Kroon, 2011	23	cohort	ever breastfed vs. never breastfed	A	762	-.39(.18)	gender, age, birth weight, BMI of the mother, educational level of the mother
Fall, 2011	28	cohort	ever breastfed vs. never breastfed	A	10912	-.67(.47)	age, sex, maternal SES, education, smoking, race, local of residence, birth weight

rct – randomized controled trial
SES- socioeconomic level
BMI- body mass index

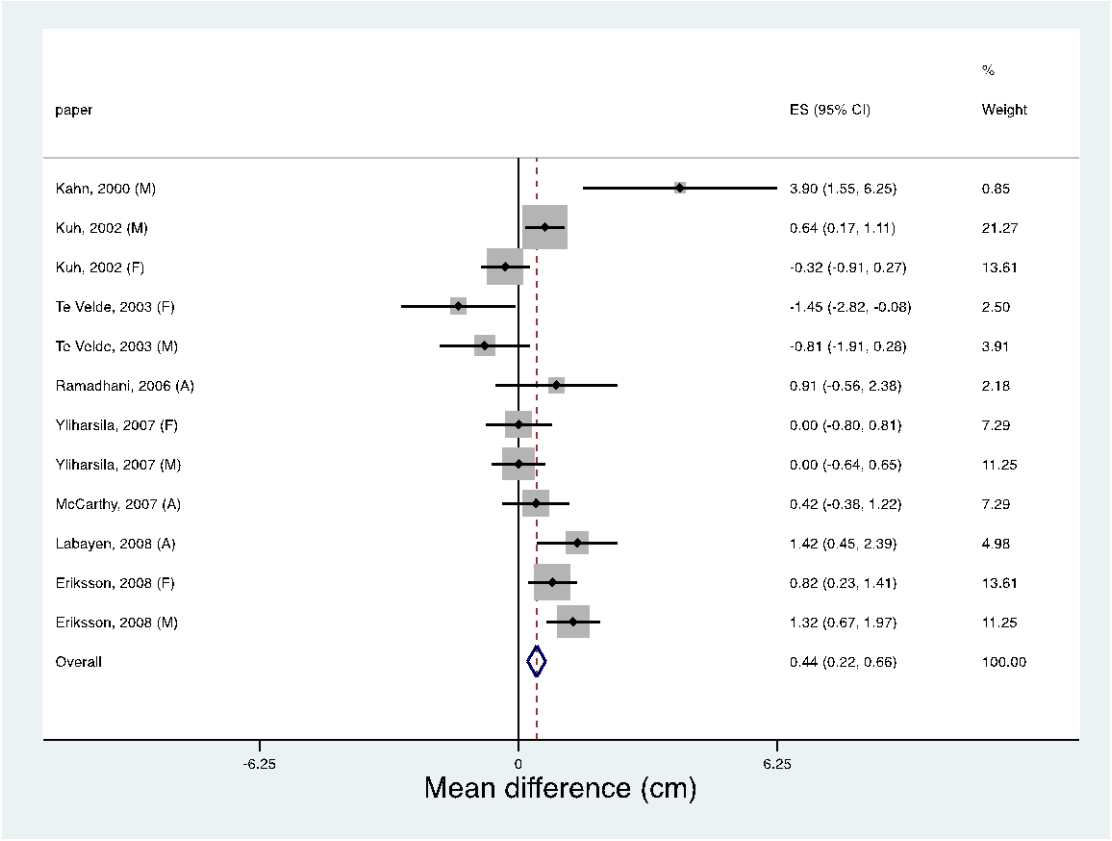

Figure 2. Mean difference of waist circunference according to birth weight

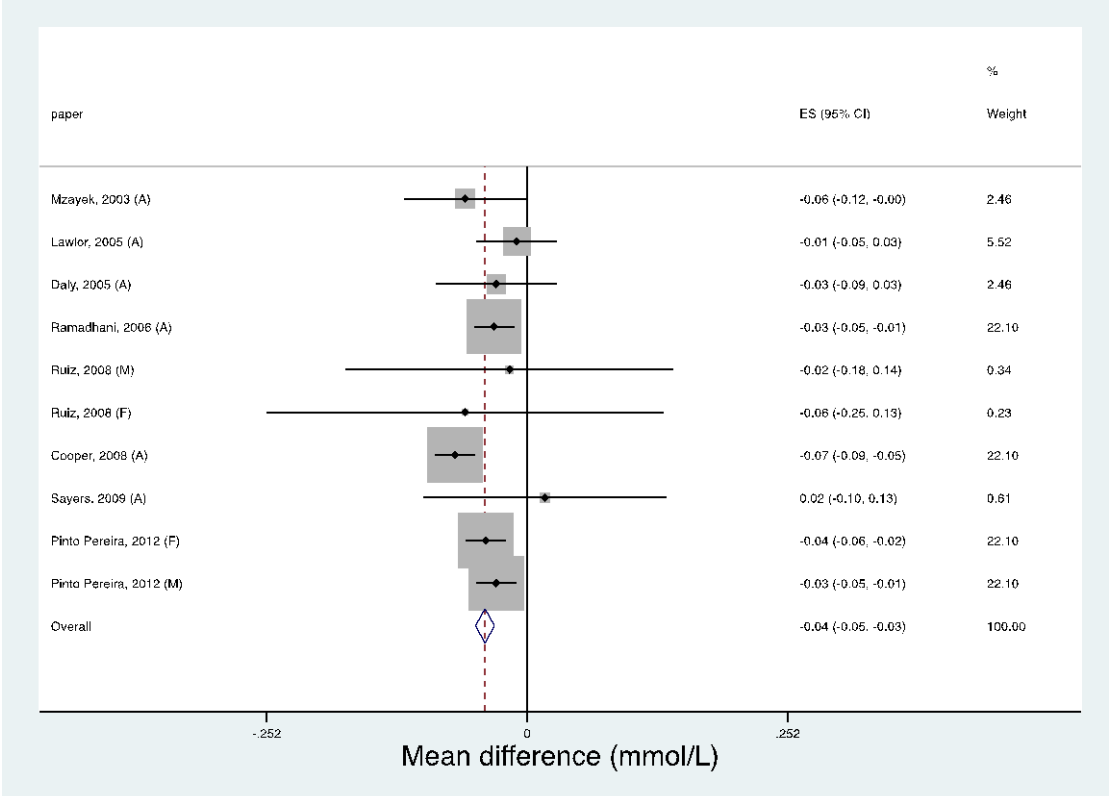

Figure 3. Mean diference of triglycerides according to Birth Weight

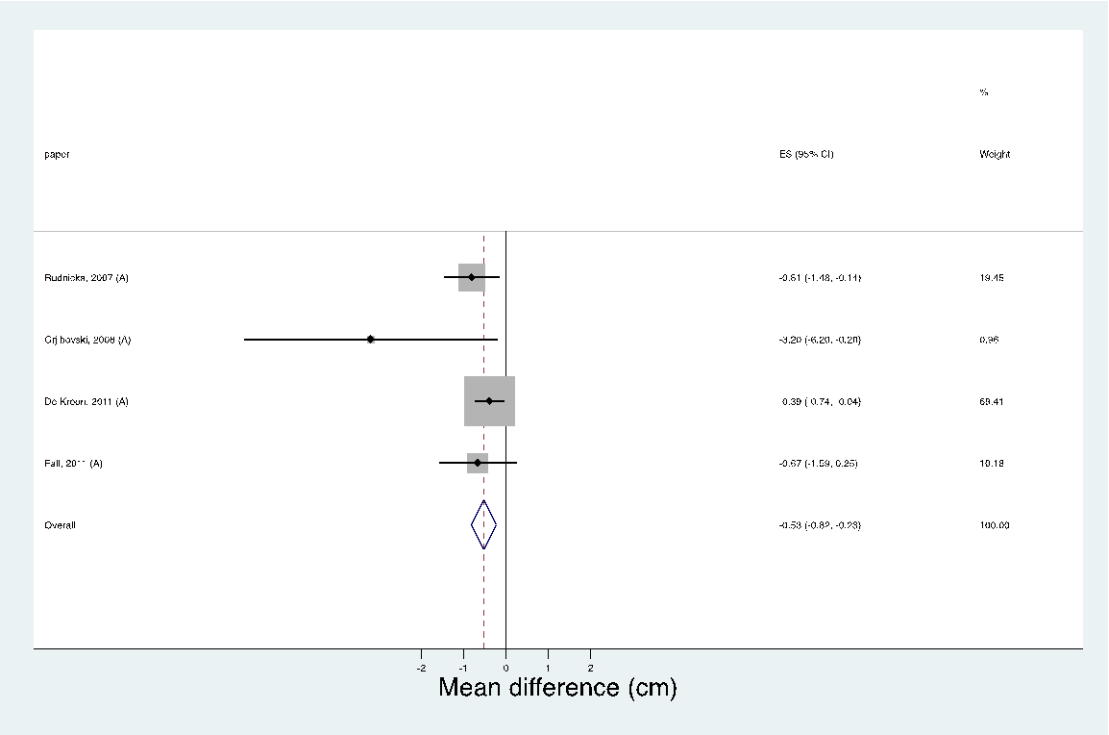

Figure 4. Mean difference in Waist Circunference according to breastfeeding

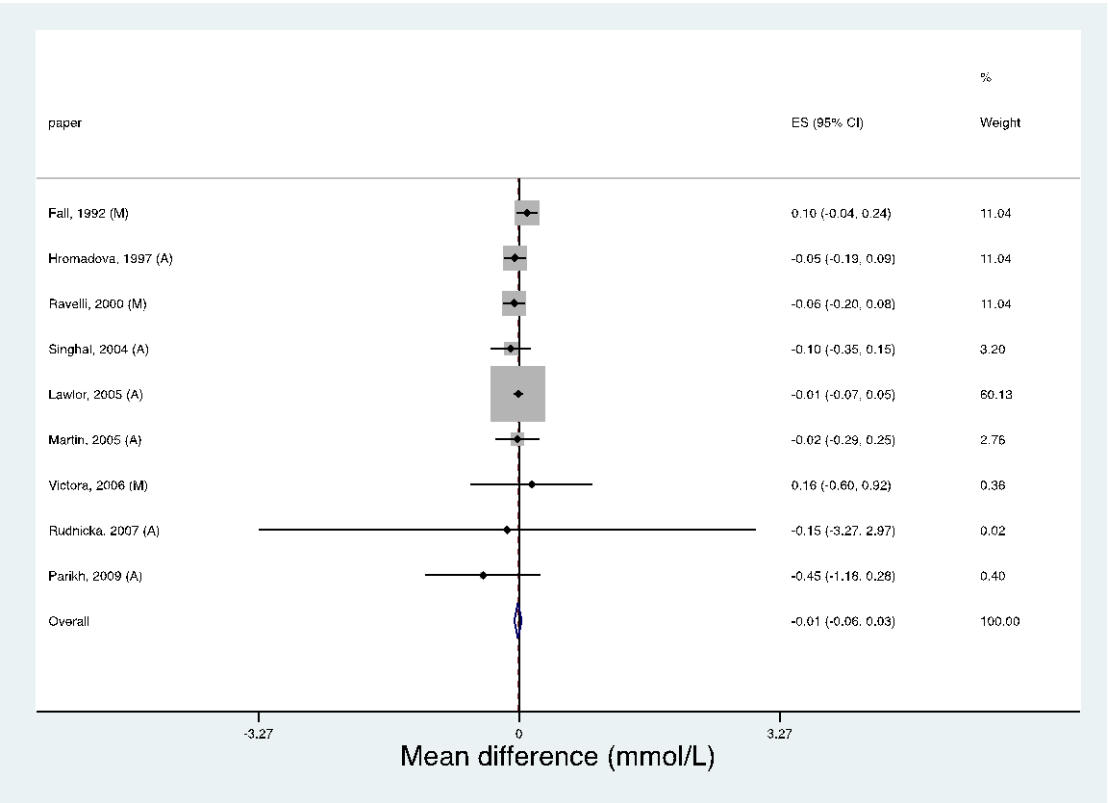

Figure 5. Triglycerides level according to breastffeding

ARTIGO 3

"Hypertriglyceridemic Waist Phenotype: Effect of birthweight and weight gain in childhood at 23 years old"

A ser submetido à revista *Circulation, USA*

Requisitos para publicação do artigo 3 intitulado "Hypertriglyceridemic Waist Phenotype: Effect of birthweight and weight gain in childhood at 23 years old" na revista "Circulation".

