

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL  
FACULDADE DE MEDICINA  
PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA



**TESE DE DOUTORADO**

***STRAIN* LONGITUDINAL GLOBAL E SÍNDROME METABÓLICA  
NO ELSA-BRASIL: UMA ANÁLISE POR ECOCARDIOGRAFIA  
BIDIMENSIONAL *SPECKLE-TRACKING***

WILSON CAÑON MONTAÑEZ

Orientadora: Profa. Dra. Maria Inês Schmidt

Co-orientador: Prof. Dr. Murilo Foppa

Porto Alegre, março de 2016

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A apresentação desta tese é exigência do Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, para obtenção do título de Doutor.

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*“Queda prohibido no sonreír a los problemas, no luchar por lo que quieres, abandonarlo todo por miedo, no convertir en realidad tus sueños”.*

*Pablo Neruda*

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## SUMÁRIO

ABREVIATURAS E SIGLAS .....	7
RESUMO .....	8
ABSTRACT .....	10
APRESENTAÇÃO .....	12
INTRODUÇÃO .....	13
OBJETIVOS .....	23
REFERÊNCIAS BIBLIOGRÁFICAS .....	24
1. <i>Strain</i> longitudinal global: um parâmetro útil para avaliar disfunção ventricular esquerda na síndrome metabólica. (Artigo 1).....	32
2. Subclinical myocardial dysfunction by strain imaging in metabolic syndrome: the ELSA-Brasil study. (Artigo 2).....	52
3. Association of global longitudinal strain with metabolic syndrome components: the role of abdominal obesity. (Artigo 3).....	72
4. CONCLUSÕES E CONSIDERAÇÕES FINAIS .....	91
5. ANEXOS .....	93
a. Aprovação do estudo ELSA-Brasil pelo Comitê de Ética em Pesquisa (HCPA)....	93

## ABREVIATURAS E SIGLAS

<b>2D-STE</b>	Ecocardiografia bidimensional <i>speckle-tracking</i>
<b>DCNT</b>	Doenças crônicas não transmissíveis
<b>DCV</b>	Doenças cardiovasculares
<b>DT</b>	Doppler tecidual
<b>DVE</b>	Disfunção ventricular esquerda
<b>ECO-D</b>	Ecodopplercardiografia
<b>ELSA-Brasil</b>	Estudo Longitudinal de Saúde do Adulto
<b>FE</b>	Fração de ejeção
<b>GLS</b>	<i>Global Longitudinal Strain</i>
<b>HVE</b>	Hipertrofia ventricular esquerda
<b>IC</b>	Insuficiência cardíaca
<b>ICFEp</b>	Insuficiência cardíaca com fração de ejeção preservada
<b>ICFEr</b>	Insuficiência cardíaca com fração de ejeção reduzida
<b>OMS</b>	Organização Mundial da Saúde
<b>SM</b>	Síndrome metabólica
<b>VE</b>	Ventrículo esquerdo
<b>VIGITEL</b>	Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico

## RESUMO

A presente tese de doutorado foi realizada com o objetivo de investigar a associação entre a síndrome metabólica (SM) e seus componentes com o *strain* longitudinal global (GLS) medido pela ecocardiografia bidimensional *speckle-tracking* (2D-STE) em indivíduos de meia idade (35 a 74 anos) no contexto brasileiro. O trabalho foi realizado com dados basais (2008-2010) da amostra aleatória do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil), que se trata de um estudo de coorte multicêntrico composto por 15105 homens e mulheres, servidores civis, ativos e aposentados de seis instituições de ensino superior e pesquisa brasileiras. Nesta tese, foram investigadas associações entre a SM e seus componentes com o GLS, para identificar disfunção ventricular esquerda subclínica nos participantes do ELSA-Brasil.

Entre os participantes que preencheram os critérios de inclusão [53% mulheres;  $52 \pm 9$  anos], 42% tinham SM. Os indivíduos com SM apresentaram piores valores de GLS [ $(-18,0 \pm 2,5\%)$ ] do que aqueles sem SM [ $(-19,0 \pm 2,4\%)$ ],  $p < 0,0001$ ], e quase duas vezes a prevalência de disfunção sistólica subclínica. Na análise de regressão linear múltipla, o GLS foi associado com SM, mesmo após o ajuste para sexo, idade, raça/cor, escolaridade, centro de investigação, frequência cardíaca e fração de ejeção do ventrículo esquerdo por 2D-STE ( $\beta = 0,58$ ;  $p < 0,0001$ ), mas o tamanho do efeito foi atenuado após ajuste para o índice de massa corporal ( $\beta = 0,39$ ;  $p = 0,004$ ). A razão de prevalência ajustada de GLS alterado foi maior na SM em comparação com aqueles sem SM para 1.0 desvio padrão (GLS= $-16,1\%$ ; RP= 1,45 [IC 95%: 1,09-1,93]) e 1.5 desvio padrão (GLS= $-14,8\%$ ; RP = 1,93 [IC 95%: 1,25 - 2,99]).

Em relação aos componentes da SM, a análise de regressão quantílica ajustada mostrou que a circunferência da cintura elevada foi independentemente associada com o GLS alterado (percentil 95), mesmo após o ajuste para os principais confundidores (p



<0,0001).

De acordo com os resultados do estudo, evidenciou-se que a SM é independentemente associada com a alteração da função sistólica do ventrículo esquerdo avaliada por GLS. Além disso, demonstrou-se que a circunferência da cintura elevada é o principal componente associado à alteração do *strain* miocárdico dentre os critérios atualmente propostos para o diagnóstico de SM. Os achados sugerem a presença de uma alteração precoce subclínica da contratilidade miocárdica relacionada com obesidade abdominal e SM.

## ABSTRACT

The present doctoral thesis aimed to investigate the association between metabolic syndrome (MetS) and its components with global longitudinal strain (GLS) measured by two-dimensional speckle-tracking echocardiography (2D-STE) in middle-age individuals (35 to 74 years) in the Brazilian context. This investigation was carried out with baseline data (2008-2010) from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) which is a multicenter cohort study composed of 15,105 men and women, civil servants, active and retired, from universities or research institutions located in six states of Brazil. In this thesis, we investigated associations between MetS and its components with GLS to identify subclinical left ventricular dysfunction in participants from ELSA-Brasil.

Among the participants who fulfilled the inclusion criteria [53% women;  $52 \pm 9$  years], 42% had MetS. Individuals with MetS had worse GLS [ $(-18.0 \pm 2.5\%)$ ] than those without MetS [ $(-19.0 \pm 2.4\%)$ ],  $p < 0.0001$ ], and about twice the prevalence of subclinical systolic dysfunction. In multiple linear regression analysis, GLS was associated with MetS even after adjusting for sex, age, race/color, educational level, study center, heart rate, and LV ejection fraction by 2D-STE ( $\beta = 0,58$ ;  $p < 0,0001$ ), but the effect was attenuated after adjusting for body mass index ( $\beta = 0,39$ ;  $p = 0,004$ ). The adjusted prevalence ratio of altered GLS was higher in MetS compared to those without MetS for the 1.0 SD (GLS=-16.1%; PR=1.45 [95% CI: 1.09 - 1.93]) and 1.5 SD (GLS=-14.8%; PR=1.93 [95% CI: 1.25 - 2.99]) cut-offs.

According to MetS components, adjusted quantile regression analysis showed that elevated waist circumference was independently associated with altered GLS (95th quantile), even after adjusting for main confounders ( $p < 0.0001$ ).

The results of this study showed that MetS is independently associated with left ventricular impaired systolic function by GLS. In addition, it was demonstrated that

elevated waist circumference is the main component associated with impaired myocardial strain among the currently proposed criteria for diagnosis of MetS. The findings suggest the presence of an early subclinical myocardial contractility impairment related to abdominal obesity and MetS.

## APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada “*Strain* longitudinal global e síndrome metabólica no ELSA-Brasil: uma análise por ecocardiografia bidimensional *speckle-tracking*”, apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal do Rio Grande do Sul, em 04 de março de 2016. O trabalho é apresentado em três partes, na ordem que segue:

1. Introdução e Objetivos.
2. Três Artigos:
  - Revisão da Literatura (Artigo 1);
  - Disfunção miocárdica subclínica por imagem de *strain* na síndrome metabólica: o estudo ELSA-Brasil (Artigo 2);
  - Associação do *strain* longitudinal global com os componentes da síndrome metabólica: o papel da obesidade abdominal (Artigo 3).
3. Conclusões e Considerações Finais.

Documentos de apoio estão apresentados nos anexos.

## INTRODUÇÃO

As doenças crônicas não transmissíveis (DCNT) são as principais causas de morte no mundo e constituem um problema de saúde pública global, e um dos principais desafios para o desenvolvimento no século XXI (WHO, 2013). DCNT, principalmente doenças cardiovasculares (DCV), diabetes, câncer e doenças respiratórias crônicas, foram responsáveis de 68% dos óbitos em 2012. Aproximadamente 74% das mortes por DCNT ocorrem em países de baixa e média renda, e estima-se que 42% dessas mortes ocorre em pessoas com idade inferior a 70 anos. As principais causas das DCNT incluem fatores de risco modificáveis, como tabagismo, consumo nocivo de bebida alcoólica, inatividade física e alimentação inadequada (WHO, 2014).

A carga crescente que as DCNT representam, particularmente para os países em desenvolvimento, motivou a Organização das Nações Unidas a convocar uma reunião de alto nível especialmente dedicada ao tema em 2011. Como resultado da reunião, as nações presentes se comprometeram a estabelecer metas para a prevenção e controle das DCNT, a serem monitoradas junto da Organização Mundial da Saúde (OMS) (United Nations, 2011).

