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FATORES DE RISCO CARDIOVASCULAR EM UMA COORTE DE MULHERES NA MENOPAUSA NO SUL DO BRASIL

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1. **Artigo Original 1:** Physical activity in climacteric women: comparison between self-reporting and pedometer. Rev Saúde Pública. 2014 Apr; 48(2): 258-65.

2. **Artigo Original 2:** Association between habitual physical activity and lower cardiovascular risk in premenopausal, perimenopausal, and postmenopausal women: a population-based study. Menopause. 2013 May; 20(5): 525-31.

3. **Artigo Original 3:** Causes of death and associated risk factors among climacteric women from Southern Brazil: a population based-study. BMC Public Health. 2014 Feb 21; 14:194.

Além dos artigos já citados, durante o período de um ano de doutorado-sanduiche realizado na Erasmus Medical Center, Departamento de Epidemiologia, Rotterdam, Holanda, através do Programa Ciência sem Fronteiras, foram desenvolvidos os seguintes trabalhos:

1. The Global Impact of Non-Communicable Diseases on Households and Impoverishment. A Systematic Review. Jaspers L, **Colpani V**, Chaker L, van der Lee SJ, Muka T, Imo D, Mendis S, Chowdhury R, Bramer WM, Falla A, Pazoki R, Franco OH. Eur J Epidemiol. 2014 Dec 21. [Epub ahead of print]
2. The Global Impact of Non-Communicable Diseases on Healthcare Spending and National Income. A Systematic Review. Muka T, Imo D, Jaspers L, **Colpani V**, Chaker L, van der Lee SJ, Mendis S, Chowdhury R, Bramer WM, Falla A, Pazoki R, Franco OH. Eur J Epidemiol. 2015 Jan 18. [Epub ahead of print]
3. The Global Impact of Non-communicable Diseases on Macro-economic Productivity. A Systematic Review. Chaker L, van der Lee SJ, Jaspers L, **Colpani V**, Muka T, Imo D, Mendis S, Chowdhury R, Bramer WM, Falla A, Pazoki R, Franco OH [Submetido ao Eur J Epidemiol]
4. The association between vasomotor symptoms and metabolic health in peri- and postmenopausal women: A systematic review. van Dijk GM, Maneva M, **Colpani V**, Dhana K, Muka T, Jaspers L, Kavousi M, Franco OH. Maturitas. 2015 Feb;80(2):140-147

LISTA DE ABREVIATURAS E SIGLAS

AF: Atividade Física

BMI: Body Mass Index [Índice de Massa Corporal]

CC: Coeficiente de Concordância

CI: Confidential Interval [Intervalo de Confiança]

CPS-II: Cancer Prevention Study

CVD: Cardiovascular Disease [Doença Cardiovascular]

DCV: Doença Cardiovascular

DM: Diabete Mellito

DP: Desvio Padrão

ESTHER: *Epidemiologische Studie Zu Chancen Der Verhütung, Früherkennung Und Optimierten Therapie Chronischer Erkrankungen In Der Älteren Bevölkerung*

GLU: Glucose [Glicose]

HDL-c: High-Density Lipoprotein Cholesterol [Lipoproteína de Alta Densidade]

HR: Hazard Ratio [Razão de Risco]

HT: Hormonal Therapy [Terapia Hormonal]

ICD-10: 10th Revision of The International Statistical Classification of Diseases [Classificação Internacional de Doenças]

IPAQ-LF: International Physical Activity Questionnaire – Long Form [Questionário Internacional de Atividade Física- Versão Longa]

IPAQ-SF: International Physical Activity Questionnaire – Short Form [Questionário Internacional de Atividade Física- Versão Curta]

LDH-c: Low-Density Lipoprotein Cholesterol [Lipoproteína de Baixa Densidade]

LPA: Leisure-Time Physical Activity [Atividade Física no Lazer]

MET: Metabolic Equivalent [Equivalente Metabólico]

NHS: *Nurses' Health Study*

NIS/RS-SES: Núcleo de Informações em Saúde da Secretaria da Saúde do Rio Grande do Sul

OMS: Organização Mundial da Saúde

OR: Odds Ratio [Razão de Chances]

PA: Physical Activity [Atividade Física]

SD: Standard Deviation [Desvio Padrão]

TC: Total Cholesterol [Colesterol Total]

TG: Triglycerides [Triglicerídeos]

TH: Terapia Hormonal

WC: Waist Circumference [Circunferência da Cintura]

WHR: Waist-to-Hip Ratio [Razão Cintura-Quadril]

SUMÁRIO

RESUMO

A menopausa é a fase da vida da mulher onde ocorre a cessação permanente da menstruação devido ao esgotamento de folículos viáveis. Este período, juntamente com o avançar da idade, aumentam os fatores de risco para doença cardiovascular (DCV).

Um estilo de vida não saudável (sedentarismo, tabagismo, ingesta abusiva de álcool) e doenças como a obesidade e o Diabete Mellito podem interagir com as mudanças biológicas causadas pela menopausa, aumentando a morbidade e mortalidade.

Apesar de estudos já terem verificado estas associações em coortes de mulheres europeias e norte americanas, poucos estudos brasileiros analisaram prospectivamente o papel de fatores de risco modificáveis e não modificáveis em mulheres no período da menopausa. Estes estudos, além de um período de seguimento de somente cinco anos, avaliaram populações mais idosas e não estratificaram por status menopáusico.

O presente estudo de base populacional, realizado em uma coorte de mulheres na pré-, peri e pós-menopausa na cidade de Passo Fundo, Rio Grande do Sul, Brasil, teve como objetivos 1) comparar dois instrumentos de avaliação de nível de atividade física, Questionário Internacional de Atividade Física-versão curta (IPAQ-SF) e pedômetro em mulheres na menopausa 2) verificar o nível de atividade física através do pedômetro e seu efeito em fatores de risco para DCV em mulheres na menopausa, 3) analisar os fatores de risco para mortalidade nesta coorte de mulheres.

O primeiro objetivo foi avaliado através um estudo transversal, aninhado a esta coorte de mulheres na menopausa no sul do Brasil. Foi observado que a concordância entre o pedômetro e o IPAQ-SF é baixa (k=0.0110; p=0.007), sendo que este último superestima o nível de atividade física em relação ao pedômetro.

O segundo objetivo foi verificado através de um estudo transversal aninhado a mesma coorte e mostrou que caminhar mais de 6000 passos/dia está associado a um menor índice de massa corpórea (IMC) e adiposidade central, menor prevalência de síndrome metabólica e diabete mellito.

O terceiro objetivo foi acessado através do um estudo longitudinal, com seguimento médio de 15 anos. Apesar do baixo número de eventos, a maior causa de mortalidade foi por DCV. O diabete mellito e a obesidade central foram associados a maior mortalidade total.

Estes resultados, em conjunto, sugerem que alguns fatores de risco tradicionais como sedentarismo, maior consumo de bebida alcoólica e obesidade estão diretamente associadas a um pior perfil cardiovascular em mulheres na menopausa. Ainda, o diabete mellito em mulheres na menopausa está associado a um maior risco de mortalidade total.

A aderência a um estilo de vida saudável, incluindo aqui a atividade física habitual, diminui fatores de risco cardiovascular e mortalidade, principalmente na pós-menopausa.

ABSTRACT

Menopause is defined as a permanent cessation of menses resulting from loss of ovarian follicle activity. This period of life, together with aging, increase the risk factors for cardiovascular disease (CVD).

An unhealthy lifestyle (inactivity, smoking habits, excessive alcohol intake) and diseases such as obesity and diabetes mellitus may interact with changes in biological processes caused by menopause increasing morbidity and mortality.

Although some cohort studies have already analyzed this relationship in European and North American populations, few Brazilian studies have prospectively analyzed the role of cardiovascular modifiable and non-modifiable risk factors on cardiovascular events and mortality in menopausal women. These studies, besides a short follow up, also evaluated older population and did not stratified by menopausal status.

This population-based cohort study, conducted in premenopausal, perimenopausal and postmenopausal women in Passo Fundo, Rio Grande do Sul, Brazil, aimed to 1) compare two methods of assessing physical activity: The International Physical Activity Questionnaire (IPAQ-short form) and pedometer in menopausal women; 2) evaluate pedometer-determined habitual physical activity, and its effect on CVD risk factors in menopausal women; 3) assess risk factors and causes for mortality in a cohort of menopausal women.

A cross sectional study, nested in this cohort study in Southern Brazil, was performed to analyze the first goal. The agreement between pedometer

and IPAQ-SF was weak (k = 0.0110, p = 0.007), while the latest overestimates the level of physical activity in relation to the former.

The second goal was also examined with a cross-sectional design, nested in the same cohort. Our results have shown that women walking at least 6000 steps/day were associated with a lower risk profile for, metabolic syndrome, diabetes mellitus and CVD.

The third goal was assessed through a longitudinal population-based study with a mean follow up of 13.4 ± 3.3 years. Despite the low number of events, the major cause of mortality was from CVD. Diabetes mellitus and central adiposity were associated with increased all-cause mortality.

Taken together these results suggest that traditional risk factors such as inactivity, excessive alcohol intake and obesity are associated with a worst cardiovascular risk profile in menopausal women. Diabetes mellitus in postmenopausal women is also associated with an increased risk of all-cause mortality.

The adherence to a healthy lifestyle, including habitual physical activity, decreases cardiovascular risk factors and mortality, especially in postmenopausal women.

INTRODUÇÃO

As taxas de mortalidade por doença cardiovascular (DCV) vêm reduzido consideravelmente nas ultimas décadas e este declínio pode ser atribuído a um melhor estilo de vida e cuidados com a saúde (Van Dam *et al.*, 2008; Mosca *et al.*, 2012). Mesmo assim, as DCV ainda apresentam alta incidência, sendo a causa número um de morbidade e mortalidade entre homens e mulheres (Mosca *et al.*, 2012; Perk *et al.*, 2012).

O processo de envelhecimento e mortalidade da população tem impacto na saúde e em politicas sociais, sendo a menopausa um importante fator modificador da mortalidade feminina (Lin *et al.*, 2010). Um estudo realizado por Schmitt et al. destaca que, entre 1979 e 2004, as DCV, neoplasias, e causas mal definidas foram as principais causas de morte em mulheres no Brasil (Schmitt Acb *et al.*, 2008).

Comparadas aos homens, as mulheres parecem experimentar DCV em um estágio mais tardio e com uma sintomatologia diferente, com percepções equivocadas em relação aos achados clínicos e tratamento (Stranges e Guallar, 2012). Nesse sentido, estudos têm demonstrado que a menopausa marca uma fase de transição onde as mudanças do perfil hormonal e de lipoproteínas resultam em modificações no perfil cardio-metabólico (Chang *et al.*, 2000; Matthews *et al.*, 2009; Agrinier *et al.*, 2010).

Fatores de risco modificáveis (estilo de vida, obesidade), não modificáveis (idade, hereditariedade) e socioeconômicos (educação, renda) possivelmente interagem com as mudanças bruscas de perfil hormonal da menopausa influenciando no processo de aterosclerose e desenvolvimento de DCV e mortalidade.

Segundo a Organização Mundial da Saúde (OMS) cerca de 25% de toda mortalidade cardiovascular pode ser prevenida com diminuição destes fatores de risco e mudanças adequadas de estilo de vida, como dieta, redução do consumo excessivo de bebidas alcoólicas, atividade física e cessação do tabagismo (OMS 2013). Estudos têm mostrado que a mortalidade está inversamente relacionada com estilo de vida saudável (Chiuve *et al.*, 2011). Em mulheres, as taxas de mortalidade são 22% menores para aquelas que aderem a um estilo de vida saudável e 63% menores para as que aderem a mais de um hábito de vida saudável (não fumar, ingesta moderada de álcool, prática de atividade física e dieta balanceada) *(Ford et al., 2011)*. Ainda, o NHS (*Nurses` Health Study*) acompanhou mulheres de meia idade e concluiu que 55% das mortes ao longo de 24 anos de seguimentos poderiam ser atribuidas a combinação de tabagismo, obesidade, sedentarismo e maus hábitos alimentares, subindo para 63% o risco em mulheres acima de 60 anos (Van Dam *et al.*, 2008)**.** Apesar das diversas campanhas para melhora do estilo de vida, o nível de saúde da população continua abaixo do ideal tendo em vista a alta prevalência de fatores de risco modificáveis (Stamler *et al.*, 1999; Daviglus *et al.*, 2003; Strandberg *et*

al., 2004; Lloyd-Jones *et al.*, 2006; Hsia *et al.*, 2010; Berry *et al.*, 2012; Silva *et al.*, 2013).

A relação entre os fatores de risco modificáveis, desfechos cardiovasculares e mortalidade em mulheres foi estudada em uma série de estudos. Meta-análises de estudos prospectivos realizadas em populações americana e européia têm demostrado que consumo moderado de álcool (<2 doses/dia) reduz mortalidade geral e cardiovascular em mulheres (Di Castelnuovo *et al.*, 2006; Ronksley *et al.*, 2011). Tanto o estudo alemão ESTHER (*Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung*) e o NHS mostraram que o risco de DCV e mortalidade é duas a três vezes maiores em mulheres fumantes comparadas a não fumantes (Kenfield *et al.*, 2008; Gellert *et al.*, 2013). Nas mulheres do NHS que permaneceram 20 anos sem fumar, estes riscos se aproximam ao de uma mulher que nunca fumou, sugerindo que a intervenção em fatores de risco modificáveis, nesse caso, o tabagismo, apresenta impacto considerável no bem estar e na saúde dessa população (Kenfield *et al.*, 2008).

De acordo com estudos como NHS e Cancer Prevention Study (CPS-II), mulheres com índice de massa corporal (IMC) ideal têm um menor risco para mortalidade cardiovascular (Van Dam *et al.*, 2008; Mccullough *et al.*, 2011).