General Preparation Instructions

Maximum Word Length: 7000 words Word count includes title page, abstract, text, references, tables, and figure legends.
Maximum Number of References: 50
Maximum Number of Figures and Figure Legends: 8
Manuscript should be typed double-spaced, including title page, abstract, text, references, figure legends, and tables. Text should only appear on one side of the page. Acceptable formats are Word or WordPerfect.
Leave a 1-inch margin on all sides. Do not use justified margins.
Cite references, figures, and tables in numeric order. For review, acceptable figure formats are GIF, TIFF, EPS, JPEG, and single slides of PowerPoint. Formats NOT supported are as follows: Object Linking and Embedding (OLE), Bitmap (.bmp), PICT (.pict), Excel (.xls), Photoshop (.psd), Canvas (.cnv), CorelDRAW (.cdr), and locked or encrypted PDFs. For publication, see acceptable figure requirements under "Accepted Manuscripts" below.
Use SI units of measure. A more conventionally used measurement may follow in parentheses. Make all conversions before manuscript submission.
Please provide sex-specific and/or racial/ethnic-specific data when appropriate, in describing the outcomes of epidemiologic analyses or clinical trials, or specifically state that no sex-based or racial/ethnic-based differences were present.
Consult the American Medical Association Manual of Style, 10th ed, New York, Oxford University Press, 2007, for style.
Manuscripts must conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (http://www.icmje.org/).
Assemble the manuscript in this order: Title Page, Abstract, Text, Acknowledgments, Funding Sources, Disclosures, References, Figure Legends, Tables, and Figures.

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The Journal Subject Codes pertaining to the article. Please refer to the Subject Code List.

Abstract and Key Words

5. Do not cite references in the abstract
6. Limit use of acronyms and abbreviations. Define at first use with acronym or abbreviation in parentheses.
7. Be concise (250 words maximum)
8. Use the following headings:
   - Background—rationale for study
   - Methods and Results—brief presentation of methods and presentation of significant results; please include sample size
   - Conclusions—succinct statement of data interpretation
   - When applicable, include a fourth heading, "Clinical Trial Registration." Please list the URL, as well as the Unique Identifier, for the publicly accessible website on which the trial is registered.
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- Typical main headings include Methods, Results, and Discussion.
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Hypertriglyceridemic Waist Phenotype: Effect of birthweight and weight gain in childhood at 23 years old

Ricardo Lanzetta Haack*

Bernardo Lessa Horta

*ricardohaack@yahoo.com.br

Abstract

Objective: Asses the effect of birthweight and weight gain during different periods in childhood on the prevalence of hypertriglyceridemic waist phenotype (HWP). **Methods:** In 1982, all hospitals births in Pelotas, South Brazil, were identified, and the 5914 liveborn, whose family lived in the urban area of the city, were examined and their mothers interviewed. This population has been followed for several times and in 2004-5 visit a blood sample was collected. HWP was defined as a triglycerides ≥ 2 mmol/L and a waist circumference ≥ 90 cm for men, and triglycerides ≥ 1.5 mmol/L and waist circumference ≥ 85 cm for woman. Poisson regression with robust adjustment of the variance was used to obtain adjusted estimates of the prevalence ratio. Conditional regression model was used to take into account the correlation between subsequent weight measures and regression to the mean. **Results:** Subjects whose weight-for-age z-score at mean age of 42 months was one or more standard deviation above the mean, according to gender and age, were 7.83 (95% confidence interval: 3.55; 17.2) times more likely of presenting the HWP than those subjects whose weight-for-age z-score at 42 months was more than one standard deviation below the mean. Among those subjects whose birthweight was adequate-for-gestational age (AGA), conditional weight at 20 months was positively associated to the risk of having the HWP [relative risk: 1.59 (95%: confidence interval: 1.32; 1.92)], whereas for small for gestational age (SGA) subjects conditional weight was not associated with the HWP [relative risk: 1.06 (95% confidence interval: 0.74; 1.5)]; the test for interaction was significant (p-value = 0.08).

Conclusion: Early weight gain among SGA infants, did not increase the risk of presenting the HWP in early adulthood, whereas among those whose birthweight was AGA, early weight gain increased the risk of the having the phenotype.

Keywords: birthweight, weight gain, triglycerides

Introduction

Evidence suggests that the development of noncommunicable diseases may be programmed by exposures in early life.(1, 2) It has been reported that intrauterine malnutrition increases the risk of cardiovascular disease in adulthood(3), and that blood pressure in adulthood is inversely related to birthweight.(4) On the other hand, other studies have suggested that chronic diseases are programmed by postnatal growth not by intrauterine growth.(5, 6)

Evidence on the long-term consequences of weight gain in childhood are conflicting, catch-up in early childhood has been associated with increased birthweight in the next generation(7) and achieved schooling.(8, 9) Meta-analysis by Owen et al (10) observed that body mass index (BMI) in early childhood was not related to the risk of coronary heart disease (CHD), whereas BMI in later childhood and early adulthood was associated with an increased risk of CHD.(10) Furthermore, rapid weight gain after 4 years, among individuals who were light at birth, has been associated with increased systolic blood pressure in adulthood.(6) Crowther et al reported that catch-up in the first year of life was not related to insulin and glucose levels, but weight gain after the first year would lead to higher insulin level.(11) Another study in Philippines described that homeostasis model assessment of insulin resistance (HOMA-IR) at 22 years was not related to weight gain from 0 to 4 months, but weight gain from 0 to 2 years was positively related to HOMA-IR among males and this association was mediated by body mass index and waist circumference in adulthood.(12) In order to help to solve the catch-up dilemma, studies should assess the consequence of rapid growth in different periods in childhood, as evidences suggest that timing of growth may have different long-term consequences.

The hypertriglyceridemic waist phenotype (HWP) has been associated to the presence of cardiometabolic risk profile (increased levels of insulin, Apolipoprotein B, C-reactive protein and small dense LDL cholesterol) and an increased risk of coronary artery disease. Even after controlling for cardiovascular risk factors (metabolic and behavior), subjects with the HWP had a higher hazard of coronary artery disease [1.28 (95%confidence interval: 1.07; 1.54) for males, and 1.67(95% confidence interval: 1.35; 2.06) for females)].(13) Furthermore, it has been reported that impaired fasting glucose is not related to coronary artery disease, among subjects that does not present the HWP.(14) This finding shows the relevance of the phenotype as a marker of subjects in high risk of cardiovascular disease. To our knowledge, the programming of the phenotype by early growth has not been previously assessed. By assessing the effect of weight gain during different periods in childhood on the phenotype, this study may help to solve the catch-up dilemma.

Methods

In 1982, all hospitals births in Pelotas, Brazil (current population 320.000), were identified, and the 5914 liveborn whose family lived in the urban area of the city were examined and their mothers interviewed. This population has been followed for several times. In 1984 (mean age 20 months) and 1986 (mean age 42 months) all households in the city were visited in search of cohort children; 87 and 84% of the original cohort were located, respectively. From October 2004 to August 2005 (mean age 23 years), we visited all households located in urban area of the city. For those who had not been located and were not known to have died, we used the last known address and existing databases (including universities, secondary schools and telephone directories) for another attempt. The subjects answered a questionnaire on sociodemographic, health

and behavioral variables. At the end of the interview, the subjects were invited to visit the research laboratory to give a blood sample. Another home visit was made, with the aim of obtaining blood samples from the interviewees who did not go to the laboratory. Further details on the methodology of the study are available elsewhere.(15)

Birthweight was assessed by the maternity hospital staff using calibrated scales; low birthweight was defined as <2500 g. Gestational age was calculated according to the recalled date of the mother's last menstrual period, and preterm birth was defined as gestational age <37 weeks. Those children whose birthweight was below the 10th centile for gestational age and sex, according to the reference developed by Williams et al,(16)were classified as small-for-gestational age (SGA).

In 1984 and 1986, subjects were weighed using a portable scale with an accuracy of 100 g and the length (1984) and height (1986) were measured using a portable stadiometer. Birthweight for gestational age z-scores were calculated using the Williams's reference.(16) In the follow-up visits, z-scores according to weight-for-age and sex were estimated, using the World Health Organization (WHO) standard.(17) Waist circumference was measured at the narrowest girth of the trunk or halfway between the costal margin and iliac crest, using a flexible 160cm (precision: 1mm) fiberglass measuring tape. Triglyceride was assessed with a colorimetric enzymatic method.

Hypertriglyceridemic waist phenotype was defined as a triglycerides ≥ 2 mmol/L and a waist circumference ≥ 90 cm for men(18), whereas for women triglycerides ≥ 1.5 mmol/L and waist circumference ≥ 85 cm were used as cut-off.(19)

Poisson regression with robust adjustment of the variance was used to obtain adjusted estimates of the prevalence ratio.(20) The following variables were considered as possible confounders: family income; household assets index (obtained through

factor analysis and based on the ownership of household goods); parental schooling at birth and maternal smoking during pregnancy.

Conditional regression was used to take into account the correlation between subsequent weight measures and regression to the mean.(21) Weight-for-age z-score at 20 months was predicted from the birth weight for gestational age z-score, and the difference (residual) between the observed and predicted weight-for-age z-score at 20 months was estimated. This residual was included in the analysis that assessed the effect of weight gain in the first 20 months. Weight-for-age z-score at 42 months was predicted using a similar approach, and the regression included birthweight for gestational age z-score and weight-for-age z-score at 20 months. In the interaction test a p value of 10% was used as the cutoff point for statistical significance.

The confidentiality of all information was ensured and informed consent was obtained in all phases of the study. The Medical Ethics Committee of the University of Pelotas, affiliated with the Brazilian Medical Research Council, approved the research protocol.

Results

In the 2004–5 follow-up visit, 4297 subjects were interviewed, representing a follow-up rate of 77.4% (added to the 282 known to have died), and a blood sample was collected from 3,914 individuals. Table 1 shows that among those subjects studied in 2004-5, the prevalence of low birthweight was 6.2% and 7.9% for male and female, respectively. In 1984, at a mean age of 20 months, 3.5% of the males and 2.7% of the females had a weight for age z-score < - 2 standard deviation. In early adulthood, triglyceride was higher and HDL cholesterol was lower among male. The prevalence of

hypertriglyceridemic waist phenotype was 5.9% and 4.5% among males and females, respectively.

Table 2 shows that birthweight for gestational age z-score was not related to the presence of the hypertriglyceridemic waist phenotype. On the other hand, weight-for-age z-score in childhood was positively related to the risk of having the HWP. Those subjects whose weight-for-age z-score at mean age of 42 months was one or more standard deviation above the mean were 7.83 (95% confidence interval: 3.55; 17.2) times more likely of presenting the hypertriglyceridemic waist phenotype than those subjects whose weight-for-age z-score at 42 months was more than one standard deviation below the mean.

Table 3 shows that early and late weight gain in childhood were related to a higher risk of having the HWP. On the other hand, Figure 1 shows that the effect of weight gain in early childhood was modified by intrauterine growth. Among those subjects whose birthweight was adequate-for-gestational age (22), conditional weight at 20 months was positively associated to the risk of having the HWP [relative risk: 1.59 (95%: confidence interval: 1.32; 1.92)], whereas for SGA subjects conditional weight was not associated with the HWP [relative risk: 1.06 (95% confidence interval: 0.74; 1.5)]; the test for interaction was significant (p-value = 0.08).

Figure 2 shows the weight trajectory from birth to 23 years of age among those subjects who presented the hypertriglyceridemic waist phenotype. In this analysis, each measurement among SGA and adequate for gestational age (AGA) infants was standardized, with mean set at zero, and the deviations from the mean are shown in standard deviations. Therefore, the values presented in these figures shows the difference in weight-for-age z-scores between those who presented and not the phenotype. A mean below zero indicated that weight-for-age was small among those

with HWP. The results were very similar to that observed with the conditional growth model. Among AGA subjects, we observed a steady increase in the difference in weight between those with and without the hypertriglyceridemic waist phenotype, whereas for SGA subjects in the first 20 months this difference did not change, with the mean difference near to zero, but after that a steady increase in the difference was also observed. Suggesting, therefore, that among SGA subjects, early weight gain was not related to the presence of the phenotype, whereas later weight gain is associated to the risk of presenting the hypertriglyceridemic waist phenotype.

Discussion

In this cohort that has been followed since birth, in a southern Brazilian city, we observed that birthweight was not related to hypertriglyceridemic waist phenotype in early adulthood. On the other hand, weight-for-age z-score in childhood was positively associated with the risk of presenting the phenotype. With respect to weight gain in childhood, among those subjects who were born small-for-gestational age, weight gain in the first 20 months was not related to the risk of having the phenotype, whereas weight gain from 20 to 42 months increased the risk. On the other hand, among adequate-for-gestational subjects, early and late weight gain in childhood increased the risk of having the phenotype.