No Brasil, as DCNT tornaram-se uma das principais prioridades de saúde pública. Em 2007, 72% de todas as mortes foram atribuídas a DCNT, atingindo fortemente os grupos mais vulneráveis, como a população de baixa escolaridade e renda. Na última década, observou-se uma redução de aproximadamente 20% nas taxas de mortalidade pelas DCNT, o que pode ser atribuído à expansão da atenção primária, melhoria da assistência e redução do consumo do tabaco desde os anos 1990.

Porém, as transições demográfica e epidemiológica que caracterizaram as mudanças de perfis de saúde-doença globalmente no século passado, embora em ritmos distintos, foram acompanhadas também de uma transição nutricional, em que as

deficiências nutricionais foram “substituídas” pelo excesso de peso. Nesse cenário, emergem novos problemas de saúde pública como a obesidade e a síndrome metabólica. (Mensah et al., 2004).

Neste contexto, a prevalência de diabetes e hipertensão tem aumentado em paralelo com o excesso de peso, devido em parte a mudanças desfavoráveis de dieta e atividade física da população brasileira. (Schmidt et al., 2011). Como resposta ao desafio das DCNT, o Ministério da Saúde do Brasil implementou o Plano de Ações Estratégicas para o Enfrentamento das DCNT, com o objetivo de promover o desenvolvimento de políticas públicas efetivas para a prevenção e o controle das DCNT e seus fatores de risco e fortalecer os serviços de saúde voltados às doenças crônicas (Brasil, 2011).

A epidemia de obesidade.

A obesidade é definida como uma condição de excesso de gordura corporal, e caracterizada como uma doença crônica complexa, multifatorial que envolve fatores ambientais, genéticos, fisiológicos, metabólicos e comportamentais (Bagchi & Preuss, 2013). A consulta de expertos da OMS sobre obesidade realizada em 1997 alertou o começo de uma epidemia crescente de obesidade que iria colocar as populações da maioria dos países em risco de desenvolver DCNT (WHO, 2000). De fato, a prevalência global de sobrepeso e obesidade aumentou aproximadamente 28% em adultos e 47% em crianças no período de 1980 e 2013 (Ng et al., 2014). O problema não afeta apenas países desenvolvidos, como há agora um aumento significativo em sobrepeso e obesidade em todo o mundo em desenvolvimento. A obesidade tornou-se um grande desafio de saúde global, e a doença hoje é considerada como a epidemia do século XXI (Rössner, 2002; Prentice, 2006). Na verdade, um novo termo, “*globesidade*”, foi cunhado para descrever o recente surto de sobrepeso e obesidade em toda a população do mundo (Bagchi &

Preuss, 2013). De acordo com dados da OMS, a obesidade no âmbito mundial mais do que duplicou desde 1980. Em 2014, 1,9 bilhão de adultos estavam acima do peso. Destes, mais de 600 milhões eram obesos. A maioria da população do mundo vive em países onde o sobrepeso e a obesidade causa mais óbitos do que o baixo peso. Além disso, quase 42 milhões de crianças menores de cinco anos tinham sobrepeso em 2010 (WHO, 2015).

Embora alguns países já têm implementado políticas públicas para o problema de sobrepeso, a obesidade e o agrupamento de fatores de risco cardiometabólicos são importantes contribuintes para o aumento do risco de desenvolver DCV (Mensah et al., 2004).

No Brasil, de acordo com dados de 2014 do inquérito VIGITEL, encontrou-se que no conjunto da população adulta das capitais dos estados brasileiros e do Distrito Federal, a frequência de excesso de peso foi de 52,5%, sendo maior entre homens (56,5%) do que entre mulheres (49,1%). Entretanto, a prevalência de obesidade foi de 17,9%, com índices mais elevados para a população de 35 a 64 anos (Brasil, 2015). Recentemente foi publicado o perfil da coorte do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) - uma pesquisa pioneira sobre doenças crônicas, como diabetes e doenças cardiovasculares, e seus fatores de risco na população brasileira (Schmidt et al., 2015). Trata-se de um estudo de coorte de 15,105 funcionários públicos (homens e mulheres de 35-74 anos - ativos ou aposentados) de seis instituições públicas de ensino superior e pesquisa das regiões Nordeste, Sul e Sudeste do Brasil, cujo objetivo principal é investigar a incidência e progressão da diabetes e doenças crônicas, principalmente cardiovasculares, e sua associação com fatores biológicos, comportamentais, ambientais, ocupacionais e sociais (Aquino et al., 2012). Os achados do ELSA-Brasil mostram uma prevalência de sobrepeso de 40,2%, sendo maior em homens (45,2%) do que em mulheres (36%). Entretanto, a

prevalência de obesidade foi de 22,9%, sendo mais alta nas mulheres (24.8%) que nos homens (20.7%) (Schmidt et al., 2015).

#### Síndrome metabólica.

A síndrome metabólica (SM) é caracterizada como um conjunto de fatores de risco cardiovasculares, incluindo obesidade abdominal, intolerância à glicose, resistência à insulina, dislipidemia e hipertensão (Grundy, 2007). Estima-se que aproximadamente 25% da população adulta do mundo tenha SM (International Diabetes Federation, 2006) e esta condição está associada ao incremento do risco de desenvolver diabetes, infarto do miocárdio, acidente vascular cerebral e morte (Mottillo et al., 2010; Wu et al., 2010). A alta prevalência da SM é um fenômeno global (Reynolds & He, 2005; Grundy, 2008) e parece estar aumentando devido a um aumento paralelo na prevalência da obesidade (Ng et al., 2014). O incremento na SM pode ser antecipada uma vez que há projeções de aumento da prevalência de obesidade no futuro (Hossain et al., 2007). Em relação a SM, achados de uma revisão sistemática que reuniu 8,505 indivíduos adultos no Brasil, mostrou uma prevalência geral de SM de 29,6%, sendo mais frequente (65.3%) em população indígena do Rio Grande do Sul e menos frequente (14,9%) em uma área rural de Minas Gerais (Vidigal et al., 2013). No ELSA-Brasil, e de acordo com os critérios da *Joint Interim Statement* para o diagnóstico de SM (Alberti et al., 2009), estima-se uma prevalência aproximada de 42% (Schmidt et al., 2015).

Na última década alguns estudos têm mostrado que o excesso de peso, obesidade, SM e a diabetes desempenham um papel importante no desenvolvimento de morbidade e mortalidade cardiovascular (Mensah et al., 2004). Além disso, tem evidência demonstrando o impacto da obesidade sobre a remodelação cardíaca com alterações estruturais e funcionais (Mahajan et al., 2015). Estudos clínicos recentes indicam que a



obesidade e a SM não só estão ligadas ao desenvolvimento de fatores de risco para doença vascular aterosclerótica, mas também são associadas com outros desfechos cardiovasculares como disfunção cardíaca, hipertrofia ventricular esquerda (HVE) e insuficiência cardíaca (IC) (Mahajan et al., 2015; Cuspidi et al., 2014; Suzuki et al., 2008).

#### Insuficiência cardíaca.

A IC é uma das principais causas de morbidade e mortalidade no mundo e afeta principalmente a população mais velha. Sua incidência e prevalência sobem acentuadamente com a idade em pessoas com mais de 60 anos, o que provoca elevados custos de saúde e cuidados relacionados, representando uma grande carga para a sociedade (Mosterd & Hoes, 2007). A IC é uma síndrome clínica complexa que resulta de qualquer alteração estrutural ou funcional de enchimento ventricular ou ejeção de sangue (Yancy et al., 2013). A síndrome de IC tem sido comparada com um iceberg. A seção visível representa casos de IC estabelecidos na comunidade: a maioria no contexto da atenção primária e os tratados pelos cardiologistas. A parte não visível “abaixo do nível da água” representa casos de IC não detectada, e aqueles com disfunção ventricular esquerda (DVE) assintomática ou subclínica considerados propensos a desenvolver IC (Hoes et al., 1998). A DVE engloba disfunção sistólica e diastólica. A prevalência de DVE sistólica e diastólica varia de 6% a 21% e aumenta com a idade (McDonagh et al., 1997; Mosterd et al., 1999; Redfield et al., 2003). Alguns estudos têm evidenciado que a DVE assintomática não tratada esta associada com o aumento do risco de desenvolver sintomas, internação ou morte por IC (Redfield et al., 2003; Jong et al., 2003). Disfunção sistólica é comumente definida em termos de fração de ejeção (FE) do ventrículo esquerdo (VE) reduzida. Disfunção diastólica refere-se a uma alteração nas propriedades de enchimento do VE. A caracterização da FE é parte fundamental na classificação

clássica de IC, permitindo a divisão dos indivíduos em dois grandes grupos com características demográficas, comorbidades, prognóstico e resposta terapêutica diferentes: IC com FE reduzida (ICFER) e IC com FE preservada (ICFEp). Recentemente tentou-se padronizar esta definição, sendo proposta a classificação dos grupos de IC tendo como ponto de corte  $FE \leq 40\%$  para ICFER e  $FE > 40\%$  para ICFEp, sendo o grupo com FE entre 41% e 49%, considerado uma categoria intermediária de ICFEp (Yancy et al., 2013; Lam & Solomon, 2014). No que concerne a ICFEp, esta corresponde aproximadamente a metade de todos os casos de IC (Owan et al., 2006). Alguns registros e estudos de base populacional mostram que a prevalência de ICFEp é maior em idosos, mulheres, e em sujeitos com história de hipertensão, dislipidemia, obesidade, diabetes e fibrilação atrial (Owan et al., 2006; Lee et al., 2009). Recentemente foi publicada uma revisão sistemática de 28 estudos em pessoas  $\geq 60$  anos, indicando que a disfunção diastólica foi muito comum com uma prevalência de 36%. Entretanto, a disfunção sistólica mostrou uma prevalência de 5.5%. Além disso, os resultados mostraram uma prevalência de 4.9% para ICFEp e 3.3% para ICFER (van Riet et al., 2016). Cabe-se ressaltar, que, apesar desses dados, ainda há inconsistências na forma de classificar os indivíduos de acordo com a apresentação dos sintomas e achados de exames cardiológicos, com implicações na decisão terapêutica.