Estudos observacionais e de intervenção sugerem que atividade fisica reduz os índices de obesidade (Sternfeld *et al.*, 2005; Swift *et al.*, 2012), melhora o controle glicêmico e reduz a pressão arterial sistêmica

(Moreau *et al.*, 2001; Jeon *et al.*, 2007; Lara *et al.*, 2010; Dwyer *et al.*, 2011; Umpierre *et al.*, 2011; Swift *et al.*, 2012). Embora de difícil identificação**,** evidências sugerem que o efeito da atividade física nesses fatores de risco relaciona-se a redução de desfechos cardiovasculares e mortalidade, embora ensaios clínicos não terem sido capazes de comprovar essa relação de uma maneira tão sólida em populações específicas, como em pacientes com diabete mellito (Wing *et al.*, 2013). Esta falta de associação pode estar relacionada ao fato desta população ser de auto risco e/ou com a seleção de um grupo controle inadequado. Estas mudanças de estilo de vida são particularmente importantes em mulheres na menopausa, visto que neste período elas possuem um menor gasto energético (Lovejoy *et al.*, 2008) e um maior risco de DCV se comparadas a mulheres mais jovens (Kannel *et al.*, 1976).

Estudos epidemiológicos têm demonstrado que a caminhada, atividade física muito praticada por mulheres, esta relacionada a redução de DCV e mortalidade (Manson *et al.*, 2002; Zheng *et al.*, 2009; Sattelmair *et al.*, 2011) . O seguimento observacional do WHI (*Women`s Health Initiative*), realizado em mulheres na pós-menopausa, mostrou que a caminhada, assim como a prática de atividade física mais vigorosa, diminui em torno de 20% o risco de eventos cardiovasculares (Manson *et al.*, 2002).

O impacto da atividade física no tratamento de fatores de risco modificáveis, na prevenção de desfechos cardiovasculares e mortalidade é variável. Além da grande heterogeneidade no delineamento e perfil amostral, os métodos de aferição de frequência e

intensidade de atividade física são variáveis e com conhecidas limitações. Nesse sentido, diversos instrumentos de quantificação de atividade física estão disponíveis como questionários validados, pedômetros e acelerômetros. Pedômetros e acelerômetros, métodos objetivos e precisos de mensuração, são mais caros quando comparados a aplicação de um questionário. Já este último, muito utilizado em estudos de larga escala e de seguimento, por ser auto-referido, pode gerar viés de aferição (Ramirez-Marrero et al., 2008; Lee et al., 2011). Ainda, pedômetros e acelerômetros possuem uma alta correlação quando avaliada passos/dia, já a associação do pedômetro com os questionários de atividade física é baixa (Harris et al., 2009; Lee et al., 2011).

A coorte de mulheres de Passo Fundo

Este estudo longitudinal de base populacional iniciou em 1995 em Passo Fundo, uma cidade no sul do Brasil com uma população de mais de 170.000 pessoas (Oppermann-Lisboa K, 1999).

Como parte do projeto, um estudo transversal foi inicialmente realizado. A primeira visita de campo ocorreu entre 1995 e 1997, com o objetivo de investigar a prevalência de sintomas climatéricos e o volume ovariano de acordo com as características de mulheres na pré- e perimenopausa que viviam na zona urbana da cidade. A amostragem foi realizada em duas etapas. Em primeiro lugar, 154 setores censitários (subdivisões geográficas da cidade definido pelo Instituto Brasileiro de

Geografia e Estatística) foram selecionados aleatoriamente. Em cada setor censitário, um quarteirão foi escolhido por sorteio. Em cada quarteirão, duas mulheres foram selecionadas randomicamente para a entrevista. Uma amostra representativa de 298 mulheres entre 35 a 55 anos, que tinha menstruado pelo menos uma vez nos últimos 12 meses, foi aleatoriamente identificada (Oppermann-Lisboa K, 1999).

Na segunda visita de campo, conduzida entre 2001 e 2002, as mulheres foram localizadas e entrevistadas. Devido a perdas de seguimento e ao aumento da população, foram incluídas 119 mulheres entre 35 e 62 anos, totalizando uma amostra de 358 mulheres (Donato *et al.*, 2006; Bastos, 2006). Neste seguimento as mulheres foram selecionadas da mesma maneira aleatória e conforme setores censitários de 1995.

Em 2010, um terceiro seguimento foi iniciado com o objetivo de verificar risco cardiovascular e taxa de mortalidade entre estas mulheres. Da amostra de 358 mulheres, 17 mulheres morreram, 22 se mudaram para outra cidade e 18 se recusaram a participar desta etapa da pesquisa. A amostra final desse terceiro seguimento foi de 301 mulheres. Essas participantes responderam a um questionário padronizado, participaram de avaliação física, uso de pedômetro e coleta de sangue e outros exames subsidiários (Colpani *et al.*, 2014).

Justificativa

Como já discutido em estudos citados nesta Introdução, melhora no estilo de vida diminui o risco para DCV e mortalidade por causas gerais. Baseados nestes dados, e na escassez de informações sobre a mulheres brasileiras no período da menopausa, principalmente sobre a ocorrência de desfechos duros, o presente estudo foi desenvolvido buscando colaborar na elucidação das hipóteses e melhor consistência dos dados sobre a população feminina na pré-, peri e pós-menopausa no sul do Brasil.

OBJETIVOS:

Estudando uma coorte de mulheres na pré-, peri e pós-menopausa no sul do Brasil, buscou-se os seguintes objetivos:

- Identificar fatores de risco para doença cardiovascular (DCV).
- Comparar dois métodos de avaliação de atividade física.
- Verificar associação entre atividade física e menor risco cardiovascular.
- Identificar as taxas de mortalidade, suas causas e fatores de risco associados.

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Artigo original 1

Physical activity in climacteric women: comparison between self-reporting and pedometer.

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Atividade física em mulheres climatéricas no sul do Brasil: comparação entre auto-relato e pedômetro.

Physical activity in climacteric women from Southern Brazil: comparison between self-report and pedometer.

Titulo resumido: Atividade física no climatério.

Resumo

Objetivo: comparar o nível de atividade física (AF) através do Questionário Internacional de Atividade Física versão curta (IPAQ-SF), com AF medida por pedômetro em mulheres climatéricas.

Métodos: estudo transversal aninhado à coorte de mulheres na pré-, peri e pós-menopausa em uma cidade do sul do Brasil. As participantes responderam a um questionário com dados sociodemográficos e clínicos. A AF foi avaliada através do IPAQ-SF e da contagem do número de passos com o uso de pedômetro. Após, as participantes foram classificadas em estratos de AF de acordo com o instrumento utilizado. Para análise estatística foram realizados os testes de correlação de Spearman, índice de Kappa, coeficiente de concordância e análise das medidas contínuas de Bland-Altman.

Resultados: A concordância (k=0.110; p=0.007) e a correlação (rho=0.136;p=0.02) entre o IPAQ-SF e pedômetro foram fracas. No gráfico de Bland-Altman, observou-se que as diferenças se afastam do valor zero tanto quanto a AF é mínima ou mais intensa. Comparando-se os dois métodos, a

frequência de mulheres inativas é maior quando avaliadas pelo pedômetro do que pelo IPAQ-SF e o oposto ocorre entre as ativas.

Conclusão: A concordância entre os métodos foi fraca. Embora de fácil aplicação, o questionário IPAQ-SF superestima a AF em relação à avaliação por pedômetro.

Descritores: Atividade física, questionário, pedômetro, menopausa.

Abstract

Objective: Compare the level of physical activity (PA) through the International Physical Activity Questionnaire short version (IPAQ-SF) with PA measured by pedometer in pre-, peri- and postmenopausal women.

Methods: Cross-sectional study nested in a cohort of women in a city from Southern Brazil. The participants completed a pretested standardized questionnaire that included demographic and clinical data. PA was assessed with a digital pedometer and the IPAQ-SF. The participants were classified into strata of PA according to the instrument used. For statistical analysis, the Spearman correlation test, Kappa index, concordance coefficient and Bland-Altman plots were used.

Results: The concordance (k = 0110, p = 0.007) and the correlation (rho = 0,136, p = 0.02) between the IPAQ-SF and pedometer were weak. In Bland-Altman plots, it was observed that differences deviate from zero value as long as the PA is minimal or more intense. Comparing the two methods, frequency of inactive women is higher when assessed by pedometer than the IPAQ-SF and the opposite occurs between active women.

Conclusion: The agreement between the methods was week. Although easy to use, IPAQ-SF overestimates the PA regarding the assessment by pedometer.

Descriptors: Physical activity, questionnaires, pedometer, menopause.

Introdução

O sedentarismo tem sido reconhecido como um fator independente de risco para o desenvolvimento de doença cardiovascular (DCV), diabetes tipo 2, síndrome metabólica e alguns tipos de câncer.[13] A atividade física (AF) é considerada importante causa evitável de mortalidade devido a doenças crônicas não transmissíveis.

Existem diferentes instrumentos disponíveis para avaliar a AF e o gasto energético. Dentre os métodos e técnicas utilizados, os questionários têm sido bastante empregados. Dos disponíveis na literatura, dois foram traduzidos e validados para a língua portuguesa. O Questionário Internacional de Atividade Física (IPAQ versão longa e curta) é o que apresenta as melhores condições para ser aplicado, com boa reprodutibilidade, embora apresente baixa validade.[13]

Outra forma de avaliação da AF é através do uso do pedômetro, um contador mecânico que registra movimentos realizados em resposta à aceleração vertical do corpo. Ele é preso na cintura do indivíduo, contando o número de passos dados em um intervalo de tempo. Possibilita a medição cumulativa das atividades ocupacionais, de lazer, domésticas e de transporte, sendo um método objetivo bastante sensível na quantificação da AF do indivíduo.[4]

Há poucos estudos com mulheres de meia idade comparando a avaliação da AF habitual através do IPAQ-SF e pedômetro.[5] Desta forma, o objetivo deste estudo foi estimar o grau de concordância e correlação entre informações sobre estrato de AF obtidas através do IPAQ-SF e do uso de

pedômetro, em uma coorte de mulheres na pré, peri e pós-menopausa da cidade de Passo Fundo, RS, Brasil.

Métodos

Estudo transversal, de base populacional, aninhado a uma coorte de mulheres na pré-, peri e pós-menopausa, da cidade de Passo Fundo-RS-Brasil, realizado no período de 2010 a 2011.

Este trabalho está integrado a um estudo mais amplo que visa identificar o risco cardiovascular em uma população feminina desta cidade. Esta coorte iniciou em 1995, quando foram randomizadas 298 mulheres, com o objetivo de avaliar a prevalência de sintomas climatéricos, níveis hormonais e medidas ecográficas pélvicas.[16] Em 2001 realizou-se o segundo seguimento, no qual as participantes da amostra anterior foram localizadas. Tendo em vista as perdas da amostra e o aumento populacional, foram incluídas novas participantes, randomizadas da mesma forma,[1,8] totalizando uma amostra de 358 mulheres, com idade entre 36 e 62 anos, na pré-, peri e pós-menopausa.

Em 2010, para o conhecimento do atual estado de saúde e risco cardiovascular destas participantes, iniciou-se o terceiro seguimento. As participantes foram localizadas através dos endereços, telefones, registros hospitalares, endereços de parentes, rádio e televisão local e, ao término desta busca, 301 mulheres foram contatadas. Destas, 292 tiveram dados de nível de AF completos para realização deste estudo e nove foram excluídas devido a dificuldades cognitivas (4), analfabeta (1) e erro no registro do número de passos(4). [4]

Foram coletados dados sócio-demográficos, como idade, educação (anos de permanência na escola), sintomas climatéricos e uso de terapia hormonal (TH) através de um questionário previamente testado[1,8]. A variável trabalho foi avaliada pela pergunta “Você está trabalhando atualmente?”. O status menopáusico foi definido com base nas características do ciclo menstrual e tempo de amenorreia: pré-menopausa foi definida como ciclicidade menstrual normal no momento do estudo; perimenopausa foi definida como alterações na frequência do ciclo menstrual imediatamente antes do estudo e pós-menopausa foi definido como 12 ou mais meses de amenorreia natural ou por ooforectomia bilateral. A categoria “histerectomia” foi criada para as mulheres que haviam sido previamente histerectomizadas, sem ooforectomia bilateral, e cujo status menopáusco não pode ser classificado. Women were classified in terms of alcohol consumption as nondrinkers, social drinkers (1 to 15 g alcohol/day), or abusers (at least 15 g alcohol/day) [24]. O consumo de álcool foi determinado com base no auto relato das participantes em relação a ingesta alcoólica (não consome, consumia, consome) [4,8] As participantes também foram categorizadas para tabagismo conforme auto-relato em: fumantes, ex-fumantes e não fumantes. As medidas antropométricas foram realizadas em duplicata e incluíram peso, altura, circunferência da cintura e razão cintura-quadril. [4]

A AF foi avaliada através do questionário IPAQ-SF e da contagem do número de passos com o uso de pedômetro. Utilizou-se o questionário IPAQ-SF e a AF foi classificada de 2 formas: conforme a quantidade de minutos de AF realizados na semana (inativas <150 min de AF/semana e ativas ≥150 min de AF /semana)[1] e também pelo equivalente metabólico minuto por semana

(inativa <600 MET/minuto/ semana, moderado de 600 a 1499 MET/minuto/semana e ativa ≥1500 MET/minuto/semana).[17]

O pedômetro digital (modelo BP 148 TECHLINE) foi usado durante sete dias consecutivos. As participantes foram instruídas quanto ao uso adequado do sensor e a não alterar suas atividades típicas durante o estudo. Ao final de cada dia foram orientadas a anotar em um diário o número de passos. Calculou-se a média dos passos através da soma diária de passos divididos pelo número de dias de uso do pedômetro. Através dessa medida, as mulheres foram classificadas em inativas (número de passos diário <6000) e ativas (número de passos diários ≥6000)[4] e ainda como ativas (número de passos ≥10.000), moderadamente ativas (número de passos entre 5.000 a 9.999 passos) e inativas (número de passos <4.999).[19]

Utilizamos essas duas classificações para efetuar diferentes análises. Os dados foram comparados em 150 min/semana (amplamente usada e preconizada pela Organização Mundial da Saúde) *vs*. ≥6000passos/dia (categorização já usada nesta mesma população em estudo prévio)[4] para análise dicotômica. Avaliou-se a correlação entre os MET/min/sem gastos (unidade de medida descrita nas Diretrizes para Processamento e Análise de Dados do IPAQ) *vs*. as três categorias sedentária, moderada e ativa, usada na população em geral[19].