With respect to the validity of the evidence, the use of standardized methods in the anthropometric evaluation in childhood minimized misclassification error. Moreover, confounders were prospectively evaluated, using standardized questionnaires and trained interviewers, reducing the likelihood of residual confounding. Follow-up rates were not related to birthweight and maternal skin color. On the other hand, subjects of families whose income was either at the lower or upper end of the

distribution and those whose mother had 12 or more years of schooling were less likely to the followed in adulthood.(23) Because weight gain in childhood and birthweight were not associated with attrition rate at the follow-up visit in 2004-5, selection bias is not likely. Because triglycerides were measured from non-fasting blood, this study would be susceptible to misclassification. But, evidence suggests that triglycerides measured from non-fasting blood predict risk of cardiovascular disease better than fasting levels.(22, 24-26) Therefore, the use of non-fasting triglycerides in the analysis of long-term consequences of weight gain on childhood on risk of HWP is acceptable. As previously mentioned, the hypertriglyceridemic waist phenotype is related to the presence of cardiometabolic risk factors and coronary artery disease.(13) Therefore, it should be considered as a marker of higher cardiovascular risk.

Few studies have evaluated the long-term consequences of rapid weight gain in childhood on triglycerides and waist circumference. In our cohort, we have already evaluated the effect of early weight gain on blood lipids among18 years old males, and weight gain from birth to 20 months of age was not associated with blood lipids. However, rapid weight gain from 20 to 42 months of age was positively associated to very low-density lipoprotein (VLDL), low-density lipoprotein cholesterol (LDL) / high-density lipoprotein cholesterol (HDL) ratio, and triglycerides.(27) Other studies have also reported that weight gain in later childhood is related to increased blood lipids level. (28-30)

Weight gain in childhood has been used as synonymous of catch-up growth, but we should be careful before labeling every weight gain as catch-up. Tanner(31) defined catch-up growth as the accelerated growth that occurs as soon as an insult removed and growth failure ends. In the present study, we were able to assess the effect of catch-up growth, by stratifying the analysis according to intrauterine growth; and observed that

early weight gain among small-for-gestational age infants, i.e. catch-up growth, did not increase the risk of presenting the hypertriglyceridemic waist phenotype in early adulthood, whereas among those whose birthweight was adequate for gestational age, early weight gain increased the risk of the having the phenotype. Suggesting, therefore, that catch-up growth in early childhood is not related to the programming of cardiovascular diseases.

Early rapid weight gain has short-term benefits, reducing mortality and morbidity.(32) Furthermore, evidence suggests rapid weight gain in early childhood is positively associated with human capital(8, 9) and is not associated to the presence of metabolic cardiovascular risk factors. (6, 27, 33) Therefore, weight gain should be stimulated in early childhood, mainly among those infants who were underweight.

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Table 1. Distribution of sample studied at 23 years of age, according to key characteristics.

Sample characteristics	Men	Women
At birth (1982)		
Birthweight in grams, mean (SD)	3279 (523)	3163 (503)
Low birthweight, n (%)	136 (6.2)	165 (7.9)
Preterm birth, n (%)	97 (5.5)	86 (5.2)
Small-for-gestational age, n (%)	268 (15.1)	229 (13.8)
1984 follow-up visit		
Weight for age z-scores, n (%)		
< - 2	70 (3.5)	51 (2.7)
- 2 to -1.01	247 (12.2)	187 (9.7)
- 1 to 0.99	1309 (64.9)	1323 (68.7)
≥ 1	392 (19.4)	364 (18.9)
Weight for age in z-scores, mean (SD)	0.06 (1.11)	0.13 (1.04)
2004/5 follow-up visit		
Triglycerides in mg/dL, mean* (SD)	97.3 (1.78)	85.9 (1.62)
HDL cholesterol in mg/dL, mean (SD)	51.6 (11.2)	59.4 (13.4)
Waist circumference in cm, mean (SD)	80.9 (10.1)	74.7 (10.5)
Hypertriglyceridemic waist phenotype, n(%)	113 (5.9)	80 (4.5)

* geometric mean

Table 2. Prevalence ratio of hypertriglyceridemic waist phenotype according to birthweight for gestational age and weight for age z-score at 20 and 42 months.

	Prevalence ratio of hypertriglyceridemic waist phenotype (95% confidence interval)		N
	Crude	Adjusted	
Birthweight for gestational age z-score	P = 0.24 *	P = 0.18 *	
< -1.28	Reference (1)	Reference (1)	433
-1.28 to 0	1.16 (0.70; 1.90)	1.04 (0.61; 1.79)	1302
> 0	1.32 (0.80; 2.16)	1.33 (0.77; 2.28)	1213
Weight for age z-scores at mean age of 20 months	P = 0.002 *	P = 0.004 *	
< - 1	Reference (1)	Reference (1)	474
- 1 to 0.99	1.30 (0.78; 2.14)	1.31 (0.78; 2.22)	2260
≥ 1	2.14 (1.25; 3.67)	2.06 (1.16; 3.65)	651
Weight for age z-scores at mean age of 42 months	P < 0.001 *	P < 0.001 *	
< - 1	Reference (1)	Reference (1)	515
- 1 to 0.99	2.35 (1.24; 4.47)	3.20 (1.50; 6.84)	2320
≥ 1	5.86 (3.03; 11.3)	7.83 (3.55; 17.2)	501

* test for linear trend
adjusted for household assets, family income, parental schooling at birth and maternal smoking during pregnancy.

Table3. Adjusted* conditional growth analyses of hypertriglyceridemic waist phenotype according to predicted weight at the mean ages of 20 and 42 months.

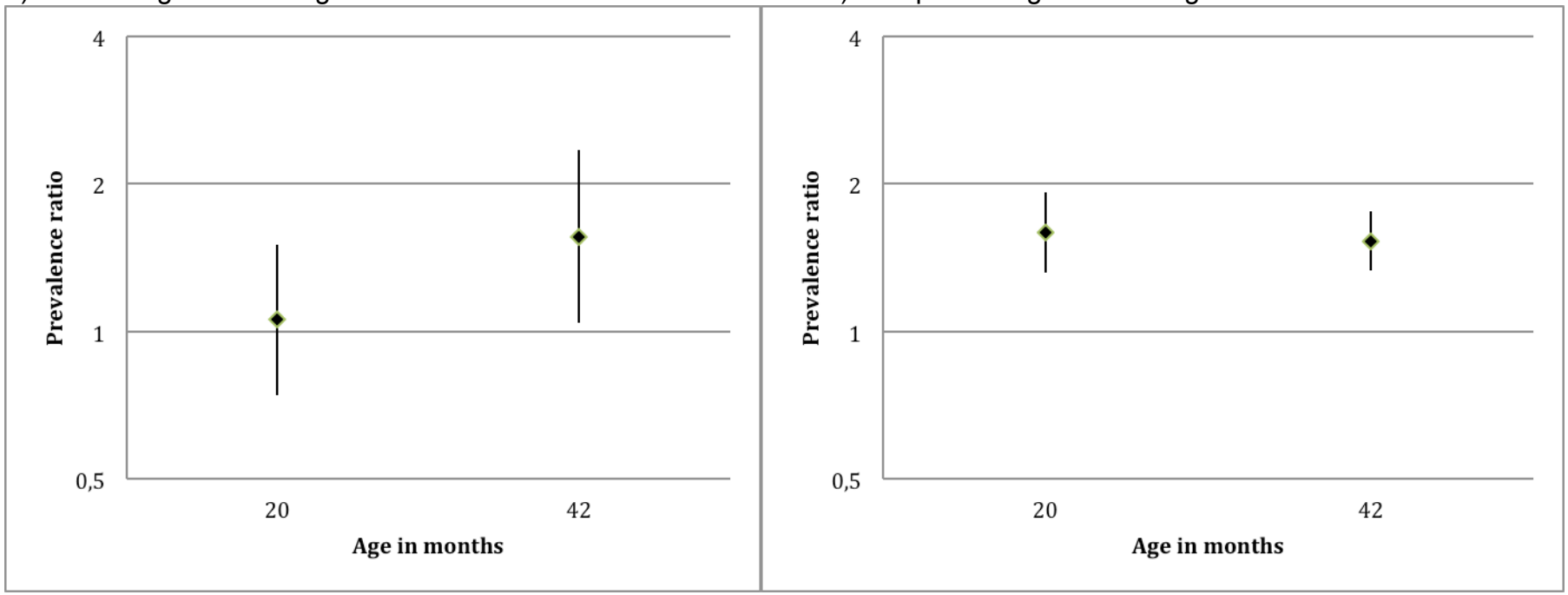
		Prevalence ratio of hypertriglyceridemic waist phenotype (95% confidence interval)	
		Crude	Adjusted
Weight at 20 months minus predicted weight (Z-scores) &	Coefficient (95% confidence interval)	1.50 (1.27; 1.76)	1.50 (1.27; 1.79)
	P-value	< 0.001	< 0.001
Weight at 42 months minus predicted weight (Z-scores) $	Coefficient (95% confidence interval)	1.51 (1.32; 1.72)	1.53 (1.34; 1.74)
	P-value	< 0.001	< 0.001

* adjusted for household assets, family income, parental schooling at birth and maternal smoking during pregnancy.
& Also adjusted for birthweight

$ Also adjusted for birthweight and weight residual at 20 months.

Figure 1. Adjusted * prevalence ratio of hypertriglyceridemic waist phenotype according to intrauterine growth

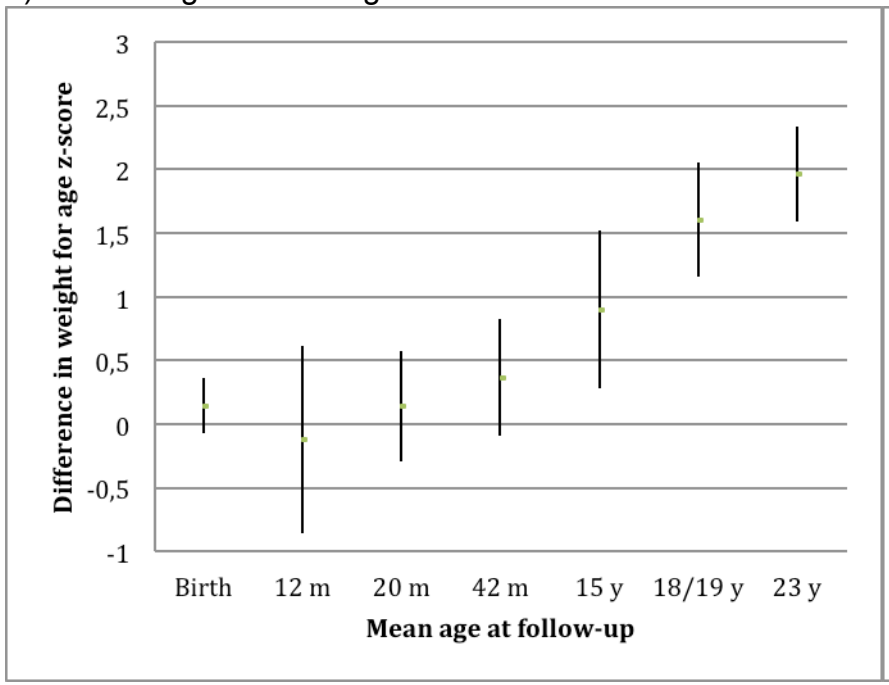
a) Small-for-gestational age b) Adequate-for-gestational age



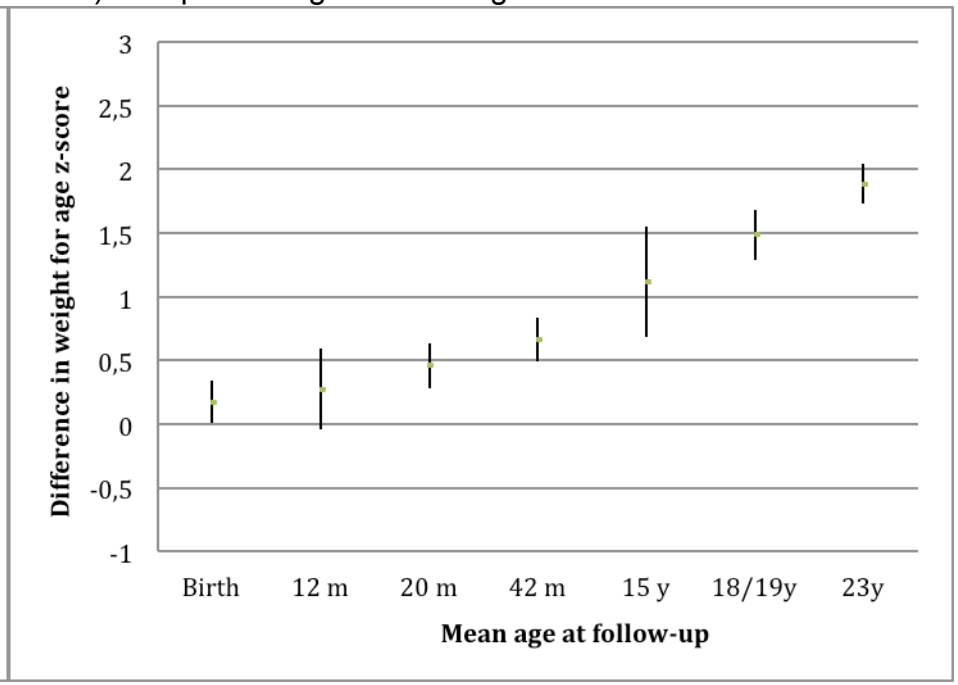
* adjusted for household assets, family income, parental schooling at birth and maternal smoking during pregnancy.