Em relação a ferramentas diagnósticas para a IC, a ecodopplercardiografia (ECO-D) é um método rápido, seguro e amplamente disponível que fornece diversas informações funcionais e anatômicas de grande importância. É útil na confirmação diagnóstica, avaliação da etiologia, do modelo fisiopatológico e hemodinâmico, do prognóstico e para indicar possíveis alternativas terapêuticas. O parâmetro mais importante para quantificação da função sistólica é a FE do VE, fundamental para diferenciar a IC sistólica da IC diastólica e para definir tratamento. A contratilidade

ventricular representa o resultado de uma complexa interação entre o estado contrátil do músculo cardíaco e os níveis de pré e pós-carga. Tradicionalmente, avalia-se a função sistólica ventricular mediante análise da mobilidade segmentar da parede ventricular e pela FE do VE. Alterações do desempenho diastólico podem ser identificadas de forma não invasiva pela ECO-D, sendo os índices derivados do fluxo diastólico transmitral e do doppler tecidual (DT) do anel mitral, os critérios mais utilizados na sua avaliação. Outros parâmetros que são utilizados na prática clínica para avaliar a disfunção diastólica são a massa do VE indexada e o volume do atrio esquerdo indexado. (Filho et al., 2004; Bocchi et al., 2009). Os índices de função diastólica alteram-se com a idade e na presença de fatores de risco cardiometabólicos (Sánchez-Barriga et al., 2001; Chen et al., 1996). A ECO-D também é importante para avaliar HVE, caracterizada pelo aumento inapropriado da massa ventricular esquerda. Alguns estudos mostram que o aumento da massa do VE está associado com a obesidade (de Simone et al., 1996) e diabetes (Devereux et al., 2000), e também está presente em indivíduos com outros fatores de risco relacionados à SM (de Simone et al., 2002; Chinali et al., 2004), onde aspectos fisiopatológicos relacionados a esta síndrome podem diretamente afetar os mecanismos de adaptação e remodelamento ventricular.

Estudos recentes usando ecocardiografia convencional e DT têm mostrado evidência de disfunção miocárdica em indivíduos com SM (Seo et al., 2011; Ingelsson et al., 2007; Gong et al., 2009). No entanto, os parâmetros ecocardiográficos convencionais para aferição da função sistólica apresentam baixa sensibilidade para a avaliação minuciosa da contratilidade miocárdica e não detectam pequenas mudanças da contratilidade ou alterações precoces.

Ecocardiografia bidimensional *speckle-tracking* e seu potencial para avaliar alterações cardíacas subclínicas em pessoas com síndrome metabólica.

Recentemente, a ecocardiografia bidimensional *speckle-tracking* (2D-STE) emergiu como uma técnica mais robusta para detectar DVE subclínica por avaliação quantitativa da deformação do miocárdio (Shah & Solomon, 2012; Voigt et al., 2015). Algumas vantagens desta nova ferramenta ecocardiográfica são claramente identificadas em relação a técnicas ecocardiográficas convencionais como o DT. A principal delas é a de não depender do ângulo de incidência do feixe de ultrassom. Além disso, as análises advindas de *speckle-tracking* são menos sujeitas a interferência por tracionamento segmentar e pelo movimento translacional do coração. A avaliação da região apical do VE, muito problemática com o DT, é mais facilmente realizada com *speckle-tracking* (Del Castillo et al., 2010; Almeida et al., 2013; Pavlopoulos & Nihoyannopoulos, 2008).

No Brasil, a prática do *strain* pela 2D-STE, é de uso relativamente novo e existe pouca evidencia publicada avaliando esta metodologia em população brasileira (Abduch et al., 2012; Leal et al., 2015; Almeida et al., 2015).

Um dos conceitos chave da metodologia *speckle-tracking* é o *strain*, expresso em porcentagem (%) e definido como a mudança fracional no comprimento de um segmento do miocárdio, normalmente relacionado ao comprimento na diástole final. O *strain* pode ser avaliado em cada região do ventrículo estudado (*strain* regional) e a média destes valores passam a representar o *strain* global, refletindo a função ventricular global. Com essa metodologia, é possível avaliar as fibras miocárdicas em seus eixos de orientação específicos (fibras subendocárdicas e *strain* longitudinal e fibras subepicárdicas e *strain* circunferencial e radial). O *strain* longitudinal analisa a deformação desde a posição apical do coração, em quatro, duas ou três câmaras e mede a deformação no sentido base-ápex da cavidade, ou seja, o encurtamento da câmara. Como o comprimento final da

cavidade (sistólico) é menor do que o comprimento inicial (diastólico), a porcentagem da deformação é negativa (Blessberger & Binder, 2010; Dandel et al., 2009).

Alguns estudos prévios em amostras pequenas sugerem que a SM está associada com a deformação longitudinal do VE e, que o *strain* longitudinal global (GLS) medido pela 2D-STE está reduzido em sujeitos com SM (Crendal et al., 2013; Almeida et al., 2014; Tadic et al., 2014; Wang et al., 2015). No entanto, esta associação ainda está por ser demonstrada em grandes amostras da população. Por outro lado, há evidência demonstrando o impacto de alterações decorrentes da obesidade e fatores de risco cardiometabólicos sobre a disfunção miocárdica com alterações estruturais e funcionais (Abel et al., 2012; Berwick et al., 2012; Voulgari et al., 2010; Papakonstantinou et al., 2013). Porém, os mecanismos fisiopatológicos que contribuem para essas alterações não são muito claros, com uma complexa interação hemodinâmica e neurohumoral, substrato metabólico, inflamação e estresse oxidativo, contribuindo para apoptose celular, disfunção endotelial, isquemia, hipertrofia e fibrose intersticial (Abel et al., 2012; Berwick et al., 2012; Papakonstantinou et al., 2013; Mahajan et al., 2015). Além disso, em termos de obesidade, há uma crescente consideração que os indivíduos “obesos metabolicamente não saudáveis” são mais propensos a complicações mecânicas da obesidade comparado com os indivíduos “obesos metabolicamente saudáveis” (Wang et al., 2015; Dobson et al., 2016).

A partir dessas evidências pode se inferir que a identificação precoce da DVE subclínica na SM e o reconhecimento do papel dos componentes desta síndrome na alteração da contratilidade miocárdica, ajudará na compreensão e predição de risco de DCV na SM. Neste sentido, uma metanálise de 16 estudos mostrou que o GLS tem um valor prognóstico superior que a FE para predizer eventos cardíacos maiores e toda causa de mortalidade (Kalam et al., 2014). Dois estudos recentes: NOMAS (*Northern*

*Manhattan Study*) e CABL (*Cardiovascular Abnormalities and Brain Lesions*) merecem destaque porque têm identificado que o GLS é um predictor independente de casos incidentes de fibrilação atrial, doença cerebral subclínica, IC e, do desfecho combinado de infarto do miocárdio, acidente vascular cerebral isquêmico e morte vascular (Russo et al., 2015; Russo et al., 2014; Russo et al., 2013).

Por fim, o propósito desta tese foi investigar em participantes de uma amostra aleatória do ELSA-Brasil, a associação da SM com o GLS do VE pela 2D-STE e identificar quais os componentes da SM são determinantes da alteração do *strain* miocárdico.

## **OBJETIVOS**

### **Objetivo Geral**

Investigar em participantes de uma amostra aleatória do ELSA-Brasil, a associação da SM com o GLS do VE obtido pela 2D-STE.

### **Objetivos Específicos**

- Explorar associações entre SM e pontos de corte de referência de GLS alterado.
- Identificar quais os componentes da SM são determinantes da alteração do *strain* miocárdico do VE.

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**1. *Strain* longitudinal global: um parâmetro útil para avaliar disfunção ventricular esquerda na síndrome metabólica. (Artigo 1).**

Global longitudinal strain: a useful parameter to assess subclinical left ventricular dysfunction in metabolic syndrome

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## Resumo

A alta prevalência da síndrome metabólica (SM) é um fenômeno global. Devido a seu aumento no risco de desenvolvimento de diabetes e doença cardiovascular, a SM terá uma enorme carga sobre as economias do mundo e a saúde pública, sem intervenções precoces e eficazes.

Um dos mecanismos propostos para aumentar o risco cardiovascular relaciona-se com a disfunção sistólica e diastólica subclínica encontradas nos indivíduos com SM. A fração de ejeção, o parâmetro mais utilizado para estimar a função sistólica tem baixa sensibilidade para a avaliação da disfunção precoce da contratilidade miocárdica.

O desenvolvimento de novas técnicas ecocardiográficas, como o *strain* longitudinal global pela ecocardiografia bidimensional *speckle-tracking* tem reforçado a capacidade de analisar a função ventricular esquerda através da avaliação quantitativa da deformação miocárdica.