Para análise dos dados, foram elaboradas estatísticas descritivas por meio de cálculo das médias e desvio padrão, ou frequências relativas (%) e absolutas (n). Comparou-se a percentagem de mulheres classificadas como ativas, moderadamente ativas e inativas entre os dois métodos, pelo teste do qui-quadrado de McNemar, verificando-se a igualdade entre as proporções de

respostas do nível de AF. Foi criada uma variável dicotômica referente à concordância entre os dois instrumentos e avaliou-se sua associação com idade, status menopáusico e anos de escolaridade através do teste de chi-quadrado. A análise paramétrica de Spearman (rho) foi utilizada como outra medida de associação entre média de número de passos, minutos de AF/semana e MET/min/sem. O valor estatístico Kappa (κ), o coeficiente de concordância (CC, %) e a análise das medidas contínuas usando a metodologia proposta por Bland-Altman[2] foram utilizados para análise da concordância entre o IPAQ-SF e o pedômetro. Essa plotagem permite avaliar a concordância entre duas variáveis (X, Y) e é possível avaliar o viés (o quanto as diferenças se afastam do valor zero), o erro (a dispersão dos pontos das diferenças ao redor das médias), *outliers* e tendência.[12]

Para empregar o teste de Bland-Altman, utilizou-se o cálculo do escore Z em ambos os instrumentos a fim de anular as unidades, tendo em vista que o pedômetro usa passos/dia e o IPAQ-SF o MET/min/sem. A fórmula para o cálculo do escore Z foi: $Z=(X–\mu)/S.D$, em que Z= escore Z; X = escore bruto individual; μ = média da variável; S.D. = desvio padrão da variável. Excluíram-se 18 participantes para esta análise pois estas não realizavam mais de 10 minutos contínuos de AF não completando os dados necessários para calcular os MET/min/sem. Em todas as análises foi considerado nível de significância de 5%. Utilizou-se o Statistical Package for the Social Sciences SPSS 20.0 e Stata 7.0.

Este trabalho teve aprovação do Comitê de Ética e Pesquisa da Universidade de Passo Fundo, do Hospital São Vicente de Paulo. As participantes do estudo assinaram Termo de Consentimento Livre e

Esclarecido.

Resultados

A amostra foi composta por mulheres com média de idade de 57,11 ± 5,36 anos, cujo número médio de anos na escola foi 8,74± 4,48, sendo que 20% referia menos de 4 anos de estudo. Dentre estas com baixa escolaridade, mais de 70% estavam no grupo das inativas. Com relação ao status menopáusico, 7,2% das pacientes estavam na pré-menopausa, 8,6% na perimenopausa, 78,4% na pós-menopausa e 5,8% eram histerectomizadas. A prevalência de pacientes tabagistas foi 19,2% e 18,0 % das participantes estavam em uso de TH. O índice de massa corporal foi 28,34 ± 7,07 kg\m^2, sendo que a maioria da amostra apresentava sobrepeso ou obesidade (tabela 1). Não houve associação entre anos de escolaridade, status menopáusico e idade com a concordância entre os dois instrumentos (p=0.191, p=0.268 e p=0.619, respectivamente).

A concordância entre os dois instrumentos, avaliada através do coeficiente de Kappa, foi fraca (passos/dia e min de AF/sem, k= 0.110; p=0.007 e passos/dia e MET/min/sem, k=0.075; p= 0.013). O CC foi 47% (número de passos e min de AF/sem) e 32% (número de passos e MET/min/sem), resultando um valor intermediário considerado de baixa concordância (tabela 2).

A correlação, avaliada pelo teste de Spearman, foi significativa porém fraca (média de passos/dia e MET/min/sem, rho =0.113; p= 0.025) (Figura 1). A figura 1 também apresenta o gráfico de Bland-Altman, onde se verifica que a

maior parte das observações encontra-se dentro do nível de concordância de 95% (± 1,96 *DP)* e que a diferença média do escore Z de ambos os testes foi próxima a zero. No entanto, observa-se que as diferenças se afastam do valor zero tanto quanto a AF é mínima ou mais intensa.

A tabela 2 descreve as frequências de participantes em cada estrato de AF de acordo com os dois instrumentos. Também corrobora os achados do Bland-Altman, mostrando que a frequência de mulheres inativas é maior quando avaliadas pelo pedômetro do que pelo IPAQ-SF e o oposto ocorre entre as ativas. Podemos verificar, ainda, que houve uma diferença significativa entre as mulheres classificadas em diferentes estratos de AF.

Discussão

No presente estudo, o número de mulheres consideradas ativas foi pelo menos 2 vezes maior quando classificadas pelo IPAQ-SF em comparação à avaliação do pedômetro, tanto pelo critério MET/min/sem como por min de AF/sem.

Os resultados apresentados mostram que informações referentes ao estrato de AF obtidas através do IPAQ-SF não são semelhante às avaliadas de forma objetiva, através do pedômetro. Os dados mostraram uma superestimação do IPAQ-SF em relação ao pedômetro, principalmente na categoria ativa.

Recente revisão sistemática sobre validade do IPAQ-SF mostrou estudos com populações de faixa etária semelhante a do presente trabalho e

que reportaram de baixa à moderada correlação entre os dois métodos.[13] Destacam-se os estudos que compararam o uso de pedômetro e o IPAQ-SF como o de De Cocker e colaboradores[6] realizado com 310 adultos saudáveis, que reportou uma baixa à moderada correlação (AF total rho= 0.28), e o estudo de Deng e colaboradores[7], com uma mostragem da população chinesa com idade média de 65 anos, uma correlação moderada (AF total rho= 0.33, P<0.001) entre os dois métodos.

Estudo brasileiro com 21 mulheres pós-menopáusicas, portadoras de osteoporose, avaliou a concordância entre o IPAQ-versão longa e o pedômetro. De acordo com o IPAQ, 71,4% das participantes eram classificadas como ativas e 28,6%, sedentárias. A concordância entre o IPAQ e o pedômetro, considerando-se o número de passos, teve Kappa de 0,21.[5] Apesar do estudo ter envolvido uma amostra de mulheres essencialmente pós-menopáusicas e utilizado o IPAQ versão longa, o mesmo também encontrou uma correlação fraca entre a AF referida e a avaliação direta com pedômetro. O presente estudo confirma estes achados através do IPAQ-SF, porém, com uma amostra maior e representativa de mulheres na pré-, peri e pós-menopausa.

A maioria das mulheres que fizeram parte da amostra estudada encontrava-se na meia-idade, não trabalhava, apresentava sobrepeso ou obesidade, adiposidade central, hipertensão e era predominantemente inativa quando avaliada pelo pedômetro.[4] Este perfil de risco cardiovascular está fortemente associado ao sedentarismo e reforça que a avaliação da AF realizada pelo pedômetro pode ter sido apropriada. Por outro lado, as participantes que caminhavam 6000 passos ou mais por dia apresentaram menor deposição central de gordura, síndrome metabólica e diabetes.[4]

Neste estudo utilizou-se o pedômetro durante 7 dias consecutivos e constatou-se diferença no número de passos em relação ao dia da semana, sendo maior durante os dias úteis e no verão.[4] Estudos sugerem que o uso do pedômetro por menos dias, desde que incluído o sábado ou o domingo, apresenta a mesma confiabilidade do uso semanal.[20,9,11,21] O uso de pedômetro no seguimento de pacientes poderia ser realizado desta forma, aumentando a aderência devido à facilidade de uso e menor tempo de intervenção. De qualquer forma, o uso do mesmo instrumento é recomendado na avaliação longitudinal da AF para facilitar a comparação dos resultados.

A variabilidade observada no nível educacional da amostra estudada não interferiu na associação e concordância entre pedômetro e IPAQ-SF. Fato diferente do observado em outro estudo, em que a correlação entre os dois métodos se tornou um pouco maior após o ajuste para sexo, idade e escolaridade.[7]

Com relação aos instrumentos utilizados, os questionários de auto-relato são mais acessíveis e permitem estimar a intensidade e modalidade de AF realizada. Seu uso pode ser preferencial nos estudos longos e de seguimento com um número grande de participantes. Por outro lado, é um método subjetivo e recordatório, o que pode aumentar as chances de erro. Os conceitos de sessão de 10 minutos e os erros de percepção da intensidade podem corroborar para erros de interpretação e resposta do IPAQ-SF[10], porém a utilização de entrevistadores para aplicá-lo ajuda a diminuir este viés. A confiabilidade do IPAQ-SF permite seu uso com cautela nos estudos de medidas repetidas, porém, não há evidências corroborando seu uso como medida de AF absoluta ou relativa.[13]

O pedômetro é um método de avaliação objetivo de AF e embora seja uma ferramenta valiosa para estimar e incentivar AF habitual e diária, ele não quantifica o deslocamento no plano horizontal e superior.[3] Não se pode esquecer, ainda, que ele é um ótimo instrumento para avaliar deslocamento (passos/dia) através das oscilações verticais do corpo, mas incapaz de avaliar atividades como ciclismo e qualquer atividade na água, não discriminando a intensidade e o tipo de AF.

Os indivíduos aceleram, desaceleram, param e sentam diversas vezes ao longo de um dia enquanto estão usando um pedômetro e isso pode interferir na avaliação de gasto energético e nível de AF. Adultos norte-americanos apresentam uma variação no tempo de repouso ou na cadência (passos/minuto) ao longo de um dia. Existe uma forte relação entre essa cadência e velocidade da caminhada e podem-se considerar 100 passos/min uma estimativa apropriada de uma atividade de 3 MET. Essas estimativas, porém, não podem ser consideradas como valores fixos de gasto total de energia em um dia. No presente estudo a cadência não foi medida individualmente; portanto, não se pode utilizar o gasto em MET como unidade de medida do pedômetro[22]. O uso do acelerômetro seria uma melhor opção para a comparação e conversão do gasto energético avaliado pelo IPAQ-SF e a distância percorrida pela participante. Alguns estudos mostraram uma correlação de moderada a forte entre a contagem do acelerômetro e MET em adultos[18], dado discordante em outros estudos[13]. Salienta-se que o acelerômetro é um método mais caro, também não distingue atividades estáticas (e.g. musculação), aquáticas e ciclismo e ainda há falhas da indústria

para uma correta e fácil conversão e interpretação dos dados brutos gerados pelo instrumento[14,15].

Uma limitação do presente estudo foi o fato de que os dois instrumentos apresentaram unidades de medida diferentes, o que poderia limitar as análises de Bland-Altman. Entretanto, o cálculo do escore Z, possibilitou a análise concorrente entre esses testes.

Este é o primeiro estudo brasileiro de base populacional que investiga estes dois métodos de avaliação da AF e relaciona com o status menopausal e anos de escolaridade. Pelo delineamento do estudo, é possível transpor seus resultados para populações semelhantes.

Considerando-se que a AF habitual é um comportamento que pode ser facilmente adotado para prevenção de risco cardiovascular, é fundamental que se utilize métodos acurados de estimativa da AF e que os mesmos possam ser considerados como instrumentos auxiliares na intervenção de modificações comportamentais, estimulando a AF.

Em conclusão, a concordância entre IPAQ-SF e pedômetro foi fraca na amostra de mulheres climatéricas avaliada. Embora de fácil aplicação, o questionário IPAQ-SF superestima a AF em relação à avaliação por pedômetro.

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Tabela 1. Características demográficas e antropométricas das participantes do estudo Passo Fundo, RS, Brasil, 2010. (n = 292)

Variável	**n**	**%**	**Média**	**DP**
Idade (anos)	–	–	57,11	5,36
Estudo (anos)				
0 a 4	58	19,9	–	–
5 a 8	91	31,2	–	–
9 a 11	85	29,1	–	–
≥ 12	58	19,9	–	–
Trabalho (sim)	129	44,2	–	–
Terapia hormonal (sim)	48	18,0	–	–
Status menopáusico				
Pré-menopausa	21	7,2	–	–
Perimenopausa	25	8,6	–	–
Pós-menopausa	229	78,4	–	–
Histerectomia	17	5,8	–	–
Estado civil				
Casada	150	51,4	–	–
Solteira	51	17,5	–	–
Separada/Divorciada	91	31,1	–	–
Uso de álcool				
Usuária	96	32,9	–	–
Ex-usuária	19	6,5	–	–
Não usuária	177	60,6	–	–
Tabagismo				

Tabagista	56	19,2	–	–
Ex-tabagista	67	22,9	–	–
Não tabagista	169	57,9	–	–
Sobrepeso/obesidade (sim)	198	68,3	–	–
IMC (kg/m^2)	–	–	28,3	7,0
Cintura (cm)	–	–	91,3	13,7

IMC: índice de massa corpórea

Tabela 2. Estrato de atividade física de mulheres na pré-, peri- e pós - menopausa, em relação ao IPAQ-SF e pedômetro, MET/min/sem *versus* passos por dia. (n = 292)

Variável	**Inativa < 4.999 passos/dia; < 600 MET/min/sem**		**Moderada 5.000 a 9.999 passos/dia; 600 a 1499 MET/min/sem**		**Ativa ≥ 10.000 passos/dia; ≥ 1.500 MET/min/sem**		**Kappa[a]**
	n	%	n	%	n	%	
Número de passos (pedômetro)	199	68,2	72	24,7	21	7,2	0.075
MET/min/sem (IPAQ-SF)	59	20,2	133	45,5	100	34,2	

IPAQ-SF: Questionário Internacional de Atividade Física - versão curta

Teste de Qui-quadrado de McNemar, p ≤ 0,001

[a] Coeficiente de Kappa p ≤ 0,05

Tabela 3. Estrato de atividade física de mulheres na pré-, peri- e pós - menopausa, em relação ao IPAQ-SF e pedômetro, Min/sem *versus* passos por dia. (n = 292)

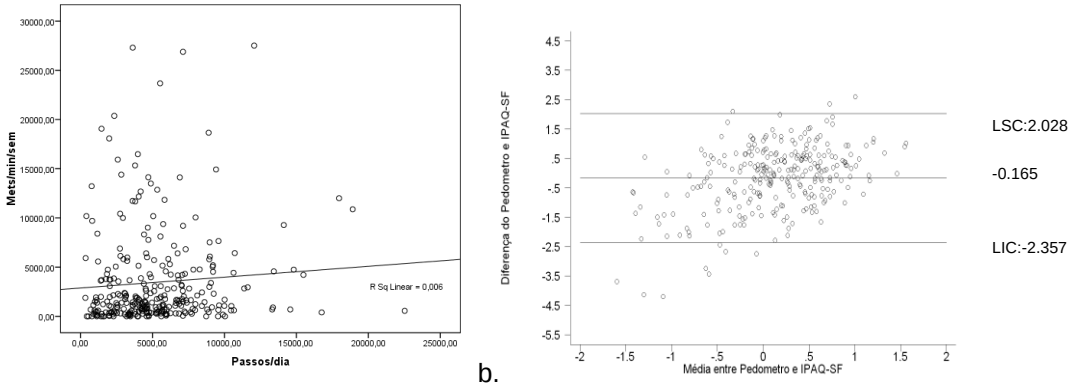
Variável	**Inativa < 6.000 passos/dia; < 150 min/sem**		**Ativa ≥ 6.000 passos/dia; ≥ 150 min/sem**		**Kappa[a]**
	n	%	n	%	
Número de passos (pedômetro)	199	68,2	93	31,8	0.110
Min/sem (IPAQ-SF)	75	26,0	214	74,0	

IPAQ-SF: Questionário Internacional de Atividade Física - versão curta

Teste de Qui-quadrado de McNemar, p ≤ 0,001.