Figure 2. Mean sex specific adjusted* weight-for-age z-scores of subjects classified as having the hypertriglyceridemic waist phenotype, according to intrauterine growth. The mean weight for age z-score in each strata (small and adequate-for-gestational age) was set to zero, with deviations from the mean expressed as standard deviations (z-scores).

a) Small-for-gestational age



b) Adequate-for-gestational age



* adjusted for household assets, family income, parental schooling at birth and maternal smoking during pregnancy.

PARTE IV. DIVULGAÇÃO DOS RESULTADOS

Muitas doenças crônicas, entre elas doença cardiovascular e câncer, têm origens comuns e estão relacionadas com sobrepeso e obesidade. A epidemia da obesidade é um problema de saúde pública mundial e um dos principais efeitos da obesidade na infância e adolescência é a sua persistência até a vida adulta e o desenvolvimento de todas as suas consequências, entre elas doença cardiovascular. Entretanto, nem todos os indivíduos obesos estão em risco, parecendo mais importante aquela obesidade de origem abdominal do que a que ocorre no sub-cutâneo.

As doenças crônicas em geral têm um longo período de latência pré-clínico, quando o indivíduo fica exposto aos fatores de risco, os quais geralmente são modificáveis através de alterações em hábitos de vida e pela adoção de medidas de prevenção primária, como reeducação alimentar e prática de atividade física. Identificar os indivíduos em risco neste período pré-clínico é importante para o estabelecimento de medidas de prevenção para o desenvolvimento de tais doenças.

No ano de 2000, pesquisadores do Canadá propuseram que o aumento na circunferência abdominal associado ao aumento nos níveis de triglicerídeos plasmáticos fosse um marcador de utilidade clínica, para identificação de indivíduos em risco de desenvolver doença cardiovascular e diabetes e chamaram a presença desta associação de fenótipo da cintura hipertrigliceridêmica.

Baseado nisso, no ano de 2010, teve início a tese de doutorado intitulada *"Cintura Hipertrigliceridêmica em adultos jovens pertencentes a uma coorte de nascimentos no sul do Brasil"* do aluno do curso de Pós-Graduação em Epidemiologia da Universidade Federal de Pelotas, Ricardo Lanzetta Haack, sob orientação do professor Doutor

Bernardo Lessa Horta e desenvolvida dentro do estudo de Coorte de Nascimentos de Pelotas de 1982.

Estudos de Coorte são um tipo de estudo epidemiológico que se caracterizam por acompanhar uma população por longos períodos e observar as mudanças no seu estado de saúde. A Coorte de 1982 de Pelotas é considerada o primeiro grande estudo epidemiológico do Brasil. Naquele ano, todas as crianças nascidas em hospitais da cidade foram avaliadas e suas mães entrevistadas, totalizando 5914 crianças. De lá para cá, já foram realizados diversos acompanhamentos com estes indivíduos, sendo os dois últimos em 2004/5 e 2012/13.

Os objetivos da presente tese seriam identificar quantos indivíduos nascidos em 1982 apresentam o fenótipo da cintura hipertrigliceridêmica, e verificar se essas pessoas apresentam níveis de colesterol total, colesterol HDL, glicemia, pressão arterial e proteína-c-reativa diferentes dos indivíduos que não apresentam o fenótipo. Também era objetivo tentar identificar se condições ocorridas precocemente na vida destas pessoas, como peso ao nascer e crescimento nos primeiros anos de vida, influenciam no desenvolvimento do fenótipo.

No acompanhamento de 2004/5, ou seja, aos 23 anos de idade - cerca de 30% dos homens e 20% das mulheres apresentavam sobrepeso ou obesidade e 5,9% dos homens e 4,5% das mulheres apresentavam o fenótipo da cintura hipertrigliceridêmica. Estes indivíduos com o fenótipo tinham valor médio de pressão arterial mais elevado, menor nível de colesterol HDL, maior média de colesterol total, proteína-c-reativa e glicemia quando comparado aos que não apresentavam o fenótipo, demonstrando que estas pessoas, apesar de serem jovens, já apresentam risco elevado para o desenvolvimento de doença cardiovascular.

Muitos estudos têm demonstrado que as crianças que ganham peso muito rápido nos primeiros anos de vida, podem ter uma chance maior de desenvolver obesidade na adolescência e na vida adulta. O presente estudo tentou identificar se ter um ganho de peso acelerado nos primeiros anos também poderia ser responsável por uma maior incidência do fenótipo da cintura hipertrigliceridêmica aos 23 anos. Entre as crianças que nasceram pequenas para idade gestacional, ou seja, com peso abaixo do esperado, ter um ganho de peso acelerado nos primeiros 20 meses não aumenta a chance de desenvolver o fenótipo. Porém, quando este ganho de peso acelerado ocorre entre os 20 e 40 meses, aumenta a chance de desenvolver o fenótipo. Já entre aquelas crianças que nasceram com peso adequado para a idade gestacional, o ganho de peso acelerado, independente do período em que ele ocorre, está associado com o desenvolvimento de cintura hipertrigliceridemica.

PARTE V. RELATÓRIO DO TRABALHO DE CAMPO

Relatório Trabalho de campo do Acompanhamento de 2004/5

1. Breve histórico da coorte de 1982

Todas as crianças nascidas em 1982 na cidade de Pelotas, cujas mães residiam na zona urbana do município no momento do parto, foram elegíveis para um estudo longitudinal sobre saúde. Entre todas as crianças nascidas vivas, menos de 1% foram perdidas e em menos de 1% dos casos as mães se recusaram a participar do estudo. Ao longo de todos esses anos, vários estudos foram conduzidos com os indivíduos deste grupo. No período de outubro de 2004 a agosto de 2005, todas as crianças da coorte, na época, com 22-23 anos de idade foram procuradas para um novo acompanhamento. O esquema apresentado abaixo descreve os acompanhamentos realizados com a coorte de 1982.

Ano Acompanhamento

1982 Todas as crianças (estudo perinatal)

1983 1/3 da coorte (nascidos entre os meses de janeiro e abril)

1984 Todas as crianças

1986 Todas as crianças 1997 27% dos setores censitários da cidade

2000 Todos os homens (alistamento militar)

2001 27% dos setores censitários da cidade (os mesmos de 1997)

2004-2005 Todas as crianças

2. Estratégias de busca dos participantes da coorte

Em agosto de 2004, começou o trabalho de localização de todos os participantes da coorte de 82. Os primeiros esforços foram concentrados em duas estratégias, sendo a primeira grande tarefa a realização do Censo da Cidade. Em seguida, a busca através de endereços antigos, obtidos em outros acompanhamentos foi realizada. As diferentes estratégias utilizadas duraram até o final de agosto de 2005 quando o trabalho de campo foi encerrado. A seguir, cada um dos métodos será descrito detalhadamente.

a) Censo da cidade

De agosto de 2004 a fevereiro de 2005, todos os domicílios da cidade de Pelotas foram visitados por uma equipe de batedores, os quais perguntaram, em cada casa, se havia algum morador nascido em 1982 ou 1993 (outra coorte de nascimentos na mesma localidade). Quando alguma pessoa nascida nesses anos era localizada, os seguintes dados eram coletados: nome do participante das coortes, data de nascimento, nome do pai, nome da mãe na época do nascimento, hospital de nascimento, endereço completo atual, bairro, ponto de referência, telefone, etc. Com base nessas informações, todos os nomes localizados foram procurados nos bancos de dados oficiais das coortes de 1982 e 1993. Esta estratégia de busca resultou na localização de 2928 participantes da coorte.

b) Endereços antigos

Com base em bancos de endereços de outros acompanhamentos (1982, 1986, 2000 e 2001), buscou-se localizar os participantes da coorte nos endereços antigos. Caso o jovem ou a família não fosse encontrada nesses endereços, os batedores eram orientados a perguntar aos vizinhos informações sobre a nova localização da família.

A busca nos endereços antigos resultou em 1627 jovens encontrados.

c) Outras estratégias

Censo **escolar** No ano de 2004, todas as escolas de Pelotas fizeram parte de um estudo antropométrico onde todos os alunos de primeira a quarta série do ensino fundamental foram medidos e pesados. Neste trabalho, um banco de dados com informações de todas as escolas municipais e estaduais foi obtido e, dessa forma, foi possível localizar alunos, os quais nasceram no ano de 1982, matriculados nestas escolas. Após, estes nomes foram verificados quanto à participação na coorte de 82 e, caso fosse confirmado, o endereço era obtido no próprio banco de dados.

CEFET Uma relação dos alunos matriculados no Centro Federal de Educação Tecnológica desde o ano de 2000 foi obtida. De posse desta listagem, todos os alunos nascidos no ano de 1982 foram investigados quanto à participação na coorte. Nos casos onde foi confirmada a participação, o endereço foi obtido na própria escola.

Inscrições **para o vestibular** Foi solicitado junto a Comissão Permanente de Vestibular da Universidade Federal de Pelotas uma relação com o nome, data de

nascimento, endereços e telefones de todos as pessoas inscritas nos processos de seleção desta universidade desde o vestibular de inverno de 2002. De posse desta listagem, todos os nomes de indivíduos da coorte de 82 que ainda não haviam sido encontrados, foram procurados nas inscrições dos vestibulares. Seguindo a mesma lógica, uma relação de inscritos no vestibular da Universidade Católica de Pelotas foi obtida, para o mesmo período.

Cadastro do Sistema Único de Saúde (SUS) O SUS realizou cadastramento de todas as famílias residentes na cidade de Pelotas e cidades vizinhas nos anos de 2002-2003. No site do datasus (www.datasus.gov.br), foi realizada uma busca através do nome da mãe de todos participantes da coorte que não haviam sido encontrados. Dessa forma, foi possível obter informações sobre as cidades em que residiam algumas mães localizadas. De posse dessa listagem, maiores informações sobre endereços e telefones de cada pessoa foram disponibilizados pelas secretarias municipais de saúde das cidades de Pelotas, Capão do Leão, Santa Vitória e Rio Grande.

Lista **telefônica (impressa e eletrônica)** A lista telefônica impressa e eletrônica foi utilizada para localizar o endereço mais recente da família a partir de nomes e sobrenomes de familiares.

Orkut Como uma estratégia alternativa de busca, o Orkut (Rede Mundial de Relacionamento) foi utilizado com intuito de encontrar os jovens ainda não entrevistados. A estratégia foi viabilizada devido à criação de uma comunidade (X-Files: Pelotas - 1982) pelos próprios jovens participantes da coorte. Os jovens que não tinham sidos contatados até então e faziam parte da comunidade em questão, receberam uma mensagem eletrônica com informações relativas ao estudo e enfatizando a importância da participação dos mesmos.

Coorte **de 2004** Em 2004, mais uma coorte de nascimentos foi realizada em Pelotas. Com o final da coleta de dados, uma relação de todas as mães foi gerada e as que nasceram em 1982 foram investigadas quanto à participação na coorte.