A detecção e tratamento precoce da doença cardiovascular subclínica pode mitigar alguns dos riscos cardiovasculares associados a distúrbios metabólicos. Com a capacidade para detectar disfunção subclínica do ventrículo esquerdo em pessoas com SM, o *strain* longitudinal global medido pela ecocardiografia bidimensional *speckle-tracking* tem o potencial de tornar-se uma ferramenta útil para a estratificação de risco nesta população.

O objetivo do artigo foi revisar os principais conceitos da metodologia *speckle-tracking*, e seu potencial uso para avaliar disfunção ventricular esquerda subclínica na SM.

***Strain longitudinal global: un parámetro útil para evaluar disfunción ventricular  
izquierda subclínica en el síndrome metabólico***

***Global longitudinal strain: a useful parameter to assess subclinical left ventricular  
dysfunction in metabolic syndrome***

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***Strain* longitudinal global: un parámetro útil para evaluar disfunción ventricular izquierda subclínica en el síndrome metabólico**

**Global longitudinal strain: a useful parameter to evaluate subclinical left ventricular dysfunction in the metabolic syndrome**

**Resumen**

La alta prevalencia del síndrome metabólico es un fenómeno global. Debido a su aumento concomitante en el riesgo de desarrollar diabetes mellitus y enfermedad cardiovascular, el síndrome metabólico tendrá una enorme carga sobre las economías del mundo y en la salud pública, sin intervenciones precoces y eficaces. Uno de los mecanismos propuestos para aumentar el riesgo cardiovascular se relaciona con disfunción sistólica y diastólica subclínica encontrada en estos pacientes. La fracción de eyección, el parámetro más utilizado para la evaluación de la función sistólica tiene baja sensibilidad para la valoración de disfunción temprana de la contractilidad miocárdica. El desarrollo de nuevas técnicas ecocardiográficas, como *strain* longitudinal global por ecocardiografía bidimensional *speckle-tracking* ha reforzado la capacidad de evaluar la función del ventrículo izquierdo mediante evaluación cuantitativa de la deformación miocárdica. La detección y manejo precoz de enfermedad cardiovascular subclínica puede mitigar algunos de los riesgos cardiovasculares asociados con trastornos metabólicos. Con la capacidad de detectar disfunción ventricular izquierda subclínica en pacientes con síndrome metabólico, el *strain* longitudinal global medido por ecocardiografía bidimensional *speckle-tracking* tiene el potencial de convertirse en una herramienta útil para la estratificación del riesgo en esta población.

**Palabras clave:** Síndrome metabólico; Función ventricular Izquierda; Disfunción Diastólica; Contracción Miocárdica.

## **Abstract**

The high prevalence of metabolic syndrome is a global phenomenon. Due to the increase of the concomitant risk of developing diabetes mellitus and cardiovascular diseases, metabolic syndrome will place a great burden on world economies and public health unless early and efficient action interventions are conducted. One of the suggested mechanisms producing increased cardiovascular risk is related to subclinical systolic and diastolic dysfunction discovered in these patients. Ejection fraction, the most frequently used parameter to assess systolic function, presents a low sensitivity to the assessment of early dysfunction on myocardial contractility. The development of new echocardiographic techniques, such as global longitudinal strain by two-dimensional speckle-tracking echocardiography, has strengthened the ability to assess left ventricle function with a quantitative assessment of myocardial deformation. Early detection and management of subclinical cardiovascular diseases can mitigate some of the cardiovascular risks associated to metabolic disorders. Given its ability to detect subclinical left ventricular dysfunction in patients with metabolic syndrome, global longitudinal strain measured with two-dimensional speckle-tracking echocardiography has the potential to become a useful tool for risk stratification in this population group.

**Keywords:** Metabolic syndrome; left ventricular function; diastolic function; myocardial contraction.

## **Introducción**

Las enfermedades cardiovasculares (ECV) son la principal causa de muerte en todo el mundo<sup>1</sup>. Recientemente, el estudio *Global Burden of Disease 2013* estimó que casi el 30%

de todas las muertes en el mundo fueron causadas por ECV<sup>1</sup>. Respecto a factores de riesgo para ECV, existe evidencia mostrando que 9 factores de riesgo medidos fácilmente (tabaquismo, lípidos, hipertensión arterial, diabetes, obesidad, dieta, actividad física, consumo de alcohol y factores psicosociales) son responsables de más del 90% del riesgo de infarto agudo de miocardio (IAM) en el mundo<sup>2</sup>.

El síndrome metabólico (SM) es un conjunto de factores de riesgo cardiometabólicos, que incluyen: obesidad abdominal, resistencia a la insulina, dislipidemia e hipertensión<sup>3</sup>. El agrupamiento de varios factores de riesgo para ECV, como alteraciones en la glucosa y el metabolismo de la insulina, obesidad abdominal, hipertensión arterial y dislipidemia han sido un asunto de fuerte debate desde la introducción del concepto de SM<sup>3</sup>.

En la mayoría de las personas con intolerancia a la glucosa o con diabetes mellitus (DM) tipo 2, hay un conjunto de varios factores de riesgo que comúnmente aparecen juntos, formando lo que ahora se conoce como el SM<sup>4</sup>. Las personas con SM tienen un incremento del riesgo para desarrollar DM y ECV, así como un riesgo adicional y substancial para el desarrollo de eventos cardiovasculares clínicamente relevantes como IAM, accidente cerebrovascular, mortalidad por ECV y mortalidad por todas las causas<sup>5-7</sup>.

En relación a desenlaces cardiovasculares sustitutos o intermedios, el SM ha sido asociado con hipertrofia del ventrículo izquierdo (VI) y dilatación auricular<sup>8-10</sup>. El SM y la DM tipo 2 están relacionados con disfunción miocárdica identificada por imagen de doppler tisular (TDI) y ecocardiografía bidimensional *speckle-tracking* (2D-STE)<sup>11,12</sup>.

2D-STE tiene la ventaja sobre TDI de ángulo independencia, ofreciendo la posibilidad de examinar no sólo la función longitudinal, sino también un componente mayor del desempeño del VI<sup>13</sup>.

El desarrollo de nuevas técnicas ecocardiográficas, como 2D-STE ha reforzado la capacidad de evaluar la función del VI mediante la evaluación cuantitativa de la deformación miocárdica<sup>14,15</sup>.

*Speckle-tracking* evalúa la contractilidad del VI. Consiste en la captura y rastreamiento de puntos del ecocardiograma bidimensional a lo largo del ciclo cardiaco, generando vectores de movimiento y curvas de deformación (*strain* y *strain rate*). La deformación medida en planos ortogonales se denomina *strain* longitudinal, radial y circunferencial<sup>16</sup>.

Recientemente, algunos estudios, han mostrado que el *strain* longitudinal global (GLS) evaluado por 2D-STE, está reducido en sujetos con SM y fracción de eyección del ventrículo izquierdo (FEVI) normal, independiente de otros factores de riesgo cardiovascular<sup>17-19</sup>. Estos datos son útiles, pues la identificación precoz de ECV subclínica puede ayudar a identificar a los individuos con mayor riesgo y mejorar los resultados clínicos en el SM<sup>20,21</sup>.

### **Epidemiología y criterios diagnósticos del SM**

Se estima que alrededor del 20-25% de la población adulta del mundo tiene SM. Separadamente los componentes del SM aumentan el riesgo de DM, ECV y mortalidad por todas las causas<sup>22-24</sup>. La prevalencia relativamente alta del SM es un fenómeno global<sup>25,26</sup>. Esta prevalencia parece estar aumentando debido a un aumento paralelo de la prevalencia de obesidad. La probabilidad de un aumento adicional del SM puede ser anticipada por causa de proyecciones de una mayor prevalencia de obesidad en el futuro<sup>27</sup>. En relación a datos de incidencia del SM, la literatura muestra pocos estudios longitudinales para determinar la incidencia de SM. Algunos de ellos fueron realizados en Estados Unidos, Europa y Asia Oriental. En general, la incidencia de SM reportada en estos estudios varía de 11% a 39%<sup>28-</sup>

Varias instituciones en el mundo han propuesto criterios para el diagnóstico del SM. Entre ellas se destacan: *Organización Mundial de la Salud (OMS)*, *National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)*, *International Diabetes Federation (IDF)*, *Association of American Clinical Endocrinologists (AACE)*, *European Group for the Study of Insulin Resistance (EGIR)* y *American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)*<sup>32</sup>.

Recientemente, algunas organizaciones internacionales establecieron un consenso para la definición de SM<sup>33</sup>. El diagnóstico de SM según este consenso requiere la presencia de al menos tres de los siguientes criterios: glicemia en ayunas (FPG)  $\geq 100$  mg/dl; triglicéridos  $\geq 150$  mg/dl (1.7 mmol/l); colesterol HDL  $< 40$  mg/dl (1.0 mmol/l) en hombres y  $< 50$  mg/dl (1.3 mmol/l) en mujeres; obesidad abdominal [circunferencia de la cintura  $\geq 94$  cm en hombres y  $\geq 80$  cm en mujeres]; y presión arterial  $\geq 130/85$  mmHg o en tratamiento para hipertensión arterial.

### **Ecocardiografía bidimensional *speckle-tracking* (2D-STE) - contractilidad y función miocárdica**

Los parámetros ecocardiográficos convencionales para evaluación de la función sistólica presentan baja sensibilidad para la valoración exhaustiva de la contractilidad miocárdica. No detectan pequeños cambios de contractilidad o alteraciones precoces<sup>16</sup>.