[a] Coeficiente de Kappa p ≤0,05.

Figura 1. Análise de correlação e concordância de medidas de atividade física entre o Questionário Internacional de Atividade Física – versão curta e pedômetro.



a. b.

LSC: limite superior de concordância; LIC: limite inferior de concordância

a. Correlação de Spearman (rho = 0.113; p = 0.025)

b. Bland-Altman para testar concordância de medidas de atividade física entre o IPAQ-SF e pedômetro, média em escore Z de passos/MET(log)

Artigo original 2

Association between habitual physical activity and lower cardiovascular risk in premenopausal, perimenopausal, and postmenopausal women: a population-based study.

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Association between habitual physical activity and lower cardiovascular risk in pre-, peri- and postmenopausal women: a population-based study

Running title: Habitual physical activity in menopause

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Abstract

Objective: Menopause is associated with increased risk of cardiovascular disease. Habitual physical activity, defined as any form of body movement with energy expenditure above resting levels, may improve health parameters. We assessed the level of habitual physical activity and its effect on anthropometric measures and cardiovascular risk factors in a cohort of pre-, peri- and postmenopausal women.

Methods: This cross-sectional study is nested in a longitudinal population-based study begun in 1995 in the city of Passo Fundo, Brazil. For the present analysis, 292 women were included. The anthropometric and metabolic profile was evaluated. Habitual physical activity was assessed by a digital pedometer during 7 days, and participants were stratified into active and inactive (≥6000 and <6000 steps/day respectively).

Results: Mean age was 57.1±5.4 years. The average number of steps/day for the total sample was 5250.7±3372.9: 3472.4±1570.2 in the inactive group (61.8%) and 9055.9±3033.4 in the active group (31.9%). A negative and statistically significant correlation was found between physical activity and smoking (p=-0.019), body mass index (p=-0.006), waist circumference (p=-0.013) and waist-to-hip ratio ≥0.85 (p=-0.043). Inactive women presented higher risk of overweight/obesity (OR=2.1, 95%CI:1.233-3.622, p=0.006) and waist circumference >88cm (OR=1.7, 95%CI:1.054-2.942, p=0.03), even after adjustment for age, menopause status, smoking, and hormonal therapy. Inactive women also had higher risk of diabetes mellitus (OR=2.7, 95%CI:1.233-6.295, p=0.014) and metabolic syndrome (OR=2.5, 95%CI:1.443-4.294, p=0.001).

Conclusions: Habitual physical activity, specifically walking 6000 or more steps daily, was associated with a decrease in cardiovascular risk and diabetes in middle-aged woman, independently of menopausal status.

Key words: physical activity, cardiovascular risk, pedometer, central adiposity, metabolic syndrome, menopause

Introduction

Cardiovascular disease (CVD) is the leading cause of death among women.[1] The incidence of CVD rises steeply after menopause. As women age, they are increasingly exposed to major CVD risk factors, as a result not only of estrogen deprivation, but also of weight gain[2,3] and of the lipid profile that accompanies the perimenopause.[4-6]

There is epidemiological evidence that physical activity (PA) is associated with reduced risk of CVD and cardiovascular mortality.[7-11] However, even though there is consensus regarding the benefits of PA to health,[12,13] there is still doubt concerning the efficacy of different types of PA in reducing CVD risk.

Habitual PA – movement associated with the complex sum of individual habits and activities that may vary from day to day, season to season and year to year,[14] including work, leisure activities, and household chores in addition to structured exercise[15] – seems to be beneficial for health. Walking, the most common form of exercise among women, is associated with both habitual and structured PA.[7,8]

Pedometers provide an accurate, objective, and low-cost method of measuring the amount of walking.[16] Previous studies have shown that a higher number of steps per day is associated with lower risk of dysglycemia[17] and improved anthropometric measures,[18,19] lipid levels[20] and diastolic blood pressure.[19,21] However, most of these studies refer to country- and culture-specific populations.

Therefore, the aim of this study was to measure pedometer-determined habitual PA in a Brazilian cohort of pre-, peri- and postmenopausal women and to assess its effect on anthropometric measures and CVD risk factors.

Methods

Participants and design

This cross-sectional study is nested in a longitudinal population-based study of menopausal status conducted in Passo Fundo, a city with a population of over 170,000 people in southern Brazil. Data for the present analysis were collected in the third field visit, between 2010 and 2011.

The first field visit took place between 1995 and 1997 to investigate ovarian volume according to the characteristics of premenopausal and perimenopausal women living in the urban area of Passo Fundo.[22] Sampling was carried out in two stages. First, 154 census sections (geographic subdivisions of the city defined by the Brazilian Institute of Geography and Statistics)[23] were randomly selected. In each census section, one block was picked by lot. Two women were chosen for interview in each block using a randomization method described previously. A representative sample of 298 women aged 35 to 55 years who had menstruated at least once in the past 12 months was randomly identified.[24] After a second field visit, conducted between 2001 and 2002, additional women were enrolled, for a final sample of 358 women.[3,25]

In the third follow-up, described in this study, participants were contacted at home or through the telephone, or located through hospital records, addresses of relatives or advertisement on the radio and local television. Of the

final sample of 358 participants, 17 died, 22 moved to another city and 18 refused to participate in this third stage.

Study protocol

The participants were interviewed using a pre-tested, standardized questionnaire covering demographic characteristics (age and self-reported skin color), education (years at school), gynecologic data, use of hormonal therapy (HT) for menopausal complaints and use of oral contraceptives (OC). The questionnaire was validated in previous studies[3,24,25,29].

Employment status was assessed by the question: “Are you currently working?” Consumption of alcohol was determined based on the respondent’s declaration of drinking alcohol, not drinking or formerly drinking alcohol. Participants were also categorized in terms of smoking status as current smokers, ex-smokers, and nonsmokers.[3] Blood pressure was measured after a 10-minute rest. The same calibrated mercury manometer attached to a 12.5 x 23 cm inflatable cuff was used in all participants, and the fifth Korotkoff sound was adopted to determine diastolic pressure. Hypertension was defined as systolic blood pressure (SBP) ≥140 or diastolic blood pressure (DBP) ≥90 mmHg or current use of antihypertensive medication.[26,27] Diabetes was determined through self-report, use of anti-diabetic drugs, or fasting blood glucose ≥126mg/dl.[28]

Menopause status was ascertained based on the characteristics of menses or time since amenorrhea: premenopause was defined as usual menstrual frequency or flow at the time of the study, perimenopause was defined as changes in menstrual frequency or flow right before the study, and postmenopause was defined as 12 or more months of amenorrhea occurring

naturally or as a result of surgical interventions such as bilateral oophorectomy.[29,30] A “hysterectomy” category was created for women who had previously undergone hysterectomy and whose menopausal status could not be classified.

Anthropometric measurements were performed in duplicate and included body weight, height, waist circumference (measured at the midpoint between the lower rib margin and the iliac crest, perpendicularly to the long axis of the body, with the participant standing balanced on both feet, spread approximately 20 cm apart, with arms hanging freely), hip circumference (widest circumference over the buttocks), and waist to hip ratio (waist circumference divided by hip circumference).[3,31-33] All procedures followed standardized recommendations[34] and the equipment calibration was periodically verified.

The questionnaire had been previously tested for reliability and reproducibility.[3] Interobserver reliability for anthropometric and blood pressure measurements was verified by repeated measurements during the first set of consultations. Pearson’s correlation coefficients were higher than 0.90 ($P<0.05$).

All participants were submitted to blood sampling in the morning between 8 and 10 a.m. after an overnight fast of 10 to 12 hours. Total cholesterol, HDL-cholesterol, triglyceride, and glucose levels were determined by a colorimetric-enzymatic method (Architect C800, ABBOTT Systems). Low density lipoprotein cholesterol (LDL-c) was determined indirectly using the following formula: LDL-c = total cholesterol - (HDL-c + triglycerides/5).[35] The metabolic syndrome was defined by the presence of at least three of the following components: waist circumference >88 cm, increased LDL-cholesterol; ≥130 mg/dL, low HDL-

cholesterol; <50 mg/dL in women, increased triglycerides (TG); ≥150 mg/dL and glucose ≥100mg/dL.[36]

Habitual PA was assessed with a digital pedometer (BP 148, TechLine, São Paulo, Brazil). The validity and reliability of pedometers has been demonstrated in previous studies[15,20,37-39].

The equipment records the number of steps/day, taken during seven days. Participants were instructed to go about their typical activities, and to remove the pedometer during showering or sleeping and at the end of each day. They also received instructions describing proper pedometer placement (on the belt or waistband) and were asked to record the total number of steps daily on a form.[15,16] The device was configured individually according to the weight (kg) and step length of each participant. Participants were classified as physically inactive (maximum of 5999 steps every day) or active (6000 or more steps per day), based on the classification of Thompson et al.[40] and on a previous study by our group.[15] Participants were encouraged not to alter their PA habits during the study. The sum of the steps was averaged over the total time period worn, i.e., 7 days.

The study protocol was approved by the local ethics committee (institutional review board equivalent). Written informed consent was obtained from all participants.

Statistical analysis

Data were expressed as means (plus or minus standard deviation, SD), median (range) or as percentages. Student's t test for independent samples or the chi-square test were used to analyze the characteristics of the sample

associated with habitual PA. Comparisons between median values were analyzed with Mann-Whitney's U test. Correlations were evaluated with Spearman's test. Logistic regression was used to estimate inactivity related-odds ratios (OR) for cardiovascular risk while controlling for confounder factors such as age, menopause status, smoking, and hormonal therapy. The variables included in the model were chosen according to clinical plausibility. The interaction between each confounding variable and PA status (adjustment) was tested by multivariate logistic regression. Collinearity was estimated for the model using variance inflation factors (VIF) and tolerances for individual variables. No collinearity was found. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 17.0 version; Chicago, IL). Data were considered to be significant at $p<0.05$.

Results

Of the 301 women in the sample, 9 were excluded due to incomplete data in relation to the level of habitual PA (4 had cognitive difficulties, one was illiterate and 4 recorded the number of steps improperly). Thus, a total of 292 women were studied.

Table 1 shows the demographic characteristics of all participants according to the level of habitual PA. The average number of steps/day for the entire group was 5250.73±3372.90, with 3472.43±1570.19 in the inactive group (61.8%) and 9055.90±3033.41 in the active group (31.9%). The number of steps per day was higher on weekdays compared to the weekend ($p<0.001$) and in summer compared to winter, autumn and spring ($p=0.004$) (Figure 1).

Age ranged from 45 to 72 (57.11±5.36) years. Most participants were white (83.9%). Mean age was similar in the inactive and active groups (57.4±5.54 vs. 56.5±4.9 years, respectively; p=0.163). Considering menopause status, 7.2% were premenopausal, 8.6% were perimenopausal, 78.4% were postmenopausal and 5.8 % had undergone hysterectomy. Fifty-one percent of the participants had 8 or less years at school, and 20% of those had 4 years or less. No association was found between habitual PA and marital status (p=0.774), years at school (p=0.339), or employment status (working outside the home) (p=0.264). Smoking was reported by 19.2% of the women and was more frequent in the group of inactive women (p=0.019). Alcohol consumption was reported by 32.9% and there was no association with habitual PA. Hormonal therapy (estrogen, estrogen/progestin or tibolone), used by 18.0% of the participants, was also unrelated to habitual PA level.

Table 2 describes the clinical and metabolic profile of all participants according to habitual PA level. Most of the women were overweight (35.3%) or obese (32.5%) and presented central fat distribution. In the inactive group, 76.8% were obese, vs. 23.1% in the active group (p=0.018). A negative correlation was found between average number of steps per day and waist circumference (WC) (r=-0.200; p=0.001), waist-to-hip ratio (WHR) (r=-0.187; p=0.001), and body mass index (BMI) (r=-0.208, p<0.001) (Figure 2).

Diabetes was diagnosed in 16.8% of participants and was significantly higher in the inactive group as compared to the active group. The prevalence of the metabolic syndrome was higher among inactive women.

Table 3 shows the risk of metabolic comorbidities associated with inactivity, adjusted for age, smoking, menopausal status, and use of HT. The

OR for overweight/obesity (OR=2.113, 95%CI:1.23-3.62, p=0.006), WC (OR=1.76, 95%CI:1.05-2.94, p=0,013), DM (OR=2.786, 95%CI:1.23-6.29, p=0.014), and the metabolic syndrome (OR=2.489, 95%CI:1.44-4.29, p=0.001) was higher in inactive vs. active women. HT was not a predictor for these metabolic comorbidities. When postmenopausal women (n = 229) were analyzed as a subgroup, the risk associated with inactivity (adjusted for age, smoking, and use of HT) was found to be stronger than that of the entire sample (Table 3).

Discussion

In this population-based study, higher levels of habitual PA were associated with a more favorable cardiovascular profile in pre-, peri and postmenopausal women. Our data agree with previous studies, such as the Women's Study[41] and the osteoporosis screening study from Aberdeen, Scotland,[42] which showed that PA decreased weight gain. Additionally, the Women's Health Across the Nation (SWAN) study suggested that regular PA is associated with beneficial changes on body composition and fat distribution in menopausal women.[18] Other studies have also indicated that PA mitigates the appearance of comorbidities such as diabetes[17,43,44] and hypertension.[45,46] However, previous studies have focused on structured PA. To our knowledge, this is the first study to assess the impact of habitual, non-structured PA on women categorized according to menopausal status.