Fenadoce Durante a Feira Nacional do Doce (FENADOCE) de 2005, uma estratégia de busca foi realizada no estande da Universidade Federal de Pelotas, nos pavilhões da feira, onde uma equipe trabalhou entre os dias 3 e 5 de junho,com a exposição de um

banner e apresentação de um vídeo sobre a pesquisa com os nascidos em 1982 em Pelotas. Esta estratégia procurou esclarecer à população sobre a pesquisa e localizar participantes da coorte que estivessem visitando a feira. Assim que era identificado alguém nascido no ano de 1982, eram solicitados alguns dados de identificação (nome completo, nome da mãe, endereço e telefone) para posterior confirmação da participação no estudo.

SINASC Existe um arquivo de dados do SINASC disponível na Secretaria de Saúde onde consta a idade das mulheres que tiveram filhos. Por exemplo, das mulheres que tiveram filhos em 2001, identificaram-se aquelas que tinham entre 18 e 20 anos. Com essa relação, uma nova busca foi feita nos registros hospitalares para ver se haviam nascido em Pelotas em 1982. Todas, assim, identificadas, foram procuradas para saber se pertenciam a Coorte de 82.

Rede **social** Desde janeiro de 2005 utilizou-se uma estratégia adicional para localizar jovens que ainda não haviam sido encontrados. Ao final da aplicação dos questionários, os entrevistadores perguntavam se a família conhecia mais alguém nascido no ano de 1982, em Pelotas. Em caso afirmativo, coletavam-se informações sobre endereço, nome do jovem, nome da mãe e telefone.

Informações **espontâneas obtidas no campo** Durante a realização de uma entrevista, algumas vezes, o próprio entrevistado comentava sobre um amigo ou conhecido também nascido em 1982. Os entrevistadores, então, solicitavam o máximo de informações possível sobre a pessoa (nome completo, nome da mãe, endereço, telefone, trabalho, etc.) para posterior confirmação da participação no estudo.

Reclink O programa Reclink foi utilizado de forma a auxiliar a busca em algumas fontes de dados citadas acima. No estudo perinatal de 1982, as mães indicaram possíveis nomes para seus filhos. Estes nomes, junto ao sobrenome da mãe, foram comparados com outras bases de dados (SINASC, lista do vestibular, SUS, coorte de 2004). O processo realizado seguiu o manual do programa que pode ser encontrado no link: http://paginas.terra.com.br/educacao/kencamargo/RecLinkII.html

A tabela abaixo descreve o número de indivíduos encontrados segundo a estratégia de busca.

Estratégia de busca	N
Censo da cidade	2928
Endereços antigos	1627
Lista telefônica	95
Inscrição do vestibular	61
SUS	53
SINASC	35
Matrículas no CEFET	17
Outras fontes	35
Total	4851

Além destes, foram identificados 282 óbitos, que -somados aos encontrados-, representam informações de 5133 indivíduos da coorte.

3. Recrutamento de pessoal

O recrutamento de pessoal foi realizado, basicamente, de duas formas: (a) consulta a pesquisadores do Centro de Pesquisas Epidemiológicas da Universidade Federal de Pelotas em busca de indicação de pessoas com experiência em outros estudos; (b) contato com professores de outras unidades da Universidade Federal e da Universidade Católica de Pelotas. Assim, foram estabelecidos os seguintes pré-requisitos: idade mínima de 18 anos, segundo grau completo, disponibilidade de 8 horas/dia de trabalho. Também foi informada a remuneração (R$ 13,00 por entrevista). Outra forma foi a indicação de pessoal pela própria equipe do estudo já selecionada.

Os candidatos recrutados pelos métodos descritos acima foram entrevistados pela equipe de pesquisa. Aqueles que preenchiam os critérios desejáveis (responsabilidade,

habilidade de expressão, seriedade, simpatia, pontualidade), eram selecionados para um período de treinamento (descrito no item 4). O número planejado de entrevistadores para realização do trabalho de campo era de 16.

Através da indicação de professores envolvidos com o trabalho, foram contratados dois digitadores, os quais, a partir de janeiro de 2005, começaram a trabalhar na digitação dos dados em dois turnos diários.

4. Treinamento de entrevistadores

Inicialmente, foi realizado um treinamento teórico-prático de aproximadamente 40 horas, incluindo leitura do questionário e manual de instruções, além da realização de medidas antropométricas, pressão arterial e espirometria.

Após, foram realizadas entrevistas simuladas e medições entre os próprios candidatos.

A padronização das medidas (peso, altura e circunferência da cintura), através da avaliação de dez pessoas, foi desenvolvida no ambulatório da Faculdade de Medicina e Posto de Saúde do Areal. Em alguns casos, a padronização das medidas foi repetida a fim de que os candidatos pudessem ser aprovados e iniciarem o trabalho de campo. Cabe destacar que nenhum dos candidatos aprovados precisou mais que duas padronizações durante o treinamento. Tais medidas foram treinadas e padronizadas conforme o método do "erro técnico da medida" (ETM), baseado nos valores do NCHS, 1977.

O primeiro treinamento foi realizado entre os dias 27/09/2004 e 04/10/2004. Em função da desistência ou demissão de alguns entrevistadores, houve a necessidade da realização de mais três treinamentos para suprir a carência de pessoal. A tabela abaixo descreve o número de candidatos aprovados em cada treinamento e o aproveitamento até o final do estudo.

5. Equipamentos utilizados

Balança: Seca UNICEF, precisão 100g, até 150 Kg; Esfigmanômetro: Omron modelo HEM 629, digital; Fita métrica cardiomed, fina, inextensível; Antropômetro de alumínio;

Espirômetro: EasyOne Diagnostic Spirometer; Glicosímetro: Advantage Roche diagnostics modelo.

6. Espaço físico

Tendo em vista que o espaço físico do Centro de Pesquisas Epidemiológicas da Universidade Federal de Pelotas não era capaz de atender todas as necessidades do estudo, uma sala foi alugada na região central da cidade, onde a maioria das atividades do acompanhamento foi realizada. A opção pela área central da cidade foi feita por questões logísticas, principalmente pela economia de vale-transporte. Apenas a digitação, validação da mesma e reuniões semanais dos investigadores da pesquisa foram realizadas no Centro de Pesquisas, sendo as demais atividades realizadas na sala central. Nesse sentido, a sala foi usada como secretaria da pesquisa, além de ser utilizada para outras atividades, tais como recepção e entrega de questionários, controle dos questionários já realizados, arquivamento de material antes do envio para digitação, reuniões com os entrevistadores e com os demais funcionários do estudo, telefonemas para controle de qualidade, calibração de material, treinamento de novos entrevistadores, localização dos endereços.

7. Estrutura de cargos do estudo

A coordenação geral do Estudo de Coorte de Nascimentos de 1982 em Pelotas, RS é dos professores Cesar Victora e Fernando Barros. A equipe do acompanhamento realizado em 2004-2005 foi composta por Bernardo Horta, Denise Gigante, Helen Gonçalves, Isabel Oliveira e Rosângela Lima. Para a supervisão e coordenação do trabalho de campo, a equipe foi constituída por Gicele Minten, Mario Azevedo Júnior e os doutorandos Aydin Nazmi, Celene Longo, Vera Silveira e Vera Vieira. Esta tarefa incluía, entre outras atividades: reuniões semanais com recebimento e entrega de questionários, esclarecimento de dúvidas, contato diário com os entrevistadores, calibragem de equipamentos, codificação de questionários e preparação de lotes de questionários para a digitação.

Uma secretária foi contratada para realização de tarefas administrativas. Entre as atividades realizadas, pode-se destacar: recebimento das fichas de identificação dos participantes da coorte (encontrados pela equipe do censo) e montagem do questionário,

agrupamento de endereços por bairro, compra de material de consumo e serviços de tesouraria (entrega de vales-transporte, cartões telefônicos, controle do pagamento de entrevistadores, reembolso de passagens rodoviárias intermunicipais, etc.).

Bolsistas de iniciação científica e alunos de graduação voluntários realizaram tarefas diversas, como ligações telefônicas, revisão de questionários, codificação e digitação dos questionários confidenciais, limpeza de espiretes e controle de qualidade das entrevistas.

8. Questionário

O questionário do acompanhamento de 2004-2005 foi composto por dois blocos e encntra-se disponível na íntegra no endereço eletrônico: http://www.epidemio-ufpel.org.br/site/content/coorte_1982/questionarios.php

a) Bloco de informações gerais – composto por 373 perguntas, incluindo questões sobre saúde, hábitos e opiniões, além de informações demográficas e socioeconômicas.

b) Bloco confidencial - composto por 37 perguntas para os homens e 38 perguntas para as mulheres, incluindo questões sobre relacionamento familiar, consumo de álcool e drogas e comportamento sexual.

9. Manual de instruções

O manual de instruções do estudo servia como guia para os entrevistadores no caso de dúvidas no preenchimento ou codificação do questionário. O mesmo apresentava ainda algumas dicas de postura geral e importância do cargo de entrevistador. Telefones de contato dos coordenadores do trabalho de campo também eram apresentados.

10. Entrevistas

O trabalho de campo compreendeu o período de 25/10/2004 a 31/08/2005. Durante todo o período, foram realizadas entrevistas domiciliares e no escritório central. Além disso, no Presídio Regional de Pelotas foram entrevistados participantes da coorte que no momento estavam cumprindo pena.

O fluxo ideal da entrevista consistia dos seguintes passos: a) Entrega do termo de

consentimento, folder e resultado dos exames realizados em 2000 (somente para os meninos); b) Confirmar as informações da página de rosto; c) Fazer a primeira medida de pressão; d) Aplicar o questionário; e) Entregar o questionário confidencial; f) Receber o questionário confidencial, colocar no envelope e lacrar; g) Realizar a espirometria, segunda medida de pressão e medidas antropométricas; h) Entregar o cartão com o resultado das medidas antropométricas, pressão e espirometria, além do endereço para a realização do exame de sangue.

A partir do dia 25 de junho de 2005, foi adotada a estratégia de, através de contatos telefônicos, convidar os participantes da coorte, que na época residiam em outras cidades, para realizar a entrevista em Pelotas, com todas as despesas de deslocamento pagas. Inicialmente, foram convidados aqueles residentes nas cidades mais próximas, abrangendo somente o estado do Rio Grande do Sul. Durante a semana, as entrevistas eram realizadas no escritório central, onde uma entrevistadora foi designada especialmente para este propósito. Nos finais de semana, foram organizados plantões na FAU para entrevistar os jovens vindos de outras cidades.

No último mês de coleta de dados, foram enviados entrevistadores para as cidades de Porto Alegre, Florianópolis, Caxias do Sul, Santa Vitória do Palmar e Serafina Corrêa, pois havia um grande número de participantes impossibilitados de virem a Pelotas, mas com interesse na participação no estudo.

11. Coleta de sangue

Na segunda etapa deste estudo, foi realizada a coleta de sangue venoso periférico dos indivíduos pertencentes a coorte de 1982, com o objetivo de se obter um banco de soro e um banco de DNA. A coleta de sangue só era realizada após a obtenção do consentimento por escrito.

Foram coletados 10 ml de sangue, por punção venosa periférica do braço de cada indivíduo, sendo 5 ml de sangue coletados com anticoagulante (EDTA 25 mM) para a extração de DNA e 5 ml sem anticoagulante, para o banco de soro. No momento da coleta, foram realizados dois exames: medida da glicose a partir de sangue da polpa digital com o Glicosímetro (Advantage), e a tipagem sangüínea através da identificação do grupo sanguíneo e fator Rh.

Como forma de ressarcimento pelo tempo e deslocamento para participar da coleta de sangue, cada indivíduo recebia dez reais (R$10,00) mais dois vales-transporte, além de um cupom para concorrer ao sorteio de um microcomputador.

A seguir serão descritas informações mais detalhadas sobre esta etapa do estudo.

a- Local As coletas de sangue foram realizadas em dois locais diferentes, conforme o período do trabalho:

25/10/04 a 31/03/05 Local: Centro de Especialidades – Secretaria Municipal de Saúde e Bem Estar, Prefeitura Municipal de Pelotas. Endereço: Rua Voluntários da Pátria, 1428. Dias: Segunda a sábado Horário: 07h 30min – 20h30min

01/04/05 a 30/09 Local: Laboratório Bioceleris - Hospital Escola da FAU/UFPel Endereço: Rua Professor Araújo esquina General Neto. Dias: Segunda a sábado Horário: 9h – 20h30min

b- Coletadores Um grupo de técnicos de auxiliar em enfermagem foi selecionado e treinado para trabalhar na coleta de sangue. No treinamento, foram discutidos aspectos técnicos da coleta de sangue, da execução dos exames de dosagem da glicemia e tipagem sanguínea e da separação do soro. Foi realizada, também, uma orientação sobre a melhor forma de abordagem aos indivíduos, uma vez que a coleta de sangue é um método invasivo, despertando diferentes reações nos indivíduos.