2D-STE, surgió recientemente como una nueva técnica y metodología desarrollada para el análisis de deformación miocárdica mediante seguimiento automático del movimiento de patrones de puntos (*speckles*) inherentes a la interfaz de ultrasonido-miocardio<sup>34</sup>.

Recientemente, dos organizaciones internacionales: *European Association of Cardiovascular Imaging (EACVI)* y *American Society of Echocardiography (ASE)* publicaron un documento de consenso para estandarizar las técnicas de análisis de

deformación miocárdica usando 2D-STE. El objetivo principal de esta guía es proporcionar las bases teóricas para explicar el significado fisiológico y cálculo matemático de los distintos parámetros para los clínicos interesados en el uso de imágenes de deformación miocárdica para la investigación y utilidad clínica, con la finalidad de asegurar un conocimiento común para las diferentes aplicaciones de esta técnica ecocardiográfica<sup>35</sup>.

*Speckle-tracking*, literalmente significa seguimiento de puntos o huellas y puede ser definido como el rastreamiento de puntos que forman la imagen bidimensional. Estos puntos también se denominan marcas acústicas digitales. Cada marca digital es formada por un pequeño conjunto de imágenes en escala gris, cuya disposición es única y caracteriza una porción particular del miocardio denominada patrón de seguimiento (*speckle pattern*)<sup>16</sup>. Esos patrones de puntos únicos como una "impresión digital" en el miocardio, son identificados y seguidos durante todo el ciclo cardíaco ([Figura 1](#)). Se generan vectores representativos del movimiento multidireccional, con sus respectivos valores y curvas graficadas en función del tiempo para varios parámetros: desplazamiento, velocidad de desplazamiento, *strain* y *strain rate* ([Figura 2 y 3](#)). Todos estos análisis integrados conforman la llamada dinámica de contracción del VI ([Video del material suplementario](#)), una forma mucho más completa y sensible para caracterizar la función sistólica<sup>16,20</sup>.

### **Conceptos claves del 2D-STE y *strain* longitudinal global (GLS)**

*Strain* (deformación) y *strain rate* (velocidad de deformación) son índices clínicos de deformación miocárdica regional y global<sup>20</sup>. Ambos fueron introducidos y validados utilizando la imagen de resonancia magnética cardíaca y sonomicrometría (en modelos experimentales) como patrones de referencia<sup>36</sup>.

El *strain* (S) es definido como el cambio fraccional en longitud de un segmento del miocardio, normalmente relacionado con la longitud al final de la diástole. El *strain*



generalmente se expresa en porcentaje (%). Si representamos el desplazamiento de las marcas acústicas en función del tiempo, tendremos una curva de deformación de este punto de la pared, en función del tiempo. Esta curva se denomina *strain rate* (SR) o velocidad o tasa de deformación y se expresa en  $s^{-1}$  o  $1/s$ <sup>16,20</sup>.

El *strain* y *strain rate* pueden ser evaluados en cada región del ventrículo estudiado (*strain* regional) y el promedio de estos valores representa el *strain* global, lo que refleja la función ventricular global<sup>37,38</sup>.

El *strain longitudinal*, mide la deformación en el sentido base-ápex de la cavidad, es decir, el acortamiento de la cámara. Como la longitud final de la cavidad (sistólica) es menor que la longitud inicial (diastólica), el porcentaje de la deformación es negativo<sup>16</sup>.

El GLS medido por 2D-STE proporciona la oportunidad de cuantificar tanto la magnitud y el tiempo de deformación regional, sistólico y diastólico. El GLS es considerado un parámetro eficaz para la cuantificación de la función ventricular izquierda, más sensible que la FEVI por ecocardiografía bidimensional<sup>39</sup>.

Recientemente fue publicado un meta-análisis<sup>40</sup> de 24 estudios que reportó que los valores normales para GLS oscilaron entre -15,9% a -22,1% (promedio, -19,7%; IC 95%: -18,9% a -20,4%). Asimismo, investigadores del estudio Framingham reportaron los valores de referencia por sexo del GLS en adultos sanos sin evidencia de ECV. Los hallazgos mostraron que el GLS fue de -14,4% a -17,1% en mujeres y -14,4% a -15,2% en hombres<sup>15</sup>.

Los valores de referencia para GLS pueden variar por la disponibilidad de diferentes equipos de imagen ecocardiográfica, así como distintas aplicaciones de *software* para el análisis de 2D-STE<sup>35</sup>.

### ***Strain* longitudinal global (GLS) y SM**

Investigadores de Francia y Australia señalaron que la identificación temprana de disincronía del miocardio del VI por 2D-STE en una población de alto riesgo, pero sin síntomas de ECV

(pacientes con SM), es importante por varias razones. En primer lugar, esta metodología proporciona un recurso adicional y más sensible para la detección de disfunción sistólica subclínica. En segundo lugar, la disincronía del VI también puede permitir la detección precoz de disfunción sistólica aislada. En este estudio, un porcentaje significativo de individuos con SM y sin función diastólica perjudicada, presentaron disincronía del VI manifestada por 2D-STE. Se identificó una fuerte interrelación entre la disincronía del VI, inflamación sistémica y obesidad abdominal en participantes con SM, independientemente del estado diabético. Lo cual puede ayudar a una mejor comprensión de la mecánica del miocardio en las primeras fases de los trastornos metabólicos<sup>41</sup>.

En el mismo sentido, Crendal *et al*<sup>19</sup> en un estudio transversal con 92 adultos con SM y 50 controles sanos, encontraron que los participantes con SM presentaron función miocárdica sistólica y diastólica perjudicada evaluada por GLS. Los resultados también mostraron que la obesidad abdominal, combinada con biomarcadores inflamatorios y marcadores de disincronía sistólica fueron fuertemente asociados con el deterioro de la función miocárdica. Los participantes con DM y un mayor número de factores de riesgo metabólicos tenían disfunción miocárdica más grave. Los investigadores también analizaron separadamente los pacientes que presentaron SM y DM versus SM sin DM. Se encontró que el GLS fue peor en el grupo de pacientes con SM y DM concomitante<sup>41</sup>.

En el estudio (*Multi-Ethnic Study of Atherosclerosis* - MESA) en Baltimore - Estados Unidos<sup>18</sup>, con 133 participantes, la prevalencia de SM fue del 31%. Los investigadores plantearon la hipótesis que el SM está asociado con deterioro de la función miocárdica, evaluada por 2D-STE. Los hallazgos mostraron que los individuos con SM presentaron valores menores de GLS comparados con aquellos sin SM. En el análisis multivariado se encontró que la presencia de SM ( $\beta = 1,3\%$ ; IC95%: 0,3 - 2,2;  $p < 0,01$ ) y la masa del VI ( $\beta = 0,02\%$ ; IC95%: 0,01- 0,03;  $p = 0,02$ ) se asociaron con un menor valor de GLS después de

ajustar por etnia, FEVI y creatinina. Los autores concluyen que el GLS del VI, es un marcador de ECV subclínica y que está comprometido en individuos asintomáticos con SM y sin historia previa de infarto del miocardio, insuficiencia cardiaca y/o FEVI <50%.

En otro estudio, investigadores serbios evaluaron la mecánica ventricular izquierda estimada por 2D-STE en 95 pacientes con SM y 65 controles sanos. El GLS fue significativamente menor en el grupo de pacientes con SM. El análisis multivariado de los criterios de SM mostró que la presión arterial media en 24h, la circunferencia de la cintura y la glicemia en ayunas se asociaron independientemente con el GLS. Los resultados también mostraron que la interacción entre el sexo y el SM afecta significativamente el GLS del VI<sup>17</sup>.

En la [Tabla 1](#) se puede observar que el GLS en pacientes con SM es significativamente menor cuando se compara con participantes controles o sin SM.

### **Disfunción ventricular izquierda (DVI) subclínica, GLS y trastornos metabólicos**

Los pacientes con trastornos metabólicos a menudo tienen evidencia de disfunción sistólica y diastólica subclínica por TDI, aun teniendo FEVI normal<sup>42</sup>. En contraste con la FEVI, el GLS medido por 2D-STE es más sensible para la detección de DVI subclínica. DVI es común, incluso en pacientes asintomáticos<sup>43</sup>. Es importante destacar que la técnica por imagen de *strain* es sensible para identificar disfunción y fibrosis miocárdica asociada con DVI en pacientes con DM tipo 2<sup>44</sup>. Datos recientes sugieren que la DVI está presente en casi la mitad de pacientes con DM tipo 2<sup>45</sup>. En este sentido, investigadores australianos realizaron un estudio de cohorte prospectivo en 230 participantes, con el objetivo de evaluar el resultado a largo plazo de DVI subclínica asociada con DM tipo 2, durante 10 años de seguimiento. Los hallazgos mostraron que 45% de la cohorte presentó evidencia de DVI detectada por GLS. Los autores concluyen que DVI subclínica es común en pacientes asintomáticos con

DM tipo 2, fácilmente detectable por imágenes de GLS y éste se asocia de forma independiente con eventos adversos<sup>46</sup>.

A pesar de su papel para evaluación fundamental de la función sistólica, la FEVI es menos sensible para la detección de enfermedad miocárdica temprana que nuevas técnicas ecocardiográficas como el GLS medido por 2D-STE<sup>47</sup>. Recientemente fue publicado un estudio americano con resultados de 678 participantes de una cohorte multiétnica de base poblacional. Los investigadores encontraron que el GLS fue significativamente más bajo en el grupo de participantes de raza negra ( $-16,5\% \pm 3,5\%$ ) que en los blancos ( $-17,5\% \pm 3,0\%$ ) e hispanos ( $-17,3\% \pm 2,9\%$ ); mientras que la FEVI no fue significativamente diferente en los tres grupos. Adicionalmente el estudio reportó que en el análisis multivariado ajustado por variables de confusión y factores de riesgo cardiovascular, los individuos de raza negra fueron significativamente más propensos a tener disfunción sistólica del VI evaluada con GLS (OR= 2,6, IC95%: 1.4 - 4.7) en comparación con los otros grupos<sup>48</sup>.