Most of the women in our study (68%) were categorized as inactive, that is, they walked fewer than 6000 steps/day.[15,20,40] Other investigators employ additional step-count cutoff points to define PA, stratifying individuals as "low

active," "somewhat active," or "highly active."[39,47-49] Our findings show that walking 6000 or more steps/day brings significant health benefits for women between 40 and 70 years of age, including lower BMI, less central adiposity, and lower prevalence of cardiovascular risk factors such as diabetes and metabolic syndrome.

While previous studies have found a decrease of PA in older populations,[50,51] in the present study the frequency of inactivity was not associated with age and menopause status. The same was true for years at school, a variable related to PA in some studies,[50,52,53] but not in others.[54] It has been argued that a higher educational level may raise awareness of health benefits, increasing and improving adherence to habitual PA,[50] but this was not the case in the present sample. Interestingly, PA level was not associated with ethnicity, working outside the home, alcohol intake, marital status, or HT use, perhaps as a reflection of the homogenous nature of this sample of women from a mid-sized South Brazilian city.

Only smoking was related to inactivity. This association has been reported in many previous studies,[51,53-56] and could indicate a lower health consciousness of smokers.[53] Also, as previously stated, smoking imposes physical difficulties to the practice of exercise, such as shortness of breath and reduced respiratory capacity.

Active women, independent of menopausal status, presented lower BMI and central adiposity. Other studies have investigated the relationship between PA and anthropometric measures, showing that a higher number of steps/day translated into a more favorable body composition, including lower % body fat, BMI, WC and WHR.[15,18,20,40,47,57,58] The Women on the Move Through Activity

and Nutrition (WOMAN) study demonstrated an improvement in physical function stemming from increased leisure time PA and reduction in body weight, BMI, and body fat.[59] Furthermore, in the present study, adverse anthropometric measures and metabolic comorbidities were significantly related to low PA level when controlled for age, smoking, HT and menopausal status. This confirms a previous proposition suggesting that increased abdominal fat seems to follow inactivity.[60]

Menopause transition and post-menopause are known to be associated not only with increasing BMI and abdominal obesity,[3] but also with a worse cardiovascular risk profile and development of the metabolic syndrome.[2,61] Evidence suggests that moderate to vigorous PA is associated with decreased risk of developing the metabolic syndrome,[62] independent of obesity[63] and that a higher number of steps is likely associated with a lower prevalence of the metabolic syndrome and its individual CVD risk factors.[64] Together with the findings of previous studies, our results suggest an inverse association between habitual PA and establishment of the metabolic syndrome, which applies particularly to women. In the present study, the most prevalent components of the metabolic syndrome were waist circumference and glucose level.

No differences were found in lipid-lipoprotein profile and resting blood pressure between physically inactive and active participants. This may be due to the relatively healthy status of this population, with normal or borderline values for blood pressure and lipids. In addition, both the intensity of physical activity and the amount of energy intake and expenditure seem to be essential to determine whether or not favorable changes in lipid profile will be induced.[65,66] The lack of information on dietary intake is, thus, a limitation to be considered. In this

sense, further studies are needed in order to assess the influence of the dietary pattern on the metabolic profile of inactive and active women.

Despite the advantages of using a pedometer to capture unstructured and low-intensity PA, this method has limitations that need to be considered. First, pedometers cannot be used in water activities. Also, PA is a complex behavior that could be measured using other strategies (energetic expenditure, resistance training). In addition, many pedometers, such as that used in the current study, lack a self-recording mechanism, and thus we depended on the accuracy of participants to record their step counts from the pedometer.

Conclusion

The present results show that habitual PA, specifically walking 6000 or more steps daily, is associated with a decrease in cardiovascular risk and diabetes in middle-age woman, independently of menopausal status. Because of the high and increasing prevalence of these comorbidities in women, and of the impact of these pathologies in terms of health expenditure, habitual PA should be considered as a major strategy for disease prevention.

Ethical Standards

This experiment complies with the current Brazilians laws applicable to research studies.

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Table 1. Demographic characteristics of pre-, peri- and post-menopausal southern Brazilian women stratified by level of habitual physical activity

Variable	All participants n=292	Inactive (<6000 steps) n=199 (68.1%)	Active (≥6000 steps) n=93 (31.9%)	p
Age (years)	57.11±5.36	57.40±5.54	56.49±4.93	0.16[a]
45-54	35.5 (107)	68.6 (72)	31.4 (33)	0.334[b]
55-64	53.2 (160)	65.6 (101)	34.4 (53)	
65-72	11.3 (34)	78.8 (26)	21.2 (07)	
White skin color				0.616[b]
Yes	83.9 (245)	67.3 (165)	32.7 (34)	
No	16.1 (47)	72.3 (80)	27.7 (13)	
Years at school	8.74±4.48	8.57±4.43	9.11±4.59	0.339[a]
0-4	19.9 (58)	70.7 (41)	29.3 (17)	0.56[b]
5-8	31.2 (91)	70.3 (64)	29.7 (27)	
9-11	29.1 (85)	69.4 (59)	30.6 (26)	
≥12	19.9 (58)	60.3 (35)	39.7 (23)	
Employment				0.264[b]
Yes	44.2 (129)	64.3 (83)	35.7 (46)	
No	55.8 (163)	71.2 (116)	28.8 (47)	
Hormonal therapy				0.735[b]
Yes	18.0 (48)	64.6 (31)	35.4 (17)	
No	82.0 (244)	68.9 (168)	31.1 (76)	
Menopausal status				0.792[b]
Premenopause	7.2 (21)	71.4 (15)	28.6 (6)	

Perimenopause	8.6 (25)	60.0 (15)	40.0 (10)	
Postmenopause	78.4 (229)	69.0 (158)	31.0 (71)	
Hysterectomy	5.8 (17)	64.7 (11)	35.3 (06)	
Marital status				0.774[b]
Married	51.4 (150)	66.0 (99)	34.0 (51)	
Single	17.5 (51)	68.6 (35)	31.4 (16)	
Widowed	14.7 (43)	74.4 (32)	25.6 (11)	
Divorced	16.4 (48)	68.7 (33)	31.3 (15)	
Alcohol intake				0.103[b]
Drinker	32.9 (96)	64.6 (62)	35.4 (34)	
Former drinker	6.5 (19)	89.5 (17)	10.5 (2)	
Non-drinker	60.6 (177)	67.8 (120)	32.2 (57)	
Smoker				0.019[b]
Current smoker	19.2 (56)	71.4 (40)	28.6 (16)	
Ex-smoker	22.9 (67)	80.6 (54)	19.4 (13)	
Non-smoker	57.9 (169)	62.1 (105)	37.9 (64)	

Values are mean ± standard deviation, or percentage % (n). [a] Independent t Student's test. [b] Chi-square.

Table 2. Anthropometric and metabolic characteristics of pre-, peri- and post-menopausal South Brazilian women stratified by level of habitual physical activity

Variable	All participants n=292	Inactive (<6000 steps) n=199 (68.1%)	Active (≥6000 steps) n=93 (31.9%)	p
BMI (kg/m^2)	28.34±7.07	29.43±6.77	27.18±5.64	0.006[a]
≤24.9	31.5 (92)	57.6 (53)	42.4 (39)	0.018[b]
25.0-29.9	35.3 (103)	68.9 (71)	31.1 (32)	
≥30.0	32.5 (95)	76.8 (73)	23.1 (22)	
Waist circumference (cm)	91.37±13.71	92.73±13.62	88.45±13.54	0.013[a]
≥88 cm	55.8 (163)	73.00 (119)	27.0 (44)	0.061[b]
Waist-to-hip ratio	0.87±0.08	0.88±0.07	0.86±0.09	0.172[a]
≥0.85	62.7 (183)	72.7 (133)	27.3 (50)	0.043[b]
Hypertension (yes)	58.6 (171)	71.9 (123)	28.1 (48)	0.128[b]
SBP mean (mmHg)	131.47±18.83	132.57±18.42	129.13±19.56	0.148[a]
DBP mean (mmHg)	84.51±12.65	85.17±11.84	83.09±14.19	0.190[a]
Diabetes (yes)	16.8 (49)	83.6 (41)	16.3(8)	0.01[b]
≥100 mg/dL (yes)	20.7 (60)	83.3 (50)	16.7 (10)	0.004[b]
Glucose (mg/dL)	95.41±31.31	98.73±36.49	88.36±12.96	0.018[c]
Total cholesterol (mg/dL)	209.86±44.27	208.96±43.89	211.79±45.24	0.614[a]

HDL cholesterol (mg/dL)	53.51±13.34	53.39±13.88	53.75±12.17	0.781[c]
LDL cholesterol (mg/dL)	127.61±38.82	124.63±36.64	133.82±42.54	0.060[a]
Triglycerides (mg/dL)	135.5 (100.7-193.5)	139.0 (105.0-196.5)	133.0(92.0-168.5)	0.169[c]
Metabolic syndrome	40.7 (119)	78.1 (94)	21.9 (25)	0.002[b]

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Diabetes: previous or glycemia ≥126 mg/dL, Hypertension: blood pressure ≥140/90 mmHg or use of antihypertensive. Values are mean ± standard deviation, median (range) or percentage % (n).

[a] Independent t Student's Test.

[b] Chi-square.

[c] Mann-Whitney U test.

Table 3. Odds ratio for metabolic comorbidities in inactive vs. active women

Variable	OR (95%CI) All participants (n=292)	p[a]	OR (95%CI) Postmenopausal participants (n=229)	p[b]
Hypertension (yes)	1.43 (0.86 to 2.39)	0.166	1.14 (0.782 to 2.499)	0.258
Diabetes (yes)	2.78 (1.23 to 6.29)	0.014	3.07 (1.21 to 7.74)	0.017
Overweight/obesity	2.11 (1.23 to 3.62)	0.006	2.05 (1.115 to 3.798)	0.021
WC ≥88	1.76 (1.05 to 2.94)	0.031	2.26 (1.252 to 4.080)	0.007
WHR ≥ 0.85	1.69 (1.01 to 2.83)	0.043	2.293 (1.27 to 4.14)	0.006
Metabolic syndrome (yes)	2.48 (1.44 to 4.29)	0.001	2.57 (1.379 to 4.815)	0.003

95%CI: 95% confidence interval; WC: waist circumference; WHR: waist-to-hip ratio.

OR: odds ratio; logistic regression.

[a] Values adjusted for age, smoke, hormonal therapy and menopausal status.

[b] Values adjusted for age, smoking and hormonal therapy.

Figure 1. Number of steps per day according to weekday and season in a sample of South Brazilian women. (n=292).

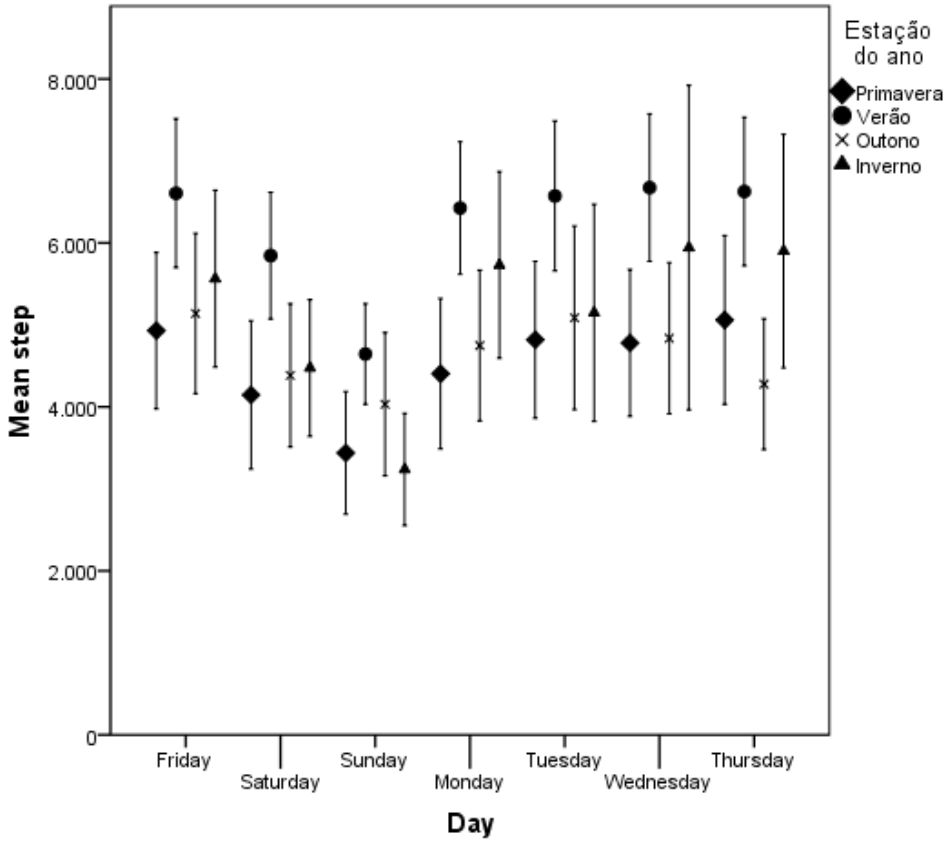
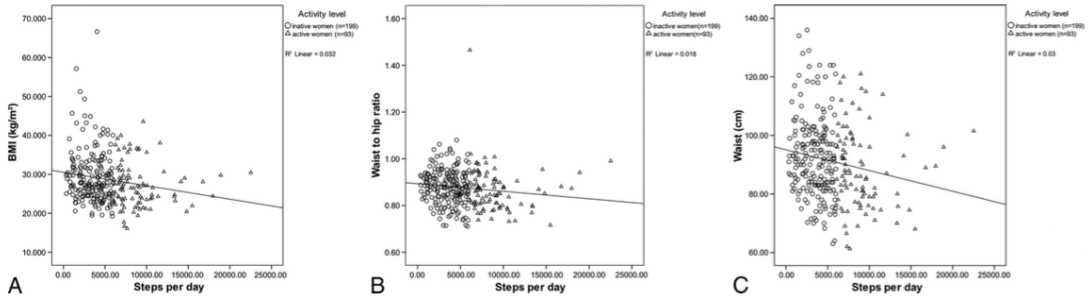


Figure 2. Correlation between habitual physical activity (number of steps/day) and body mass index (kg/m^2) (A), waist to hip ratio (B) and waist circumference (C). Pearson's correlation: r = -0.20; P=0.001 (n inactive = 199, n active = 93).



Artigo original 3

Causes of death and associated risk factors among climacteric women from Southern Brazil: a population based-study.