Inicialmente, foram contratados dois técnicos de enfermagem que se revezavam nos dois turnos estipulados: das 07h30min às 14h; das 14h às 20h30min.

Foi oferecido o valor mensal de seiscentos reais (R$ 600,00) pela bolsa de trabalho. Entretanto, como foi observada uma necessidade de reforço entre o período de 11h às 18h, foi contratado, a partir do mês de fevereiro, mais um técnico de enfermagem. Dessa forma, nos horários em que se tinha maior aporte de indivíduos para coletar sangue, o serviço contava com duas pessoas. Uma ficava encarregada da parte burocrática de preenchimento de papéis e identificação dos tubos; a outra, da coleta de sangue e realização dos exames. Com isso, os indivíduos foram melhor atendidos, não tendo que esperar muito tempo, o que resultou em maior grau de satisfação dos

participantes.

A partir do mês de fevereiro, foi iniciada a coleta domiciliar, sendo contratado mais um técnico de enfermagem, que dispunha de uma motocicleta para sua locomoção. Foi estipulado o valor de R$ 10,00 mais dois vales- transporte para cada coleta de sangue realizada. O sangue coletado em casa era levado ao local fixo de coleta da coorte de 82 (Centro de Especialidades ou laboratório da FAU), sendo recebido para registro e processamento pelo técnico em enfermagem de plantão no serviço de coleta.

No final do mês de julho e durante o mês de agosto, foi montado um esquema intensivo de entrevistas e coletas de sangue para os indivíduos que moram fora de Pelotas. De segunda a sexta feira, um dos coletadores contratados foi destinado para fazer a coleta de sangue no escritório central da coorte de 82. No laboratório da FAU, ficaram os outros dois coletadores, cobrindo os turnos das 9h às 15h30min e das 14h às 20h0min, respectivamente. Nos finais de semana, incluindo sábado e domingo, as entrevistas e as coletas foram realizadas nas dependências do laboratório da FAU.

Do dia 1 ao dia 15 de setembro, o atendimento para coletas de sangue foi mantido no horário das 9h às 20h30min, de segunda à sábado. Esse esquema garantiu o serviço de recebimento e processamento do sangue coletado nos domicílios. Além disso, nos domingos funcionou um esquema de plantão no laboratório para o recebimento de sangue coletado nos domicílios.

Entre os dias 16 e 30 de setembro, o horário de atendimento para coletas foi reduzido das 17h30 às 20h30min, sendo mantido de segunda a segunda.

No último mês de trabalho (setembro/05), com o objetivo de se intensificar o trabalho, as coletas domiciliares contaram com seis técnicos de enfermagem. Quatro deles dispunham de motocicleta e dois usaram um serviço de moto-táxi contratado pela pesquisa. Foi estipulado o valor de R$15,00 por coleta. Para os que usavam a própria motocicleta, foram oferecidos dois vales-transporte por coleta feita, além do valor em dinheiro. Os coletadores receberam cartões telefônicos para facilitar a localização e agendamento das coletas de sangue.

c- Exames

Três exames foram realizados na coleta de sangue: - Dosagem de glicemia: através de sangue da polpa digital com o Glicosímetro (Advantage); - Grupo sanguíneo e Fator RH: através de sangue venoso coletado com EDTA; - Extração de DNA: através de sangue coletado por punção venosa periférica do braço ou, em alguns casos, sangue extraído da ponta do dedo para armazenagem em papel filtro especial (Gentra).

d- Logística

Como já explicado anteriormente, todos os entrevistados eram convidados ao final da entrevista a participar da coleta de sangue. Entretanto, outras estratégias foram adotadas para reverter atrasos e recusas desta etapa do estudo. No quadro abaixo, estão descritas as estratégias utilizadas.

e- Entrevistados residentes em outra cidades

No período de 25/06 a 31/08/05, foi adotada a estratégia de subsidiar a vinda de entrevistados residentes em outras cidades. Essas entrevistas e coleta de sangue foram realizadas em dois locais diferentes:Finais de semana: FAU Segunda a sexta -feira: Escritório central

12. Banco de dados

Foram construídos dois bancos de dados no programa Epi-Info 6.0, sendo um para cada bloco (informações gerais e confidencial). Estes bancos foram sendo atualizados ao longo do trabalho de campo conforme a necessidade de criação de novos códigos.

13. Digitação e validações

Os questionários foram organizados em lotes de 50 unidades, para o questionário de informações gerais, e de 200 para o questionário confidencial. Dois digitadores realizavam digitações independentes com base nos questionários originais. Os dados eram, então, comparados, usando-se os programas "validate" do Epi-Info 6.0 e Stata 8.0.

Nos casos de inconsistências entre as duas digitações, uma folha de erros era impressa

para os digitadores e os mesmos conferiam nos questionários originais as respostas corretas. Esta rotina era realizada no último dia de trabalho da semana. O processo era repetido até que não fossem detectados erros. As dúvidas eram repassadas ao supervisor de digitação. Após validados, os bancos de dados eram transferidos do Epi-Info 6.0 para o Stata 8.0. Depois da finalização da digitação e validações, os dados foram transferidos para os pacotes estatísticos Stata 8.0 e SPSS 11.5, para a realização da limpeza dos dados e posterior análise.

O trabalho de digitação foi realizado entre os meses de janeiro a dezembro de 2005.

14. Controle de qualidade

O controle de qualidade do trabalho de campo é fundamental para assegurar a qualidade do estudo. Três aspectos qualitativos foram considerados nesta etapa: (a) a satisfação dos entrevistados com o trabalho realizado pelo entrevistador, buscando uma relação amistosa para futuros acompanhamentos; (b) identificação de possíveis fraudes no trabalho dos entrevistadores; (c) a repetibilidade de algumas perguntas do questionário.

Aproximadamente 10% dos participantes visitados receberam uma segunda visita ou contato telefônico, envolvendo aplicação de um questionário reduzido para verificação dos aspectos qualitativos anteriormente citados (Anexo 10). Os resultados do controle de qualidade não detectaram nenhum indício de fraude no preenchimento dos questionários.

No processo de coleta de sangue, um *check list* sobre a realização das medidas antropométricas, pressão arterial, espirometria e preenchimento do confidencial no momento da entrevista foi aplicado (Anexo 11).

15. Brindes

Todos os jovens que participaram da coleta de sangue preencheram um cupom para concorrer, no final do estudo, ao sorteio de um computador (Anexo 12).

16. Reuniões de trabalho

O trabalho de elaboração dos questionários iniciou três meses antes do trabalho de

campo. Semanalmente, a equipe de pesquisadores envolvidos com a coorte de 1982 se reunia para discussão dos temas, variáveis a serem investigadas e melhores alternativas para a coleta dos dados.

Durante o trabalho de campo, uma reunião semanal era realizada pela coordenação geral do estudo a fim de discutir o andamento da coleta de dados e de sangue, resolução de eventuais problemas e tomada de decisões sobre novas estratégias de ação.

17. Confraternizações

Ao longo do trabalho, três jantares foram promovidos. O objetivo principal desses encontros foi de manter uma integração entre o grupo e promover um encontro informal entre toda a equipe de pesquisa.

18. Montagem de lotes

Os questionários eram organizados em lotes de 50 unidades para o bloco de informações gerais e 200 para o bloco confidencial. Todos os questionários estavam etiquetados para assegurar a identificação. Cada folha de rosto dos lotes continha os números dos questionários que o compunham. Os lotes eram montados e enviados para os digitadores pelos supervisores do trabalho de campo.

Ao receberem os lotes, os digitadores conferiam se os mesmos realmente continham todos os questionários indicados na folha de rosto. Estando tudo correto, assinavam um documento confirmando o recebimento do lote completo. Os lotes, então, eram digitados e, após validação, armazenados em local destinado para este fim.

19. Divulgação na imprensa

Com o intuito de esclarecer e divulgar a população da realização do acompanhamento de 2004-5, uma reportagem foi publicada no jornal de maior circulação da cidade no início do estudo.

20. Reversão de recusas

No caso de algum jovem recusar a entrevista, o questionário era encaminhado para um

segundo entrevistador que fazia uma nova tentativa. Se a recusa persistisse um terceiro contato era feito pela equipe de supervisão do trabalho de campo.

Da mesma forma, quando havia recusa para a coleta de sangue ao entrevistador que aplicava o questionário, um segundo contato era feito pela equipe de supervisão do trabalho de campo.

21. Uniformes

Os entrevistadores receberam uma camiseta personalizada para auxiliar a identificação da equipe de pesquisa nas ruas da cidade. Essa medida foi adotada também por motivo de segurança, evitando que os entrevistadores fossem vistos como estranhos nos diversos bairros visitados.

22. Entrega dos questionários e aferição dos equipamentos

Semanalmente, os entrevistadores entregavam os questionários realizados e aferiam os equipamentos. Durante esses encontros, os mesmos eram instruídos quanto à qualidade dos questionários entregues naquele momento e nas semanas anteriores, podendo esclarecer as dúvidas geradas na revisão.

23. O "livrão"

Um livro foi confeccionado para controle dos questionários entregues às entrevistadoras e devolvidos durante o trabalho de campo. Os nomes dos 5914 participantes da coorte de 1982 e de suas mães estavam registrados nele. Quando a entrevistadora recebia o questionário, registrava-se no livro o seu nome e data. Quando o questionário retornava, a data desse retorno era preenchida. O livro grifava os participantes da coorte falecidos.

24. Aspectos financeiros

O controle financeiro do estudo ficou a cargo de um dos pesquisadores e do administrador do Centro de Pesquisas Epidemiológicas da Universidade Federal de Pelotas. A secretária informava o total de entrevistas feitas mensalmente por cada entrevistador para os pesquisadores que, por sua vez, repassavam ao administrador. Os digitadores e demais funcionários receberam salários fixos, pagos diretamente pelo

administrador. A distribuição de vales-transporte para os entrevistadores seguia o esquema descrito acima.

25. Questões éticas

Alguns participantes da coorte ou familiares, durante a realização da entrevista, solicitavam atendimento médico com especialista por algum problema de saúde. Os pesquisadores eram comunicados, e os casos eram encaminhados ao ambulatório da Faculdade de Medicina da UFPel ou Secretaria da Saúde, em casos específicos. Sempre que possível, os casos foram encaminhados para atendimento gratuito e de qualidade.

26. Percentuais de localização e acompanhamento

Das 5914 crianças nascidas vivas em 1982, foram localizadas 5133 (86,8%), sendo que destas, 280 foram detectadas como mortas. Dentre os localizados, 4297 foram entrevistados, que acrescidos ao número de óbitos, representam um percentual de acompanhamento de 77,4%.

Com relação ao exame de sangue, 3914 indivíduos participaram do estudo, compreendendo um percentual de acompanhamento de 71,0% (incluindo os óbitos) e de 91,1% do total de entrevistas.

Contribuição do autor no trabalho de campo

O autor deste trabalho participou do acompanhamento de 2012/13 desde as etapas iniciais de seu planejamento até a sua execução. Além disso, participou de treinamento de entrevistadores e examinadores, assim como na calibração de diversos equipamentos. Foi responsável, também, pelas medidas de pressão arterial e foi supervisor do trabalho de campo durante toda sua execução.

É apresentado o relatório do campo de 2004/5, pois a presente tese utiliza dados apenas do nascimento até este acompanhamento. No planejamento do estudo, ficou definido, a priori, que o acompanhamento de 2012/13 não seria utilizado por questões logísticas de

tempo para a conclusão da tese em tempo hábil.