La agrupación de factores de riesgo para ECV que tipifica el SM es considerado a ser la fuerza de conducción de una nueva epidemia de ECV. Debido a su aumento concomitante en el riesgo de DM y ECV, el SM tendrá una enorme carga sobre las economías del mundo y en la salud pública, sin intervenciones precoces y eficaces<sup>22-24</sup>. La detección y manejo precoz de ECV subclínica puede mitigar algunos de los riesgos cardiovasculares asociados con trastornos metabólicos. Con la capacidad de detectar DVI subclínica en pacientes con trastornos metabólicos, el GLS por 2D-STE tiene el potencial de convertirse en una herramienta útil para la estratificación de riesgo en este tipo de población<sup>14,49</sup>.

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**Tabla 1. *Strain* longitudinal global en pacientes con síndrome metabólico (SM) versus participantes controles**

Estudio	Año	<i>n</i>	GLS pacientes	GLS	Valor de <i>p</i>
			con SM	Controles	
			Promedio ± DS	Promedio ± DS	
Tadic <i>et al</i> <sup>17</sup>	2014	160	-18.6 ± 1.6	-21.1 ± 2.0	< 0.001
Almeida <i>et al</i> <sup>18</sup>	2014	133	-12.1 ± 2.5	-13.9 ± 2.3	< 0.01
Crendal <i>et al</i> <sup>19</sup>	2013	108	-16.8 ± 2.8	-21.2 ± 2.6	< 0.001

DS: Desviación estándar; GLS: *strain* longitudinal global.

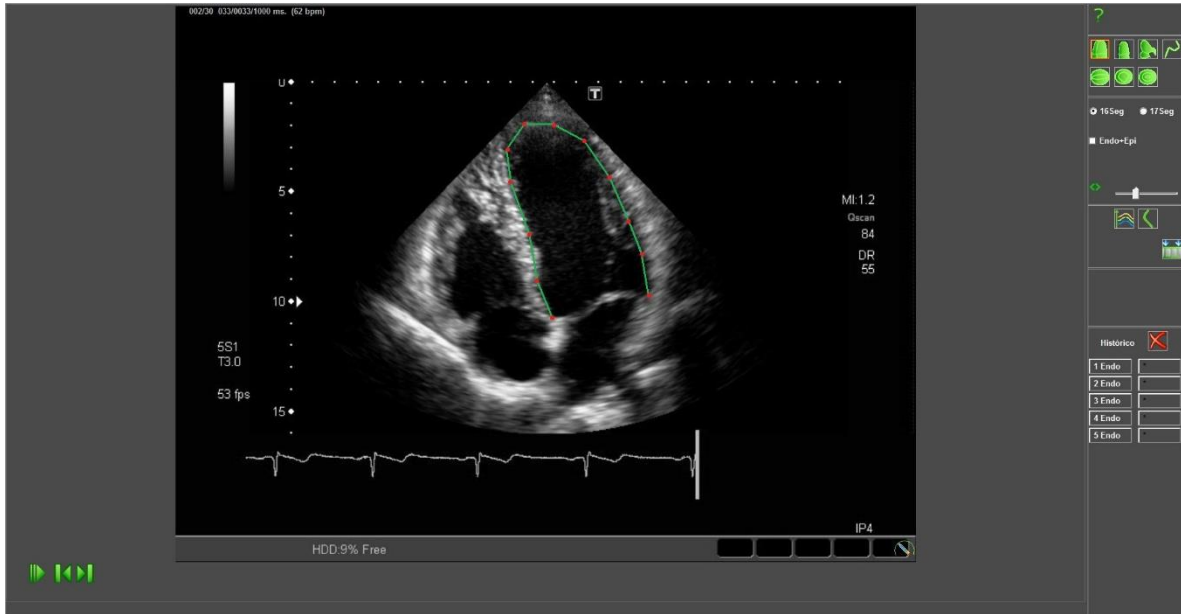


Figura 1. Demarcación de 8 a 12 puntos sobre el borde endocárdico del ventrículo izquierdo por metodología *speckle-tracking*.

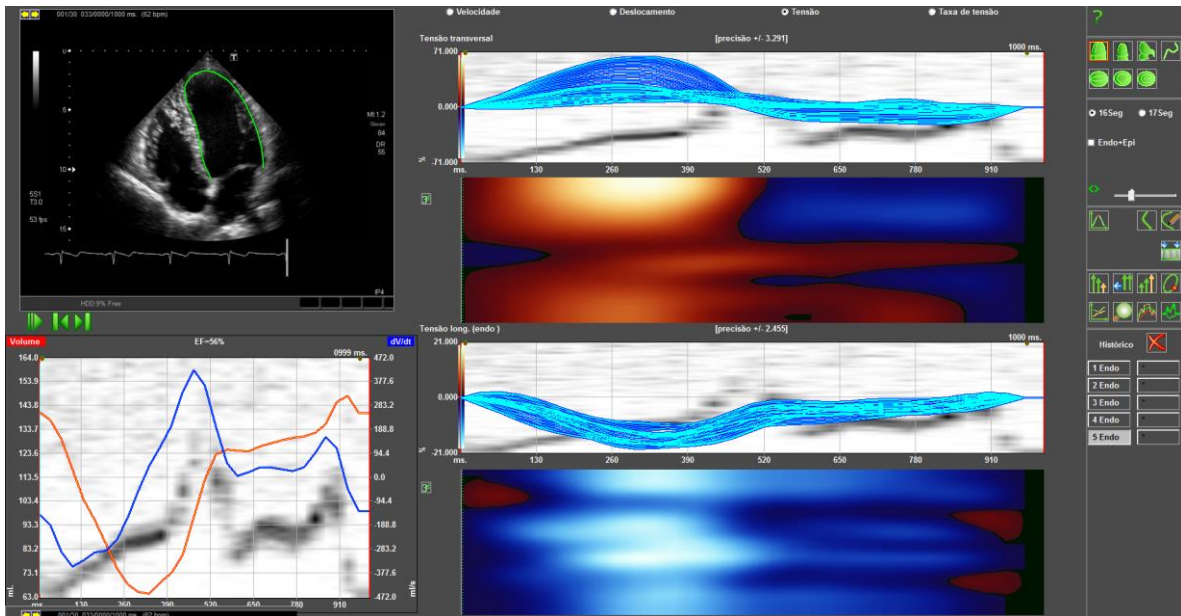


Figura 2. Representación paramétrica del *strain* longitudinal global.

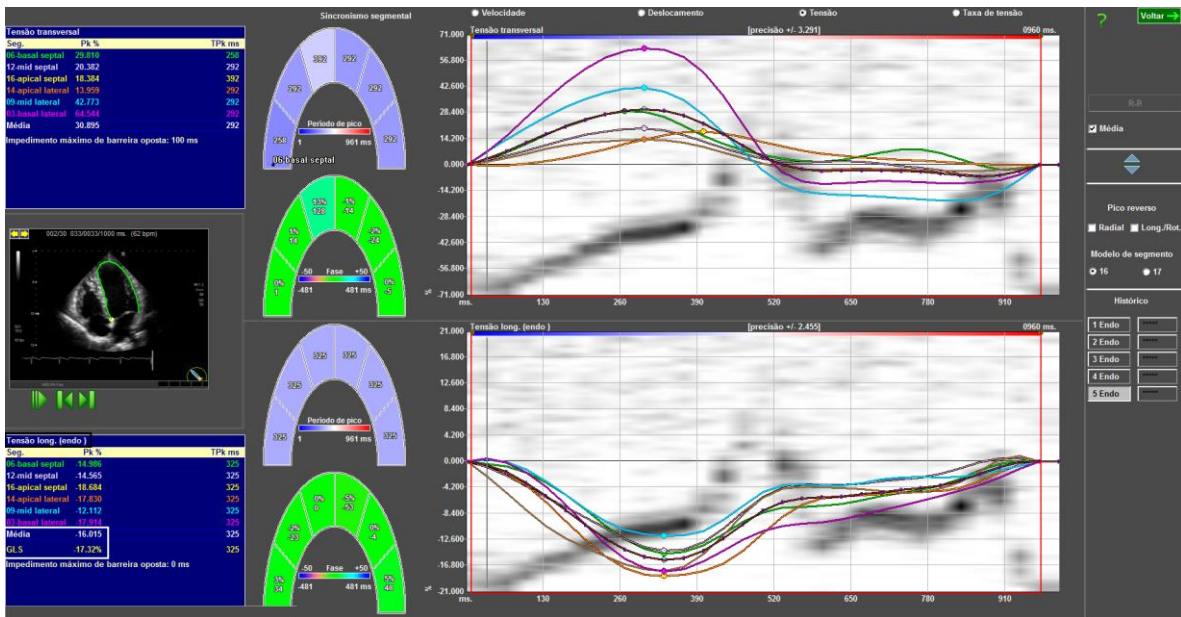


Figura 3. Análisis de *strain* longitudinal global por segmentos.