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Causes of death and associated risk factors among climacteric women from Southern Brazil: a population based-study

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Abstract

Background: Aging and menopause are particular cardiovascular risk factors for women, due to estrogen deprivation at the time of menopause. In addition, studies show that diabetes mellitus (DM), smoking, hypertension, high body mass index (BMI), and serum lipids are associated with increased risk of cardiovascular disease (CVD), the main cause of female mortality in Brazil. Therefore, the aim of this study was to assess the mortality rate, causes of death, and associated risk factors in a cohort of climacteric women from Brazil.

Methods: A longitudinal population-based study of menopausal status is currently underway in the city of Passo Fundo, a city in South Brazil. In 2010, a third follow-up of this population was performed to assess cardiovascular risk and mortality rate for the period between 1995 and 2011. For this analysis, 358 participants were studied. At baseline, participants had completed a standardized questionnaire including demographic, lifestyle, medical and reproductive characteristics. In addition to the contacts with patients or families, mortality data were obtained through review of medical records in all city hospitals and the Center for Health Information (NIS/RS-SES). Deaths were classified according to the ICD-10. Multivariate-adjusted hazard risk (HR) and 95% confidence intervals (CI95%) were estimated using Cox proportional hazards regression. Survival curves were estimated using the Kaplan-Meier curve.

Results: There were 17 (4.7%) deaths from all causes during the study period. Seven (41.2%) deaths were caused by CVD, including four cases of stroke and three cases of myocardial infarction. Six (35.3%) deaths were due to cancer, and four (23.5%) were due to other reasons. In the age and smoking-adjusted

multivariate models, diabetes (HR 6.65, 95%CI: 1.94–22.79, p = 0.003) and alcohol intake (HR 1.23, 95%CI: 1.01-1.49, p = 0.035) were associated with all-cause mortality. A significant association was found between abdominal obesity (WHR≥0.85) and mortality (HR = 2.97, 95%CI: 1.04 – 8.50, p = 0.042).

Conclusion: CVD was the main cause of mortality in this cohort. DM and/or central adiposity were strongly associated with all-cause mortality. Lifestyle and dietary factors seem to be related to risk of mortality in middle-aged women.

Keywords: menopause, mortality, risk factors

Background

Life expectancy is increasing in the world as well as in Brazil, where recent data from the National Geography and Statistics Institute [1] show that females and males are now expected to reach 77.3 and 69.7 years of age respectively, as compared to 72.9 and 65.1 years only a decade ago. This population aging process will have an impact on health and social policies. However, only a few studies are available about middle-aged female mortality, especially in Brazil [2, 3], where a vast territory and socioeconomic diversity contribute to a scenario of public health inequity. Cultural and economic differences may influence diet, health, and behavioral factors and consequently mortality rates. Thus, knowledge of the pattern of mortality risk is useful to support actions of prevention and control.

Aging and menopause may be considered as particular cardiovascular risk factors for women, due to estrogen deprivation at the time of menopause [4]. Also, studies have consistently shown that diabetes mellitus (DM) [5, 6], smoking [7, 8], hypertension [9, 10], high body mass index (BMI) [11-13] and serum lipids [14] are associated with increased CVD risk. Therefore, even though CVD mortality has decreased in recent decades [15, 16] following improvements in prevention, diagnosis, and timing of treatment [17], along with gradual improvement in economic conditions, more widespread access to drugs [18], heath surveillance, and policies of health promotion [15], CVD remains a major cause of death [15], and the main cause of female mortality in Brazil [15, 17, 19].

Based on these data, and on the scarcity of literature about this subject, the present study aims to assess mortality, CVD risk factors and causes of

death in a cohort of pre-, peri- and postmenopausal women in the South of Brazil.

Methods

Study population

Participants were selected from the population-based cohort of the longitudinal menopause study that has been underway in the city of Passo Fundo, South Brazil, since 1995 [20, 21]. As part of this project, an initial cross-sectional study was performed between 1995 and 1997 to investigate the prevalence of climacteric symptoms among pre- and perimenopausal women.

The sample size calculation was carried out using the Epi Info software , based on a population of 16.958 women aged 35-55 years. It was estimated that 20% of women would show classic climacteric symptoms, accepting an error of 15%. Due to the occurrence of potential losses, additional 10% was added, resulting in a calculated sample of 318.

Sampling was carried out in two stages. First, 154 census sections (geographical subdivisions of the city defined by the Brazilian Institute of Geography and Statistics) were randomly selected. One block in each census section was picked by lot; two women were interviewed in each block after the randomization method described previously [20, 21]. Briefly, one block was turned clockwise (and the other, counterclockwise) from a raffled corner (A,B,C or D), and the houses were visited. If there was a woman who lived there in the ages 35 to 55, she was invited to participate in the study. Then, two houses were skipped and the process was repeated.

In the first segment 302 women were randomicaly selected to participate in the study. Only 4 gave up because of personal decision, not related to medical conditions. Therefore, a representative sample of 298 women aged 35 to 55 years who had menstruated at least once in the past 12 months was randomly selected by through multistage technique.

In the second segment, 59 among the participants of the first segment were lost. We considered losses if the women could not be found and when there was a negative answer after 3 essays to continue to participate. The losses were: refuse (n=19, 6.4%), domicile adress change (n= 21, 7%), change of residence city (n=15=5%) and death (n=4, 1.3%). In view of potential losses to follow-up and of the increasing city population, 119 additional women aged 35 to 62 years were sampled to guarantee enough statistical power for the analysis. There was no statisticaly differences on age, age of menarche, blood pressure, BMI, climacteric symptoms, and educational level between the 59 lost women and the 358 cohort participants.

The final sample was 358 women. The sample was selected at random based on the first census sections, and two women were interviewed in each block. They were interviewed at home, using validated pre-tested questionnaires, as previously reported [21] [22] [23] [24]; (Figure 1).

Mortality, causes of death, and CVD risk factors

In 2010, a third follow-up was initiated in order to assess cardiovascular risk and mortality rate. All 358 participants or their relatives were reached, and information regarding participant deaths was obtained for the period ending in November 2011. In addition to the interviews, the medical records of city

hospitals and the Center for Health Information (NIS/RS-SES) were reviewed. All deaths between 1995 and 2011 were included in this analysis.

Medical records were reviewed to collect information on age at death, date, and cause of death. The causes of death were coded using the International Classification of Diseases, 10th revision [25]. Deaths were analyzed for all-cause and cardiovascular causes (ICD-10: I00-I99), neoplasms (ICD-10: C00-C97), and respiratory causes (ICD-10: J00-J99).

Ethics approval for the study was granted by the Research Ethics Committees at the University of Passo Fundo and the São Vicente de Paulo Hospital. All study participants signed an informed consent.

Social characteristics

The participants were interviewed using a pretested standardized questionnaire covering demographic characteristics (age and self-reported race) and education (years of successful formal education, described as years at school). Skin color was classified according to self-report [21, 22]. Women were classified in terms of alcohol consumption as nondrinkers, social drinkers (1 to 15 g alcohol/day), or abusers (at least 15 g alcohol/day) [24]. Smoking status was categorized as current, ex-smoker, or nonsmoker [22]. Physical activity was investigated through a previously tested standardized questionnaire [23]; for each type of physical activity, the metabolic equivalent [26] and overall calorie expenditure were calculated. Women who expended at least 1000 kcal/week (approximately 3.5 hours per week walking, climbing stairs, swimming, playing sports, doing yard work, and so forth) were considered to be physically active, whereas the others were classified as sedentary [22].

Women were classified according to their baseline menopausal status: premenopause was defined as no change in menstrual frequency or flow; perimenopause was defined as changes in menstrual frequency or flow in the 12 months before the study; and postmenopause was defined as 12 months or more of amenorrhea, including as a result of medical interventions such as bilateral oophorectomy [21, 22]. A “hysterectomy” category was created for women who had undergone hysterectomy and whose menopausal status could not be classified [27].

The use of hormone therapy (HT), estrogen, estrogen plus progestogen or tibolone was verified by asking the women to show the medication box or the physician’s prescription [21, 22].

Anthropometric measurements

Body weight and height was assessed at the beginning of the study in 1995. Weight (kg) was measured to the nearest 100 g using a Filizola® scale, Model 31 (Ind Filizola-SA, São Paulo, Brazil), and height (cm) was measured to the nearest 0.1 cm with a wall-mounted fixed stadiometer. Special attention was taken to ensure that the participants were positioned with the Frankfort plane [28] horizontal and that they were barefoot. These were used to calculate BMI, dividing weight in kilograms by height squared (m^2), and categorized as <25.0, 25.0–29.9, and ≥30.0 kg/m^2 [29].

Other anthropometric measurements were made in duplicate between 2001 and 2003, including waist circumference (WC) (measured at the midpoint between the lower rib margin and the iliac crest, perpendicularly to the long axis of the body, with the participant standing balanced on both feet, spread

approximately 20 cm apart, with arms hanging freely), hip circumference (widest circumference over the buttocks), and waist to hip ratio (WHR) (waist circumference divided by hip circumference) [21, 22, 28]. All procedures followed standardized recommendations [30] and the equipment was periodically calibrated.

Clinical variables

Previous diagnosis of DM was verified based on physician report or current use of anti-diabetic medication. Self-report of hypercholesterolemia or use of anti-cholesterol medication was used to define dyslipidemia.

Blood pressure was measured after a 10-minute rest. The same calibrated mercury manometer attached to a 12.5 x 23 cm inflatable cuff was used in all participants, and the fifth Korotkoff sound was adopted to determine diastolic pressure. Hypertension was defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication [31, 32].

All participants were submitted, in 2003, to blood sampling between 8 and 10 a.m. after an overnight fast of 10 to 12 hours. Total cholesterol, high-density cholesterol (HDL-c), triglycerides, and glucose levels were determined by a colorimetric-enzymatic method (Architect C800, ABBOTT Systems). Low density lipoprotein cholesterol (LDL-c) was determined indirectly using the following formula: LDL-c = total cholesterol - (HDL-c + triglycerides/5) [33, 34].

Statistical Analyses

Continuous variables are reported as means ± SDs. Categorical variables are reported as frequencies (%). Differences in baseline clinical characteristics between groups were analyzed by the Student *t* test (for continuous variables with normal distribution), Mann-Whitney's U test (for continuous variables with skewed distribution), or χ^2 test (for categorical variables). Survival time for each participant was defined as the time between the date of study entry and the occurrence of death. Univariate predictors of mortality during follow-up were analyzed by Cox regression models and calculation of hazard rate ratios with 95%CI. For the estimation of hazard ratios, a Cox regression model was fit including relevant independent variables to estimate the associations between baseline characteristics and mortality. Multivariate analysis included only variables with a p-value of 0.05 or lower on univariate analysis. Adjusted hazard ratios (HR) and 95% confidence intervals (CI95%) for mortality were estimated with Cox proportional-hazards model. The model was adjusted for age and smoking. The final model included all variables with $P < 0.05$ or according to clinical plausibility. Collinearity for the model variables was evaluated using variance inflation factors and tolerances. No collinearity was found. Survival curves were estimated using the Kaplan-Meyer method. Log-rank p-values were calculated to test for significant differences between mortality and DM. All statistics analyses were performed using SPSS 20.0 software. $P < 0.05$ was considered statistically significant for all analyses.

Results

Baseline characteristics

A total of 358 women were studied during a mean follow-up of 13.4 ± 3.3

years. Table 1 shows the distribution of baseline characteristics in survivors and non-survivors. The mean age of the overall sample was 44.29 ± 6.0 years. Most participants were white (86.3%), with low levels of schooling (8.4 ± 4.7years). Considering menopause status, 162 (47.1%) were premenopausal, 134 (39%) were perimenopausal, 37 (10.3%) were postmenopausal, and 11 (3.2%) had undergone a hysterectomy. Of the 358 individuals included in the study, 177 (49.4%) reported having hypertension; 56 (15.6%) used HT, and 14 (3.9%) were diabetic. Smoking, a well-known risk factor for CVD, was found in 96 (26.8%) of the overall sample, and in 8 (47.1%) deceased patients. Survivors were significantly younger and almost half were premenopausal. They also had higher education level and fewer cases of previous DM. Age at menopause was available in the second follow-up, in 2001, and did not differ between survivors and non-survivor groups (47.52 ± 6.33 versus 45.53± 4.99 years, p=0.116, respectively).

Table 2 describes the metabolic profile of participants. In general, they had low level of physical activity during their leisure time and showed baseline overweight and central adiposity. A relatively healthy lipid profile was observed, with normal or borderline values. WHR and HDL-c were significantly different in survivors and non-survivors.

Causes of death

The mean age at death was 57.8 ± 5.5 years. In the 13 years analyzed, 17 (4.7%), deaths from all causes were recorded. Among these, seven (41.2%) deaths were caused by CVD, including four cases of stroke and three myocardial infarctions. There were six (35.3%) deaths due to kidney (n = 1),

breast (n = 1), lung (n = 2) and uterine (n = 2) cancer, and four (23.5%) deaths due to other reasons, such as polytrauma, asthma, and diabetes. Concerning non-survivors, 7 women had previous hysterectomy and 2 of them were associated to cancer as death cause. The others 5 were submitted to hysterectomy due to benign causes, not directly related to death.

Survival estimates

The survival for the entire cohort in 6, 12 and 15 years was 98.6%, 96.8% and 94.3%, respectively (Figure 2).

In a univariate analysis (table 3), older age (HR = 1.14, 95%IC:1.05-1.24, p = 0.002), WHR **≥** 0.85 (HR = 3.63, 95%CI:1.28-10.30, p = 0.015), DM (HR = 10.44, 95%CI: 3.37– 32.37, p < 0.001), and menopausal status (postmenopause HR = 16.74, 95%CI:3.64-77.43, p<0.001; hysterectomy HR = 11.80, 95%CI:1.15-122.22, p = 0.038) were associated with a major probability of death. Years at school was statistically meaningful in the univariate model (HR = 0.89, 95%CI: 0.79-0.99, p = 0.044), suggesting a protective association of higher level of education.