PARTE VI. ANEXOS

The hypertriglyceridemic waist phenotype in young adults from the Southern Region of Brazil

Cintura hipertrigliceridêmica em adultos jovens no Sul do Brasil

Cintura hipertrigliceridémica en adultos jóvenes en el sur de Brasil

Ricardo Lanzetta Haack [I]
Bernardo Lessa Horta [I]
Denise Petrucci Gigante [I]
Fernando C. Barros [I]
Isabel Oliveira [I]
Vera M. Silveira [I]

[I] *Universidade Federal de Pelotas. Pelotas. Brasil.*

Correspondence
R. L. Haack
Universidade Federal de Pelotas
Rua Marechal Deodoro 1160, 3o piso. Pelotas. RS 96020-220. Brasil.
ricardohaack@yahoo.com.br

Abstract

The present study aimed to assess the prevalence of the hypertriglyceridemic waist phenotype and its associated factors among subjects that have been followed up from birth. In 1982, all maternity hospitals in the city of Pelotas, in the Southern Region of Brazil, were visited and all births were recorded. Babies whose parents lived in the urban area of Pelotas were subsequently followed up on several occasions. A 22 to 23-year follow-up of this birth cohort was carried out in 2004 and 2005. The presence of the hypertriglyceridemic waist phenotype was defined as waist circumference ≥ 90cm and triglyceride levels ≥ 177mg/dL for males, and waist circumference > 85cm and triglyceride levels > 133mg/dL for females. The prevalence of the hypertriglyceridemic waist phenotype was 5.9% and 4.5% among men and women, respectively. Among males, a sedentary lifestyle during leisure time, smoking and obesity were associated with the presence of the hypertriglyceridemic waist phenotype, whereas among females the condition was positively associated with skin color, family income, obesity and dietary fat intake.

Waist Circumference; Abdominal Obesity; Triglycerides

Resumo

O presente estudo teve como objetivo determinar a prevalência do fenótipo da cintura hipertrigliceridêmica e seus fatores associados entre indivíduos que foram seguidos desde o nascimento. Em 1982, as maternidades de Pelotas, sul do Brasil, foram visitadas e todos os nascimentos foram identificados. Em 2001-2005, buscou-se acompanhar toda a coorte. A presença de fenótipo da cintura hipertrigliceridêmica foi definida como circunferência da cintura ≥ 90cm e triglicerídeos ≥ 177mg/dL para o sexo masculino, e circunferência da cintura ≥ 85cm e triglicerídeos ≥ 133mg/dL para as mulheres. A prevalência de fenótipo da cintura hipertrigliceridêmica foi de 5,9% e 4,5% entre os homens e mulheres, respectivamente. Para os homens, o sedentarismo no lazer, tabagismo e obesidade estiveram associados com fenótipo da cintura hipertrigliceridêmica. Por outro lado, entre as mulheres, fenótipo da cintura hipertrigliceridêmica foi positivamente associado com a cor da pele, renda familiar, obesidade e consumo de gordura.

Circunferência da Cintura; Obesidade Abdominal; Triglicerídeos

Introduction

Chronic non-communicable diseases, such as cardiovascular disorders, cancer and diabetes are the leading causes of mortality worldwide, accounting for approximately 60% of all deaths [1,2]. In the United States, the American Cardiology Association estimates that more than one in three adults have some form of cardiovascular disease [3].

In 2000, Lemieux et al. [4] reported that adults with increased waist circumference and high plasma triglyceride levels were more likely to present metabolic markers of cardiovascular risk and called this association the hypertriglyceridemic waist phenotype. Several studies have reported that this condition is associated with the cardiometabolic risk profile (higher levels of insulin, Apolipoprotein B, C-reactive protein and small dense LDL cholesterol) as well an increased risk of coronary artery disease [4,5,6,7,8,9,10]. Studies have identified the following factors related to the presence of hypertriglyceridemic waist phenotype: sedentary lifestyle [11,12,13], obesity [9,11,14], lower levels of schooling [11,13], and low intake of grains [15]. However, despite the marked association between cardiovascular disease and metabolic risk factors, few studies have evaluated the risk factors for hypertriglyceridemic waist phenotype, especially in young adults.

This study aimed to assess the prevalence of hypertriglyceridemic waist phenotype and its association with skin color, family income, smoking, sedentary lifestyle, fat consumption and fiber intake among 23-year-olds from a city in the Southern Region of Brazil.

Methods

During 1982, all maternity hospitals in the city of Pelotas were visited on a daily basis and 7,382 births were recorded. Those babies whose parents lived in the urban area of Pelotas (N = 5,914) were examined and have been followed up on several occasions. Further details regarding study methodology have been described elsewhere [16].

A 22 to 23-year follow-up of this birth cohort was carried out between October 2004 and August 2005. The subjects that were located answered a questionnaire and were examined and asked to donate a blood sample collected by venipuncture.

The presence of hypertriglyceridemic waist phenotype was defined as waist circumference > 90cm and triglycerides > 177mg/dL for males, and waist circumference ≥ 85cm and triglycerides ≥ 133mg/dL for females [4,14,17]. Waist circumference was measured using a fiberglass tape (Cardiomed, 1mm precision, Curitiba, Brazil), halfway between the iliac crest and last costal arch. Pregnant women or those who had had children in the last six months were excluded. Triglyceride levels were assessed using the colorimetric enzymatic method.

The following metabolic cardiovascular risk factors were measured:

- Blood pressure was measured at the beginning and at the end of the interview using a calibrated digital wrist blood pressure monitor (Omron HEM-628, Kyoto, Japan) on the left arm. Before each measurement the individual should sat rest for at least five minutes. Mean arterial pressure was estimated as 2/3 mean diastolic blood pressure plus 1/3 mean systolic blood pressure.
- Random blood glucose was assessed from blood drawn from the fingertip using a portable glucose meter (Accu-Check Advantage, Roche, Indianapolis, USA). Since glucose levels are related to fasting time, glucose estimates were corrected for the time elapsed since the last meal [18].
- HDL cholesterol was measured with a Selectra 2 analyzer (Merck, Darmstadt, Germany) using an ultra sensitive direct method.
- High-sensitivity C-reactive protein (hs-CRP) was measured using the chemiluminescent immunoassay system (Siemens, DPC Immulite 2500, Los Angeles, USA). Measurements below the lower detection limit of 0.1mg/L were converted to 0.05mg/L. Subjects with hs-CRP > 10mg/L, pregnant women and those using oral contraceptives were excluded from the hs-CRP analysis.

The following socioeconomic, demographic and behavioral characteristics were also assessed as possible risk factors:

- Self-reported skin color;
- Family income in adulthood;
- Leisure-time physical activity: a score representing weekly physical activity based on the sum of time spent walking and on moderate physical activity and time spent on vigorous activities multiplied by two was calculated using the long version of the previously validated *International Physical Activity Questionnaire* (IPAQ) [19]. Subjects with a score of less than 150 minutes were classified as sedentary;
- Tobacco smoking: subjects who smoked at least one cigarette per day were considered as smokers;
- High fat and low fiber diet: dietary pattern in the preceding 12 months was evaluated using the *Block Questionnaire*, which includes 24 scored items regarding the weekly consumption of each food. Individuals who scored less than 20 points were considered as having a low dietary

fiber intake and those who scored 25 points and above were considered as having a high dietary fat intake [29].

Triglycerides and hs-CRP values were asymmetrically distributed and a natural log transformation was performed with these variables and results are given as the back-transformed geometric means.

A sex-stratified statistical analysis was performed using the software Stata 12.0 (Stata Corp., College Station, USA). Chi-square test with Yates correction for 2x2 tables was used to test comparisons between proportions and analysis of variance was used to compare means. Multivariate analysis was performed using Poisson regression with robust adjustment of variance based on the hierarchical model shown in Figure 1.

In order to assess whether the presence of enlarged waist and hypertriglyceridemia was related to higher values of cardiovascular risk factors, an interaction term was included in the analysis of the association between waist circumference and triglyceride levels and cardiovascular risk factors.

The study was approved by the Ethical Review Board of the Faculty of Medicine of the Pelotas Federal University, and written informed consent was obtained from participating subjects.

Results

A total of 4,297 subjects were interviewed between October 2004 and August 2005. After taking into account 282 recorded deaths, this number corresponds to a follow-up rate of 77.4%.

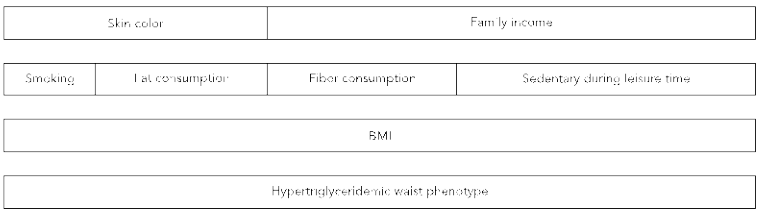
Table 1 shows that approximately 75% of the sample was white. Prevalence of overweight and obesity was 23.1% and 7.5% among men and 17.9% and 9.1% among women, respectively. Table 1 also shows the mean values for triglyceride levels, HDL cholesterol, non-fasting blood glucose, high-sensitivity C-reactive protein and blood pressure for men and women. Prevalence of the hypertriglyceridemic waist phenotype among men and women was 5.9% and 4.5%, respectively. Furthermore, 69.9% of men and 68.6% of women had a low dietary fiber intake and 54.8% of men and 45.4% of women had a high dietary fat intake. Approximately 25% of the sample was smokers and 80% of women and 50% of men were sedentary during leisure time.

Table 2 shows that HDL cholesterol levels were higher and blood pressure, non-fasting blood glucose and body mass index were lower, in individuals with normal waist circumference and triglyceride levels. The presence of hypertriglyceridemia, or enlarged waist circumference, was associated with slight changes in metabolic cardiovascular risk factors, lower HDL cholesterol and higher blood pressure and hs-CRP. The test of interaction between hypertriglyceridemia and each of the cardiovascular metabolic risk factors was statistically significant suggesting that the presence of the phenotype accentuates metabolic cardiovascular risk factors.

Tables 3 and 4 present the prevalence, prevalence ratio and adjusted prevalence ratio of the hypertriglyceridemic waist phenotype according to sample characteristics by gender. With respect to males, being sedentary during leisure time, smoking and obesity was associated with the hypertriglyceridemic waist phenotype, whereas among females the condition was positively associated with skin color, family income, fat consumption and body mass index.

Figure 1

Hierarchical model for the hypertriglyceridemic waist phenotype.



BMI: body mass index.

Table 1

Key characteristics of the study sample.

Sample characteristics	Male	Female
Skin color [n (%)]		
White	1,658 (74.9)	1,580 (75.9)
Non white	555 (25.1)	503 (24.2)
Family income (tertiles) [mean R$ (SD)]		
1st	463.2 (171.2)	443.8 (179.8)
2nd	1,054.3 (206.3)	1,046.1 (205.6)
3rd	3,170.8 (2,696.4)	3,189.6 (2,518.4)
Body mass index (kg/m2) [n (%)]		
< 18.5	107 (4.9)	150 (7.2)
18.5 -24.9	1,424 (64.6)	1,370 (65.8)
25.0-29.9	509 (23.1)	372 (17.9)
≥ 30.0	166 (7.5)	190 (9.1)
Sedentary during leisure time [n (%)]	1,091 (49.3)	1,676 (80.5)
Smoking [n (%)]	611 (27.6)	492 (23.6)
Triglycerides (mmol/l) [geometric mean (SD)]	1,00 (1.78)	1,03 (1.62)
Waist circumference (cm) [mean (SD)]	80,9 (10.1)	75,6 (11.1)
HDL cholesterol (mg/dL) [mean (SD)]	51,6 (11.2)	59,4 (13.5)
Non-fasting glucose (mg/dL) [mean (SD)]	99,8 (15.6)	94,8 (14.1)
Hs-CRP (mg/dL) [geometric mean (SD)]	0,78 (3.17)	1,31 (3.33)
Mean arterial blood pressure (mmHg) [mean (SD)]	91,6 (11.9)	84,6 (11.1)
Hypertriglyceridemic waist phenotype [n (%)]	113 (5.9)	80 (4.5)

Table 2

Biological cardiovascular risk factors and the hypertriglyceridemic waist phenotype.

	Hypertriglyceridemic waist phenotype [mean (95%CI)]				p-value of interaction
	No	Only hypertriglyceridemia	Only enlarged waist	Hypertriglyceridemic waist phenotype	
HDL cholesterol (mg/dL)	56.0 (55.5; 56.5)	55.2 (53.7; 56.6)	53.0 (51.7; 54.3)	48.9 (47.3; 50.6)	0.02
Non-fasting blood glucose (mg/dL)	96.8 (96.3, 97.4)	98.5 (97.0; 100.1)	98.9 (97.3; 100.5)	101.5 (99.6, 103.5)	0.50
Mean blood pressure (mmHg)	87.1 (86.7; 87.5)	88.6 (87.5; 89.8)	91.9 (90.6, 93.3)	97.9 (96.2, 99.5)	< 0.00
Hs-CRP (mg/dL)	0.82 (0.78; 0.86)	1.26 (1.17; 1.42)	1.72 (1.52; 1.93)	2.03 (1.79; 2.34)	0.06
BMI (kg/m2)	22.2 (22.1, 22.3)	23.2 (22.9, 23.4)	30.5 (30.0, 30.9)	31.7 (31.1, 32.3)	< 0.00
Total [N (%)]	2,745 (74.6)	376 (10.2)	368 (10.0)	193 (5.2)	

BMI: body mass index; 95%CI: 95% confidence interval.