**2. Subclinical myocardial dysfunction by strain imaging in metabolic syndrome: the ELSA-Brasil study. (Artigo 2).**

Disfunção miocárdica subclínica por imagem de *strain* na síndrome metabólica: o estudo ELSA-Brasil.

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## Resumo

A disfunção sistólica subclínica é um dos mecanismos propostos para o aumento do risco cardiovascular associado à síndrome metabólica (SM) e pode ser detectada por ecocardiografia bidimensional *speckle-tracking* (2D-STE). O objetivo do estudo foi investigar a associação entre SM e o strain longitudinal global (GLS) do ventrículo esquerdo (VE) pela 2D-STE, um indicador de disfunção sistólica subclínica.

A partir da amostra aleatória do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) - um estudo de coorte multicêntrico de funcionários ativos ou aposentados com idades compreendidas entre 35 a 74 anos - foi medido o GLS naqueles participantes livres de doença arterial coronariana ou insuficiência cardíaca, e investigou-se sua associação com a SM, definida de acordo com os critérios do *Joint Interim Statement* para a população de origem europeu.

Entre os 1076 participantes que preencheram os critérios de inclusão [53% mulheres;  $52 \pm 9$  anos], 454 (42%) tinham SM. Os indivíduos com SM apresentaram piores valores de GLS [ $(-18,0 \pm 2,5\%)$ ] do que aqueles sem SM ( $-19,0 \pm 2,4\%$ ),  $p < 0,0001$ ] e quase duas vezes a prevalência de disfunção sistólica subclínica. Na análise de regressão linear múltipla, o GLS foi associado com SM, mesmo após o ajuste para sexo, idade, raça/cor, escolaridade, centro de investigação, frequência cardíaca e fração de ejeção do VE por 2D-STE ( $\beta = 0,58$ ;  $p < 0,0001$ ), mas o tamanho do efeito foi atenuado após ajuste para o índice de massa corporal ( $\beta = 0,39$ ;  $p = 0,004$ ).

A SM é independentemente associada com a alteração da função sistólica do VE medida por GLS. Este achado sugere a presença de uma alteração precoce subclínica da contratilidade miocárdica relacionada com SM.

**Subclinical Myocardial Dysfunction by Strain Imaging in Metabolic Syndrome:  
The ELSA-Brasil Study**

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## ABSTRACT

*Background:* Subclinical systolic dysfunction is one of proposed mechanisms for increased cardiovascular risk associated with metabolic syndrome (MetS) and can be detected by left ventricular (LV) global longitudinal strain (GLS) using 2D speckle-tracking echocardiography.

*Objective:* To investigate the association between MetS and impaired GLS.

*Methods:* From a randomly selected sample of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) - a multicenter cohort study of civil servants aged 35 to 74 years - we measured GLS in those free of coronary artery disease or heart failure, and investigated its association with MetS, defined according the Joint Interim Statement criteria for people of European origin.

*Results:* Among the 1076 participants who fulfilled the inclusion criteria [53% women;  $52 \pm 9$  years], 454 (42%) had MetS. Individuals with MetS had worse GLS [ $(-18.0 \pm 2.5\%)$ ] than those without MetS [ $(-19.0 \pm 2.4\%)$ ,  $p < 0.0001$ ], and about twice the prevalence of subclinical systolic dysfunction. In subjects with MetS, worse GLS was associated with worst values for waist circumference, systolic and diastolic blood pressure (all  $p$  values  $< 0.01$ ). In multiple linear regression analysis, GLS was associated with MetS even after adjusting for sex, age, race/color, educational level, study center, heart rate, and LV ejection fraction ( $\beta = 0.58$ ;  $p < 0.0001$ ), but the effect was attenuated after adjusting for body mass index ( $\beta = 0.39$ ;  $p = 0.004$ ). The adjusted prevalence ratio of altered GLS was higher in those with MetS compared to those without MetS for the 1.0 SD (GLS=-16.1%; PR=1.45 [95% CI: 1.09 - 1.93]) and 1.5 SD (GLS=-14.8%; PR=1.93 [95% CI: 1.25 - 2.99]) cut-offs, but was not statistically significant higher for the 2.0 SD (GLS=-13.5%; PR=1.63 [95% CI: 0.81 - 3.28]) cut-off.

*Conclusion:* MetS is independently associated with worst LV function at different GLS cutoffs. This finding suggests the presence of an early subclinical LV functional impairment related to MetS.

**Keywords:** Metabolic Syndrome; Ventricular Function, Left; Myocardial Contraction; Two Dimensional Speckle Tracking Echocardiography.

## INTRODUCTION

Metabolic syndrome (MetS) is characterized as a cluster of common cardiovascular (CV) risk factors including abdominal obesity, elevated blood pressure, impaired glucose tolerance, insulin resistance, elevated triglycerides, and low high-density lipoprotein cholesterol concentrations (1). This condition affects about 25% of the adult population, and is associated with an increased risk of developing diabetes, myocardial infarction, stroke, and death (2,3). Ischemia, metabolic substrate, inflammation and direct myocardial dysfunction have been demonstrated as potential mechanisms involved in this increased cardiac risk in MetS and in diabetes type 2 (T2D) (4,5,6). MetS and T2D have been associated with systolic and diastolic dysfunction identified by tissue Doppler imaging (TDI) (7,8), however, ejection fraction, the most used parameter for evaluation of systolic function has low sensitivity for assessment of early myocardial contractility dysfunction (9). The development of new echocardiographic techniques such as global longitudinal strain (GLS) by two-dimensional speckle-tracking echocardiography (2D-STE) has strengthened the ability to assess subclinical left ventricular (LV) dysfunction by quantitative assessment of myocardial deformation (10,11). Previous studies using 2D-STE have shown the association of subclinical CV disease with MetS and T2D (12,13,14). Nonetheless, this association is yet to be demonstrated in free-living samples of the population. Therefore, this study aim to investigate, in middle-aged adults free of prevalent heart disease, the association between MetS and impaired LV GLS by 2D-STE.

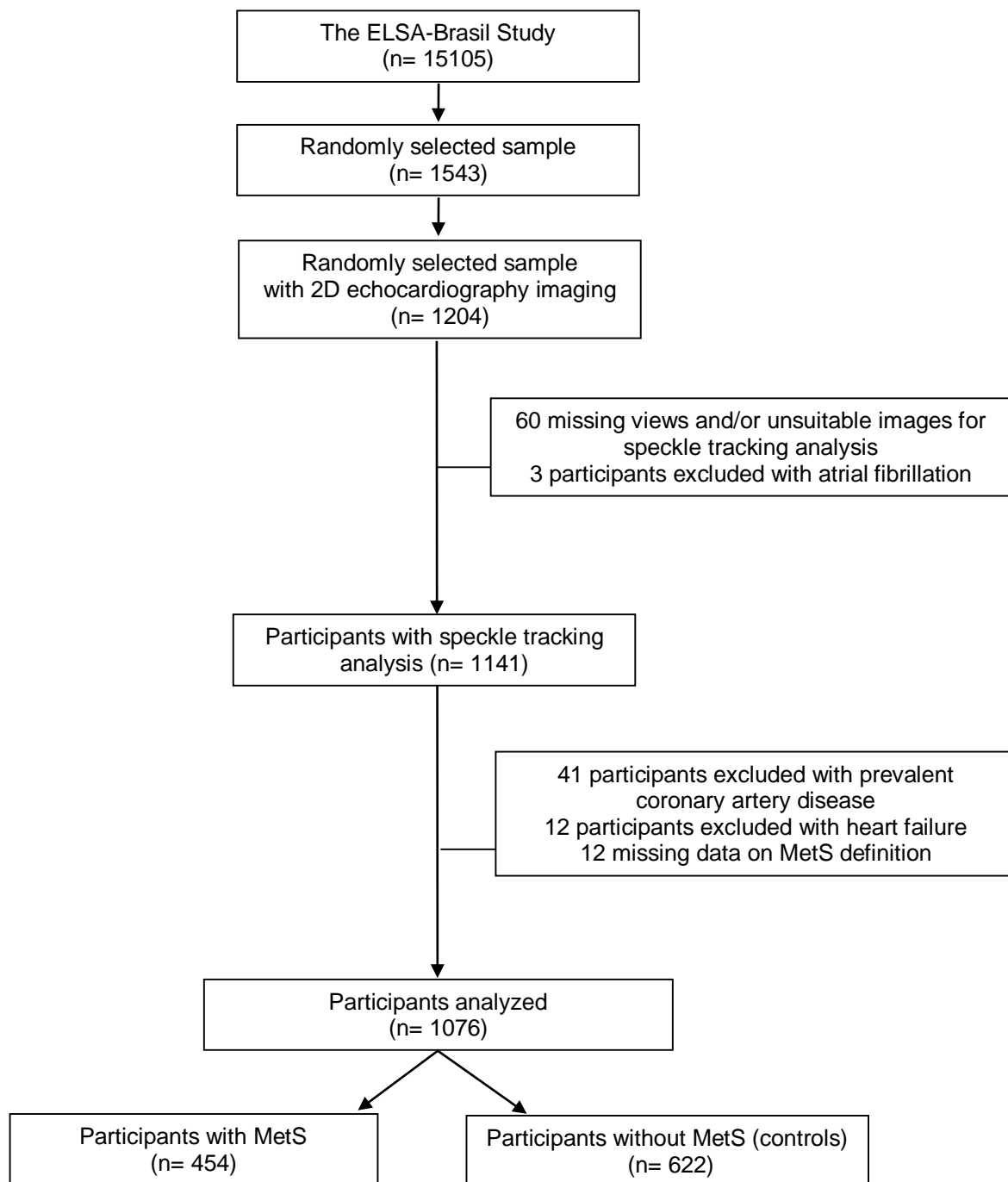
## METHODS

### Study population

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a cohort study of 15,105 men and women, civil servants from universities or research institutions located in six states of Brazil (baseline assessment was carried out from August 2008 to December 2010). All active or retired employees aged 35 to 74 years were eligible for the study. The details of the study, including design, eligibility criteria, sources and methods of recruitment, and measurements obtained, have been described elsewhere (15,16). The ELSA-Brasil was approved by the Research and Ethics Committees of the institutions involved, and all participants provided written informed consent. This



current study investigated a predefined randomly selected sample of participants who were submitted to 2D echocardiography. We included participants who underwent 2D-STE and were evaluated for all MetS components. Exclusion criteria were echocardiography missing views and/or unsuitable images for 2D-STE, atrial fibrillation, clinically diagnosed coronary artery disease or heart failure, and missing data on MetS definition (Figure 1).