Table 4 presents the results of multivariate analysis for mortality hazard ratio resulting from the Cox regression model, taking into account the confounding factors (age and smoking). Previous diagnosis of DM and WHR **≥** 0.85 remained the leading risk factors for all-cause mortality, similar to those found in the crude analysis and increasing the risk of death. Diabetic women had higher HR for mortality (HR = 6.65, 95%CI: 1.94-22.79, p = 0.003). There was a trend for postmenopausal status to be associated with the risk of death (HR = 6.22, IC: 0.96–40.14, p = 0.055). Alcohol intake ≥ 10g was an

independent risk factor for mortality (HR = 1.23, 95%CI: 1.01-1.49, p = 0.035). The magnitude of the association between abdominal obesity (WHR ≥ 0.85) and mortality was 3 times (HR = 2.97, 95%CI: 1.04 – 8.50, p = 0.042).

Figure 3 shows Kaplan-Meier curves for DM diagnosis. The results support the findings of the adjusted model, according to which mortality is increased in the presence of diabetes.

Discussion

To the best of our knowledge, this is the first Brazilian population-based study evaluating survival and causes of death in pre-, peri- and postmenopausal women. This prospective follow-up study including women in their middle age indicates that CVD was the main cause of mortality. In addition, postmenopausal status, DM, and central adiposity were associated with increased risk of mortality, independently of age and smoking. The present results support the findings of two previous studies investigating Brazilian postmenopausal women aged 60 to 80 years [2,3].

Coronary heart disease is the leading cause of death in women aged 60 years or older [35]. In Brazil, diseases of the circulatory system are a significant cause of mortality [19]. A study by Schmitt et al. [36] underscores that, between 1979 and 2004, cardiovascular diseases, neoplasms, and ill-defined causes were the main causes of death in women in Brazil; these results are similar to those observed in the present study. Therefore, despite the small number of deaths (4.7%), our study supports data from previous studies, sustaining the notion that CVD are the main cause of death in women in Brazil [15, 17, 19].

There was an increased risk of mortality in women with DM, a recognized

clinical condition associated with risk for cardiovascular mortality [6, 37, 38]. The association between DM and CVD has been suggested to be stronger in women than in men [6, 37, 39]. Cardiovascular mortality is 3 to 5 times higher in diabetic compared to non-diabetic women, and 2 to 3 times higher in diabetic vs. non-diabetic men [40]. A relatively larger mortality for women with DM compared with those with prior CVD would suggest insufficient attention to CVD prevention in these women [39]. It has been suggested that physicians have a less aggressive management of CVD in women that in men, despite the greater cardiac disability in women [41]. Gender disparities are also evident both in the clinical presentation as well as misperceptions and barriers to preventive strategies [42].

It has also been suggested that diabetic women have accelerated atherogenesis. This process is not completely understood, but it is at least in part related to more severe lipid and lipoprotein abnormalities, particularly elevated levels of triglycerides and reduced levels of HDL-c, among diabetic women [43, 44]. Increased levels of endothelin-1 associated with atherogenesis induce smooth muscle hypertrophy, stimulate vasoconstriction, and activate the renin-angiotensin system. Simultaneously, reduced prostacyclin and nitric oxide activity enhances platelet aggregation and adhesiveness, leading to endothelial dysfunction. These facts may contribute to the poorer outcomes in DM [45, 46].

Concerning the relationship between BMI and mortality, an association between these aspects is widely accepted [12, 47-49]. Even though this association was not identified in the present study, BMI is believed to be a surrogate measure of general adiposity. However, BMI measures do not distinguish between fat mass and lean mass [50]. Furthermore, changes in

lifestyle patterns, such as reduction of calorie intake and increased physical activity, reduce body fat and increase muscle mass. Individuals within the overweight category may be fit and muscular rather than having excess fat [51], and a U-shaped relationship has been described, with increased mortality only at the extremes of underweight and BMI > 45 kg m [49-51]. In addition to this, data from the MacArthur Successful Aging Study suggest that WHR is the most suitable measure for risk stratification of high functioning, especially in older adults [52]. All these aspects reinforce our findings that measures of central adiposity are a good indicator of mortality rates.

The influence of HT on the risk of mortality still needs to be appropriately defined. In our study, univariate analysis showed a trend toward higher mortality among HT users, and age probably had an effect on this group. HT is considered a Class III intervention and is not effective for secondary CVD prevention in postmenopausal women [53, 54]. The results from the Women's Health Initiative study, the Heart and Estrogen/Progestin Replacement Study, and the Women's Estrogen for Stroke Trial indicate that the use of estrogen alone or estrogen plus progestin does not prevent, and could actually increase, the risk of CVD in older postmenopausal women or in those with established CV disease [54-58]. Conversely, in women younger than 60 years and within 10 years of menopause, estrogen therapy has been associated with decreasing risk of mortality [59]. In the present study, we found a borderline significance for postmenopausal status as a risk factor for all-cause mortality. However, the low number of women in post-menopause may have hindered an adequate statistical power to detect differences. This result, therefore, needs independent confirmation and should be interpreted with caution.

Menopausal status is an important modifier factor in female mortality [60]. Previous analyses show an association of central adiposity with postmenopausal status [22, 61]. Also, when the risks of inactivity were assessed for DM, metabolic syndrome, and hypertension, stronger risk has been detected for post- compared to pre- and perimenopausal women [27]. Postmenopausal women are more prone to central adiposity [62] and development of occult DM than premenopausal individuals [60], and these risk factors are deeply linked to CVD and consequently to mortality.

Interestingly, in the present study, hysterectomy with ovarian conservation was associated with risk for death, that was dependent of age. These results are in agreement with previous studies that reported no association [63] or slight association with mortality, which attenuates with age and could reflect an acceleration of ovarian failure[64].

Even without presenting a significant HR for death in the crude model, alcohol is a recognized risk factor linked to mortality. This was observed in the present adjusted model. A study with data from the Nurses' Health Study demonstrates that small to moderate alcohol ingestion is related to lower mortality [10]. In a meta-analysis, a J-shaped relation was observed between mortality and alcohol intake; and this inverse association rather disappeared in women drinking lower doses than men [65]. In the present study, we found a greater risk of mortality in drinkers. This may reflect the fact that alcohol intake increases the relative risk of death in the presence of other pathologies, such as breast cancer [66].

Moreover, our study suggests that women who had more years in school had a reduction in the risk of death, as previously reported [67]. This association

may be explained by the fact that women with more years in school usually seek health care, have more knowledge of prevention and thus their disease may be detected at an earlier phase with more successful outcomes. However, this difference lost significance in the multivariate analysis, probably because of the lower number of events among these women, limiting the statistical power of the analysis.

Strengths of this study are the use of a population-based cohort and a long follow-up period. Moreover, this study had a carefully data collection and adds to the literature, given the lack of information about the causes of mortality and cardiovascular risk factors during menopause in Brazil. Conversely, limitations include the lack of information on duration and treatment of DM and hypertension. Our analyses focus on leisure physical activity because it was the only category of physical activity measure in our 2001-2003 follow-up. This may have led to an underestimation of the level of physical activity, with misclassification (participants who were active in other types of physical activity could have a higher metabolic equivalent (MET) than that which was calculated and this would influence mortality). It is important to highlight that our sample is composed of relatively young women, which explains the low number of events (death). This may be related to the health status of this population in the baseline. In addition, because of the lower number of deaths among these women, CIs were wide for some variables. However, when data were adjusted for age and smoking, 95%CI values became lower, showing the influence of age on the other risk factors for all-cause mortality.

Our results should be viewed as hypothesis generating and will require further evaluation in other studies. Equally, longer follow-up of these women is

needed to better understand the influence of risk factors on the cardiovascular mortality in the Brazilian women population.

Conclusions

The present results indicate that CVD was the main cause of mortality in this cohort, and that DM and/or central adiposity were strongly associated with all-cause mortality in middle-aged women from South Brazil. Lifestyle and dietary factors seem to be related to risk of mortality in middle-aged women.

Abbreviations

BMI: Body mass index; CI: Confidence interval; CNCD: chronic non communicable diseases; CVD: Cardiovascular disease; DM: Diabetes mellitus; GLU: levels of plasma glucose; HR: Hazard ratio; HDL-c: high-density lipoprotein; cholesterol; HT: Hormonal therapy; LDL-c: light-density lipoprotein cholesterol; LPA: Leisure physical activity in the last year; MET: metabolic equivalent; TC: plasma total cholesterol; TG: Triglycerides; WHR: waist-to-hip ratio; WC: waist circumference.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

VC, KO and PMS were involved in the conception and design of the study, data collection and analysis, and drafted the article. All the authors read and approved the final manuscript.

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Table 1. Demographic characteristics of participants at baseline

Characteristic	Overall group (n=358)	Survivors (n=341)	Non-survivors (n=17)	p[a]
Age (years)	44.29 ± 6.01	44.13 ± 6.01	48.00 ± 4.48	0.009
White skin color (yes)	86.3	87.0	76.5	0.263
Educational level (years)	8.44 ± 4.77	8.55 ±4.73	6.29 ± 5.21	0.062
0-4	24.6	22.9	52.9	0.046
5-8	28.5	29.1	17.6	
9-11	21.5	21.8	17.6	
≥12	25.4	26.2	11.8	
Menopausal status				
Premenopause	47.1	48.2	23.5	0.040
Perimenopause	39.0	38.8	41.2	
Postmenopause	10.3	9.8	29.4	
Hysterectomy	3.2	3.1	5.9	
Smoker (yes)	26.8	26.0	47.1	0.055
Alcohol intake (g)	0.18(0-1.78)	0.21(0-1.82)	0.08 (0-0.57)	0.213
Nondrinkers	29.3	28.5	41.2	0.480
Social drinkers	66.5	67.4	52.9	
Abusers	4.2	4.1	5.9	
Hypertension (yes)	49.4	49.3	52.9	0.767
Diabetes (yes)	3.9	2.9	23.5	<0.001
Dyslipidemia (yes)	6.7	6.5	11.8	0.395

Hormonal therapy	15.6	15.0	29.4	0.109

[a]Continuous variables were compared using the Student's t-test and expressed as means ± standard deviation. Categorical variables were compared using Pearson's chi-square test and expressed as percentage. Abusers: alcohol intake ≥15 g/day.

Table 2. Anthropometric and metabolic characteristics of participants at baseline

Characteristic	Overall group (n=358)	Survivors (n=341)	Non-survivors (n=17)	p[a]
LPA (MET) [c]	5.68 (0-13.85)	5.60(0-13.40)	7.41(1.6-17.92)	0.482
≥2000 cal/sem	7.5	7.4	11.8	0.051
1000-1999 cal/sem	16.2	15.9	23.5	
<1000 cal/sem	76.3	76.8	64.7	
BMI (kg/m2) [b]	27.35 ± 5.46	27.39 ± 5.55	26.60 ± 3.11	0.343
≤ 24.9	37.7	38.4	23.5	0.968
25-29.9	35.8	34.3	64.7	
≥ 30.0	26.5	27.3	11.8	
WHR (cm) [c]	0.83 ± 0.075	0.83 ± 0.072	0.90 ± 0.09	<0.001
≥ 0.85	43.0	41.3	76.5	0.004
WC (cm) [c]	85.28 ± 12.25	85.11 ± 12.35	88.73 ± 9.66	0.235
≥ 88	38.3	37.6	47.1	0.445
TC (mg/dl) [c]	200.01 ± 41.64	200.70 ± 40.03	198.0 ± 47.68	0.794
≥ 200	48.0	47.8	50.0	0.872
HDL-c (mg/dl) [c]	52.45 ± 10.91	52.35 ± 10.54	57.68 ± 9.97	0.049
<50	40.7	41.3	25.0	0.190
LDL-c (mg/dl) [c]	122.11 ± 35.89	119.95 ± 39.34	114.50 ± 41.18	0.386
≥ 160	14.9	14.6	12.5	0.783
TG (mg/dl) [c]	114.0(79.25-157.5)	114.0(79.25-	116.5(73.25-	0.886

		159.75)	150.5)	
≥ 150	27.4	27.5	23.5	0.716
GLU(mg/dL) [c]	79.0(71.0-86.0)	79.0 (70.25-86.0)	81.0(72.5-93.5)	0.258
≥ 126	4.5	4.1	12.5	0.114

[a]Continuous variables were compared using the Student's t-test and Mann-Whitney's U test and expressed as means ± standard deviation. Categorical variables were compared using Pearson's chi-square test and expressed as percentage. [b]Data from baseline. [c]Data from 2003 interviews. BMI: body mass index; GLU: levels of plasma glucose; HDL-c: high-density lipoprotein cholesterol; LDL-c: light-density lipoprotein cholesterol; LPA: leisure physical activity in the previous year; MET: metabolic equivalent; TC: plasma total cholesterol; TG: triglycerides; WC: waist circumference; WHR: waist-to-hip ratio.

Table 3. Crude mortality hazard ratio (HR) and 95% confidence intervals (95%CI) for survival in 358 women from a South Brazilian cohort between 1995-2010

Predicting factor	**HR**	**95%CI**	**p**
Age (years)	1.14	1.05-1.24	0.002
Years at school[1]	0.89	0.79-0.99	0.044
0 – 4	5.24	1.13-24.28	0.034
5 – 8	1.46	0.24-8.70	0.682
9 - 11	1.87	0.31-11.18	0.493
White skin color (yes)	0.42	0.13-1.30	0.135
Menopausal status[2]			
Perimenopause	2.50	0.73 - 8.60	0.145
Postmenopause	16.74	3.64 -77.43	<0.001
Hysterectomy	11.80	1.15 - 122.22	0.038
Smoker[3] (yes)	2.47	0.95-6.39	0.063
Alcohol intake[4]			
Social Drinker	0.54	0.20 – 1.44	0.216
Abusers	0.98	0.12 – 7.94	0.983
Alcohol intake[6]	1.19	0.98-1.45	0.074
Hypertension (yes)	1.58	0.60-4.18	0.353
Diabetes (yes)	10.44	3.37-32.37	<0.001
Dyslipidemia (yes)	1.83	0.42-7.99	0.423
HT (yes)	2.86	0.99 – 8.19	0.051
LPA[5,a]			
1000-1999 cal/sem	0.87	0.16- 4.74	0.870

<1000 cal/sem	0.52	0.12 – 2.35	0.395
BMI (kg/m^2)	0.98	0.89-1.08	0.649
WHR ≥ 0.85 [a]	3.63	1.28-10.30	0.015
WC ≥ 88 cm[a]	1.02	0.99-1.06	0.236
TC ≥ 200 mg/dL[a]	1.08	0.40-2.87	0.881
HDL-c <50 mg/dL[a]	0.47	0.15-1.46	0.194
LDL-c ≥ 160 mg/dL[a]	0.79	0.18-3.48	0.755
TG ≥ 150 mg/dL[a]	0.80	0.26-2.45	0.696
GLU ≥ 126 mg/dL[a]	3.06	0.69-13.46	0.140

[1]reference: >12 years at school. [2]reference: premenopause. [3]reference: nonsmoker. [4]reference: nondrinker. [5]reference: ≥ 2000 cal/sem. [6]Risk attributable per each 10 gr alcohol/day. [a]Data from 2003 interviews. P-value significance: ≤0.05. CI: confidence interval. BMI: body mass index; GLU: levels of plasma glucose; HDL-c: high-density lipoprotein cholesterol; HT: hormonal therapy; LDL-c: light-density lipoprotein cholesterol; LPA: Leisure physical activity in the last year; MET: metabolic equivalent; TC: plasma total cholesterol; TG: triglycerides; WC: waist circumference; WHR: waist-to-hip ratio.