Discussion

The present study may be considered a cross-sectional analysis because we only analyzed data gathered in the 2004/2005 follow-up visit of 1982 Pelotas birth cohort.

With regard to the limitations of this study, it is important to mention that the measurement of food consumption is a significantly challenging task and the instrument used has not yet been formally validated for use with the Brazilian population. However, it should be noted that more complex methods of measuring food frequency were tested and showed similar results to the *Block Questionnaire* [20].

Another important limitation is that, despite being a nested cohort study with good information on confounders, cross-sectional studies are vulnerable to reverse causality.

Table 3

Prevalence, prevalence ratio and adjusted prevalence ratio of the hypertriglyceridemic waist phenotype by sample characteristics (males).

Characteristics	n	p-value (%)	PR (95%CI)	PR * (95%CI)
Skin color		p = 0.13	p = 0.13	p = 0.21
White	1,425	6.4	1.00	1.00
Non-white	489	4.5	0.70 (0.45; 1.11)	0.74 (0.45; 1.18)
Family income (tertiles)		p = 0.23	p = 0.23	p = 0.35
1st	605	5.0	0.70 (0.45; 1.08)	0.80 (0.53; 1.23)
2nd	650	5.5	0.78 (0.51; 1.18)	0.73 (0.46; 1.15)
3rd	659	7.1	1.00	1.00
Smoking		p = 0.06	p = 0.07	p = 0.05
No	1,378	6.5	1.00	1.00
Yes	536	4.3	0.66 (0.42; 1.03)	0.65 (0.41; 1.01)
Sedentary lifestyle during leisure time		p = 0.05	p = 0.05	p = 0.03
No	967	4.9	1.00	1.00
Yes	947	7.0	1.43 (1.00; 2.06)	1.49 (1.03; 2.14)
Fat score (g)		p = 0.50	p = 0.50	p = 0.51
< 25	48	5.5	1.00	1.00
≥ 25	65	6.2	1.13 (0.79; 1.63)	1.14 (0.78; 1.69)
Fiber score (g)		p = 0.55	p = 0.55	p = 0.49
< 20	1,335	5.7	1.00	1.00
> 20-29	579	6.4	1.12 (0.77; 1.64)	1.15 (0.78; 1.69)
BMI (kg/m2)		p < 0.00	p < 0.00	p < 0.00
< 25.0	3	0.2	1.00	1.00
25.0-29.9	40	9.0	39.90 (12.40; 128.50)	39.91 (12.32; 129.32)
≥ 30.0	70	48.6	215.00 (68.60; 674.40)	209.53 (66.58; 659.38)

* Adjusted for variables of the same level and upper level.

BMI: body mass index; PR: prevalence ratio; 95%CI: 95% confidence interval.

Recent studies indicate that the atherosclerosis process starts at an early age and is linked to obesity and other components of the metabolic syndrome during childhood [21]. The identification of asymptomatic individuals at high risk of coronary heart disease and diabetes has important public health implications for prevention of cardiovascular diseases, given the increased incidence of these diseases [22]. The prevalence of the hypertriglyceridemic waist phenotype was 5.9% among males and 4.5% among females and its presence was associated with a higher level of metabolic cardiovascular risk. A number of authors [8,9,10,14,23,24,25,26,27], including Lemieux et al. [4,5] and Hiura et al. [7], have also reported such an association, demonstrating that the hypertriglyceridemic waist phenotype is an important marker of cardiovascular risk.

Studies show that the prevalence of this phenotype among adults of both sexes ranges from 12.7 to 36.5% [10,13,17,27]. In 2003, Kahn observed a prevalence rate of 24.8% among a sample of adults aged 18 to 90 years in the United States; the same study found that prevalence was lowest (6.2%) among the 18 to 24 year age group [23]. Prevalence among healthy adults in Israel, the Netherlands and Spain was 12.7%, 31% and 14.5%, respectively [13,17,27]. A study of a sample of 14,770 adults aged between 35 and 74 years carried out in China by Yu et al. [28] in 2010 showed that the hypertriglyceridemic waist phenotype was present in 35.4% of men and 33.6% of women. Prevalence was 9.6% among men and 23.6% among women in a study of Iranians aged between 30 and 55 years [29].

Although research involving young people is rare, two studies conducted with adolescents in Iran in 2006 and 2008 reported prevalence rates of 6.4% [30] and 8.5% [11], respectively.

In the present study, individuals with the hypertriglyceridemic waist phenotype had lower HDL cholesterol and higher mean blood pressure, non fasting blood glucose levels and hs-CRP levels than those with normal waist circumfer-

Table 4

Prevalence, prevalence ratio and adjusted prevalence ratio of the hypertriglyceridemic waist phenotype by sample characteristics (females).

Characteristics	n	p-value (%)	PR (95%CI)	PR * (95%CI)
Skin color		p = 0.01	p = 0.05	p = 0.01
White	1,333	5.1	1.00	1.00
Non-white	435	2.8	0.54 (0.30; 0.99)	0.45 (0.25; 0.82)
Family income (tertiles)		p = 0.00	p = 0.00	p < 0.00
1st	642	6.5	2.73 (1.48; 5.03)	1.92 (0.99; 3.73)
2nd	584	4.3	1.78 (0.92; 3.45)	3.11 (1.69; 5.74)
3rd	542	2.4	1.00	1.00
Smoking		p = 0.78	p = 0.78	p = 0.88
No	1,349	4.5	1.00	1.00
Yes	419	4.8	1.07 (0.65; 1.76)	0.96 (0.59; 1.58)
Sedentary lifestyle during leisure time		p = 0.24	p = 0.24	p = 0.51
No	357	3.4	1.00	1.00
Yes	1,411	4.8	1.43 (0.78; 2.61)	1.23 (0.67; 2.24)
Fat score (g)		p = 0.00	p = 0.00	p = 0.01
< 25	57	5.9	1.00	1.00
> 25	23	2.8	0.48 (0.30; 0.77)	0.52 (0.32; 0.85)
Fiber score (g)		p = 0.47	p = 0.47	p = 0.24
< 20	1,214	4.3	1.00	1.00
> 20-29	554	5.1	1.18 (0.75; 1.85)	1.31 (0.84; 2.05)
BMI (kg/m2)		p < 0.00	p < 0.00	p < 0.00
< 25.0	5	0.4	1.00	1.00
25.0-29.9	23	7.5	19.50 (7.50; 50.90)	20.18 (7.67; 53.08)
≥ 30.0	52	33.8	88.20 (35.80; 217.50)	87.74 (34.69; 221.92)

* Adjusted for variables of the same level and upper level.

BMI: body mass index; PR: prevalence ratio; 95%CI: 95% confidence interval.

ence and triglyceride levels. Similar findings have been reported in another studies [5,6,7,8,9,10,12,13,14,17,23,24,25,26,27,31,32], suggesting that the presence of an enlarged waist and increased triglyceride levels is related to metabolic cardiovascular risk factors. Therefore, the presence of the hypertriglyceridemic waist phenotype should be considered a marker for the presence of cardiovascular disease risk factors.

A sedentary lifestyle during leisure time, smoking and obesity were factors associated with the presence of the hypertriglyceridemic waist phenotype in males. Three other studies have also reported that a sedentary lifestyle increases the prevalence of the hypertriglyceridemic waist phenotype [11,12,13]. In females, a sedentary lifestyle during leisure time was also associated with an increase in the prevalence of the condition but the association was not statistically significant. The variables associated with the presence of the hypertriglyceridemic waist phenotype in women were white skin color, low family income, low dietary fat intake and obesity.

We also found that physical activity had a protective effect even among obese individuals.

Studies involving adults aged between 45 and 79 years have reported that obesity is related to the presence of the hypertriglyceridemic waist phenotype [9,11,14,30]. We also observed that body mass index was positively related to prevalence of the hypertriglyceridemic waist phenotype which was present in four in every ten obese individuals included in this study. This indicates that, even among young adults, there is a direct relationship between obesity and a higher risk of carrying a phenotype that is strongly related to the presence of atherogenic risk factors, thus reinforcing the need to prevent obesity at an early age.

Other studies have reported that low socioeconomic status is related to a higher risk of the presence of the hypertriglyceridemic waist phenotype [11,13]. The present study observed that the association between income and prevalence of the condition is positive among males and a negative among females. A previous study [33] posed the hypothesis that poorer women have

more children and therefore a larger waist circumference; however, even after controlling for socioeconomic status, this factor was still associated with the presence of the phenotype in women. On the other hand, the association vanished after controlling for obesity and overweight. Therefore, the association between low socioeconomic status and presence of the hypertriglyceridemic waist phenotype is mediated by overweight/obesity.

Esmaillzadeh et al. [15] reported that a higher consumption of refined grains was associated with higher prevalence of the hypertriglyceridemic waist phenotype, and Alavian et al. [11] showed that the risk of the presence of the hypertriglyceridemic waist phenotype rose with the consumption of solid hydrogenated fat and white bread. Given these findings, an inverse association is unlikely. One possible explanation is that our analysis is cross-sectional, and therefore susceptible to reverse causality bias. Among females, for example, low dietary fat intake is also positively associated with overweight and obesity. However, given that they are overweight or obese it is possible that these individuals have a low dietary fat intake because they are dieting. On the other hand, a longitudinal analysis of a subset of 19-year-old girls found that the risk of the presence of the hypertriglyceridemic waist phenotype was not dependent on dietary fat intake ($p = 0.57$).

Smoking is a well-known cardiovascular risk factor and its association with other factors continues to be a subject of research. In our study, smoking was inversely associated with the presence of the hypertriglyceridemic waist phenotype among men; with a prevalence of 6.5% among smokers compared to 4.3% in nonsmokers ($p = 0.06$). In this study, 18.2% of male smokers were overweight, compared to 25% of nonsmokers, and 5.9% were obese, compared to 8.2% of nonsmokers ($p < 0.05$). No significant differences were found between triglyceride levels between smokers and nonsmokers.

In conclusion, prevalence of the hypertriglyceridemic waist phenotype among young adults is strongly associated with cardiovascular risk factors. The association between waist circumference and triglyceride levels seems to be a good and cost effective method and less invasive alternative for screening individuals at risk of developing cardiovascular disease.

Resumen

El presente estudio tuvo como objetivo determinar la prevalencia del fenotipo de la cintura hipertrigliceridémica y sus factores asociados entre individuos que fueron observados desde su nacimiento. En 1982, las maternidades de Pelotas, sur de Brasil, fueron visitadas y todos los nacimientos fueron identificados. En 2004-2005, se decidió realizar un seguimiento de toda la cohorte. La presencia del fenotipo de la cintura hipertrigliceridémica se definió como una circunferencia de la cintura ≥ 90cm y triglicéridos ≥ 177mg/dL para el sexo masculino y circunferencia de la cintura ≥ 85cm y triglicéridos ≥ 133mg/dL para las mujeres. La prevalencia del fenotipo de la cintura hipertrigliceridémica fue de un 5,9% y un 4,5% entre los hombres y mujeres, respectivamente. Para los hombres, el sedentarismo en el ocio, tabaquismo y obesidad estuvo asociado con el fenotipo de la cintura hipertrigliceridémica. Por otro lado, entre las mujeres, el fenotipo de la cintura hipertrigliceridémica fue positivamente asociado con el color de la piel, renta familiar, obesidad y consumo de grasa.

Circunferencia de la Cintura; Obesidad Abdominal; Triglicéridos

Contributors

B. L. Haack contributed to study design, data analysis and interpretation and to drafting and approval of the final version of this paper. B. L. Horta contributed to study design and to drafting and approval of the final version of this paper. D. P. Gigante, B. C. Barros, I. Oliveira and V. M. Silveira contributed to study design, critical review and approval of the final version of this paper.

Acknowledgments

The 1982 birth cohort study is currently supported by the Wellcome Trust initiative entitled Major Awards for Latin America on Health Consequences of Population Change. Previous phases of the study were supported by the International Development Research Center, The World Health Organization, Overseas Development Administration, European Union, PRONEX, CNPq and Brazilian Ministry of Health.

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Submitted on 16/Apr/2012
Final version resubmitted on 22/Oct/2012
Approved on 06/Dec/2012