Table 4. Adjusted mortality hazard ratio (HR) for diabetes, central obesity, menopausal status and alcohol intake and 95% confidence intervals (95%CI) for survival in 358 women from a South Brazilian cohort between 1995-2010

Predicting factor	**HR[a]**	**95%CI**	**p**
Diabetes	6.65	1.94- 22.79	0.003
WHR ≥0.85	2.97	1.04 – 8.50	0.042
Menopausal status			
Perimenopause	2.26	0.66-7.78	0.196
Postmenopause	6.22	0.96-40.14	0.055
Hysterectomy	4.26	0.33-55.78	0.270
Alcohol intake[b]	1.23	1.01-1.49	0.035

[a]Values adjusted for smoking and age. [b]Risk attributable per each 10 gr alcohol/day. P-value significance: ≤0.05. CI: confidence interval; HR: hazard ratio; WHR: waist-to-hip ratio.

Figure 1. Flowchart of the process of study selection and lost to follow-up in the three phases of the study.

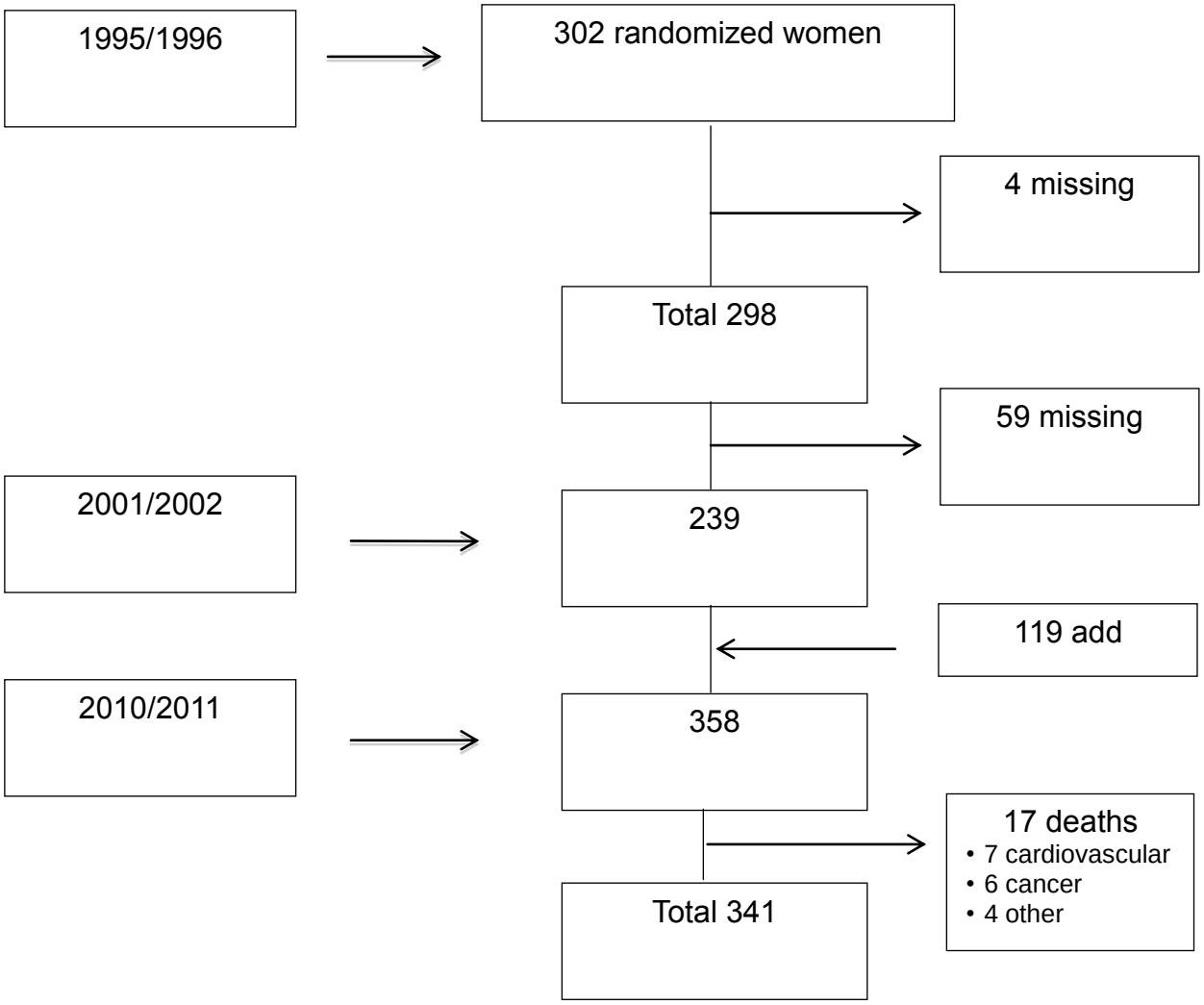


Figure 2. Kaplan-Meier estimates of survival among women (n = 358)

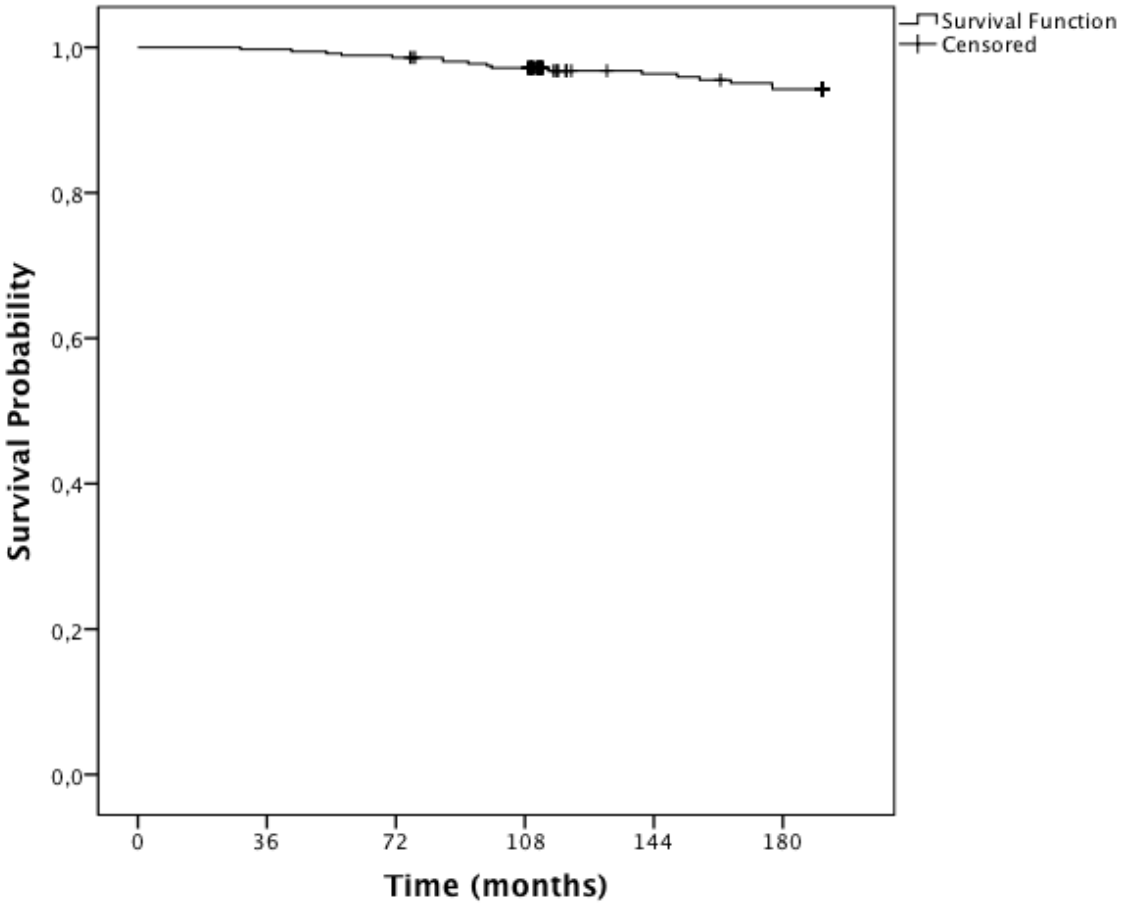
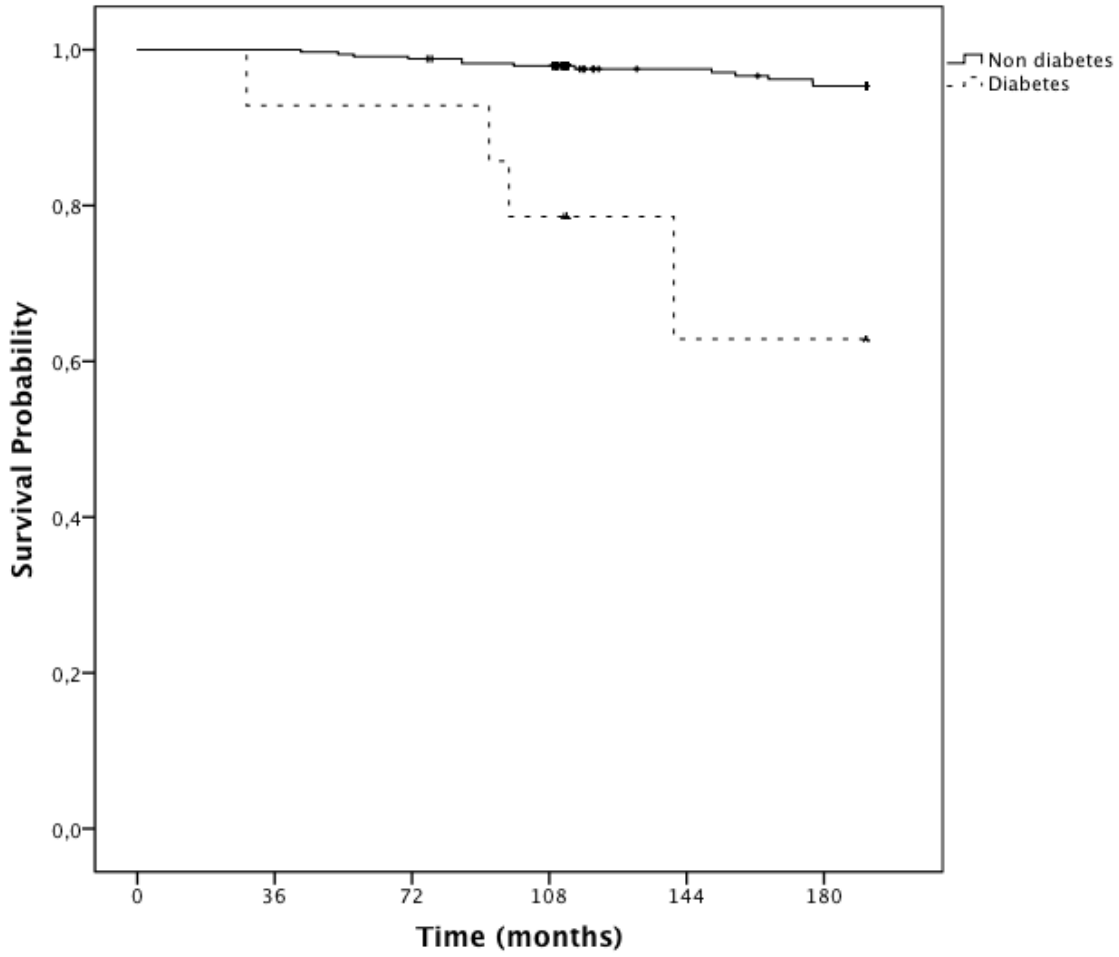


Figure 3. Kaplan-Meier estimates of survival among women, according to diabetes prevalence (n = 358)



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Postmenopause	6.22	0.96-40.14	0.055
Hysterectomy	4.26	0.33-55.78	0.270
Alcohol intake[b]	1.23	1.01-1.49	0.035

[a]Values adjusted for smoking and age.

[b]Risk attributable per each 10 gr alcohol/day.

P-value significance: ≤0.05. CI: confidence interval; HR: hazard ratio; WHR: waist-to-hip ratio.

Considerações Finais

No presente estudo verificou-se uma associação entre menor número de fatores de risco cardiovascular e menor morbidade e mortalidade em uma coorte de mulheres no período da pré-, peri e pós
-menopausa.

A investigação das causas e fatores de risco para DCV e mortalidade é importante para caracterização da população brasileira, visto que embora a morte por DCV esteja diminuindo em mulheres, ela continua sendo a maior causa de morte, dado confirmado nesta coorte.

Entre os estudos nesta tese de doutorado incluídos, destaca-se a atividade física habitual como um importante fator para melhora deste perfil de risco para DCV. A realização de mais de 6000 passos/dia nessa população foi associada a um menor risco cardiovascular, síndrome metabólica e diabete melito. Além disso, verificou-se que a escolha de um instrumento acurado e ideal para cada situação a ser estudada é importante para melhor avaliação do nível de atividade física.

Devido à elevada e crescente prevalência de obesidade, diabete melito e dos diferentes componentes da síndrome metabólica em mulheres e do impacto destes problemas em saúde pública, a aderência a um estilo de vida saudável deve ser considerada como uma importante estratégia para a prevenção da DCV e mortalidade. Sendo assim, são necessários estudos de intervenção que determinem as melhores estratégias de prevenção e manejo destes fatores de risco a fim de diminuir o risco de mortalidade e DCV no período da menopausa.