**Figure 1. Participants' eligibility criteria for evaluation of global longitudinal strain**

## Cardiovascular risk factors assessment

Participants completed a comprehensive set of standardized medical history questionnaires determining medication use and previous clinical diagnoses (15). Serum concentrations of triglycerides, high-density lipoprotein (HDL) and fasting glucose were measured by enzymatic colorimetric assay and hexokinase method using a validated equipment (ADVIA 1200 Chemistry, Siemens®, Deerfield, United States). Anthropometry measures were performed following a standardized protocol. Waist circumference was measured at the midpoint between lower edge of arc of the rib (excluding the floating ribs) and mid-axillary line of iliac crest, using a standard tape measure. Blood pressure was measured three times in a seated position using a validated oscillometric device (Omron HEM-705CP IntelliSense®, Bannockburn, United States). The mean of last measurements was used in the analysis (15,17). Hypertension was defined according the VII Joint National Committee criteria (18).

## Metabolic syndrome definition

MetS was defined according to the Joint Interim Statement criteria for people of European origin (19). Participants with at least three of the following criteria were considered as having MetS: 1) fasting plasma glucose (FPG) level  $\geq 100$  mg/dL (5.5 mmol/L) or use of medication for hyperglycemia; 2) raised concentration of triglycerides  $\geq 150$  mg/dL (1.7 mmol/L) or specific treatment for this lipid anomaly; 3) reduced concentration of HDL-cholesterol  $< 40$  mg/dL (1.0 mmol/L) for men and  $< 50$  mg/dL (1.3 mmol/L) for women or specific treatment for this lipid anomaly; 4) abdominal obesity [waist circumference  $\geq 94$  cm for men and  $\geq 80$  cm for women]; 5) blood pressure  $\geq 130/85$  mmHg, or treatment for hypertension.

## 2D echocardiography and speckle-tracking analysis

All echocardiograms were performed by trained cardiologists following recommendations by the European and North American Cardiology Societies (20,21). All studies were obtained using identical equipment (Aplio XG, Toshiba Corporation, Toshigi, Japan) with a 2.5 MHz sector

transducer. Sequences of three consecutive heartbeats in each echocardiographic window were selected and recorded in digital format and then transferred to the ELSA echocardiography reading center, together with an image acquisition form reporting image quality and preliminary findings assessment. All studies were blindly read at the reading center, under a pre-specified protocol in a dedicated workstation (ComPACS Review Station 10.5, Medimatic Solutions Srl, Italy) (17).

#### Left ventricular global longitudinal strain and reproducibility

The quantitative assessment of myocardial deformation followed current procedures and guidelines for speckle-tracking echocardiography (11,22), using a commercially available software (2D Cardiac Performance Analysis©, TomTec-Arena™ 1.2 Imaging Systems, Unterschleißheim, Germany).

For analysis, endocardial borders were traced at the end-diastolic frame in the apical two and four chamber views. End-diastole was delimited by the QRS complex, or as the frame after mitral valve closure. The 2D-STE software tracks speckles patterns along the endocardial border throughout the cardiac cycle. Subsequently, GLS was measured and computed automatically (in 6 segments from each view) and presented as peak average in %. Intra and inter-observer variability for GLS measures were assessed in a sample of 20 randomly selected participants. Coefficient of variation was 5.6% and 8.7%, respectively. Intraclass correlation coefficients were 0.77 (95% CI: 0.59 to 0.95) and 0.68 (95% CI: 0.44 to 0.91), respectively.

#### Statistical analysis

Data are presented as mean  $\pm$  standard deviation (SD) for continuous variables and as a total number and proportions for categorical variables. Student's *t* test was used to assess differences in continuous variables between the groups studied, whereas Fisher and chi-square test was used for categorical analysis. We categorized GLS measures in quartiles for participants with MetS to illustrate statistical differences with clinical and demographic characteristics. Multiple linear regression analysis was performed to adjust for potential confounders in the relationship between GLS and MetS. Robust

Poisson regression was used to determine the association between MetS and impaired GLS, when the latter was defined categorially. We tested these models using different proposed cut-offs for GLS (23,24,25,26,27,28). All tests were two-sided and  $p$ -values  $< 0.05$  were considered statistically significant. Statistical analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

### Participant characteristics

Of the 1,204 participants with echocardiography, GLS was not measurable in 60 (5%) due to missing views or inadequate image quality, and 3 atrial fibrillation; 53 participants were excluded due to prevalent coronary artery disease or clinically diagnosed heart failure, and 12 additional participants were excluded due to missing data for the MetS definition. The final study population consisted of 1,076 participants (53% women;  $52 \pm 9$  years), from which 454 (42%) fulfilled diagnostic criteria for MetS. Participants with MetS were generally older, more obese, and had higher prevalences of hypertension and diabetes. [Table 1](#) shows the clinical and demographic characteristics of all participants.

**Table 1. Clinical and demographic characteristics of 1076 participants randomly selected from the baseline of the ELSA-Brasil study**

	<b>MetS (n=454, 42%)</b>	<b>Without MetS (n=622, 58%)</b>	<b>P-value</b>
<b>Demographic parameters</b>			
Age (years)	53 ± 8	51 ± 9	<0.0001
Sex (female)	216, 47.6%	359, 57.7%	0.001
Race/color (white)	204, 44.9%	336, 54.0%	0.004
Height (cm)	166 ± 9	165 ± 9	0.13
BMI (kg/m <sup>2</sup> )	29.0 ± 4.2	24.8 ± 3.6	<0.0001
Educational level			<0.0001
Never attended school or incomplete elementary school	37, 8.1%	22, 3.5%	
Complete elementary school or incomplete secondary school	36, 7.9%	25, 4.0%	
Complete secondary school	158, 34.8%	202, 32.5%	
University degree	223, 49.1%	373, 60.0%	
<b>Clinical and laboratory parameters</b>			
Waist circumference (cm)	98 ± 10	85 ± 10	<0.0001
Glucose (mg/dL)	120 ± 34	104 ± 19	<0.0001
Triglycerides (mg/dL)	184 ± 104	100 ± 46	<0.0001
HDL-cholesterol (mg/dL)	51 ± 12	61 ± 15	<0.0001
Systolic blood pressure (mmHg)	127 ± 17	116 ± 14	<0.0001
Diastolic blood pressure (mmHg)	80 ± 10	73 ± 9	<0.0001
Hypertension	257, 56.7%	102, 16.4%	<0.0001
Diabetes mellitus	141, 31.1%	57, 9.2%	<0.0001
Heart rate (bpm)	70 ± 11	67 ± 10	<0.0001
<b>Echocardiographic parameters</b>			
LA diameter (cm)	3.6 ± 0.4	3.4 ± 0.4	<0.0001
LA volume (ml)	50.3 ± 14.1	46.4 ± 12.5	<0.0001
LA BSA-indexed volume (ml/m <sup>2</sup> )	27.0 ± 7.0	26.6 ± 6.3	0.45
Mitral E to e' ratio	7.7 ± 2.0	6.9 ± 1.7	<0.0001
LV diastolic diameter (cm)	4.5 ± 0.4	4.4 ± 0.4	0.002
LV mass (g)	148 ± 37	124 ± 33	<0.0001
LV mass index-BSA (g/m <sup>2</sup> )	79.3 ± 17.2	71.0 ± 15.0	<0.0001
LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	38.0 ± 8.8	32.1 ± 7.3	<0.0001
LV ejection fraction - Teicholtz (%)	67 ± 7	66 ± 7	0.07
Relative wall thickness	0.43 ± 0.07	0.39 ± 0.06	<0.0001
<b>2D-STE parameters</b>			
Global longitudinal strain (%)	-18.0 ± 2.5	-19.0 ± 2.4	<0.0001
LV ejection fraction - four-chamber view (%)	57.4 ± 7.6	58.8 ± 7.1	0.003
LV ejection fraction - two-chamber view (%)	59.7 ± 7.1	61.1 ± 8.0	0.002

Data are shown as mean ± SD or n, %.

MetS: metabolic syndrome; BMI: body mass index; HDL: high-density lipoprotein; LA: left atrium; BSA: body surface area; LV: left ventricle; 2D-STE: two-dimensional speckle-tracking echocardiography.

## Left ventricular global longitudinal strain and metabolic syndrome

In overall sample, the mean of GLS was  $-18.6 \pm 2.5\%$ . Individuals with MetS had lower GLS [ $-18.0 \pm 2.5\%$ ] compared to the participants without MetS ( $-19.0 \pm 2.4\%$ ),  $p < 0.0001$ , indicating worse LV function (Figure 2).

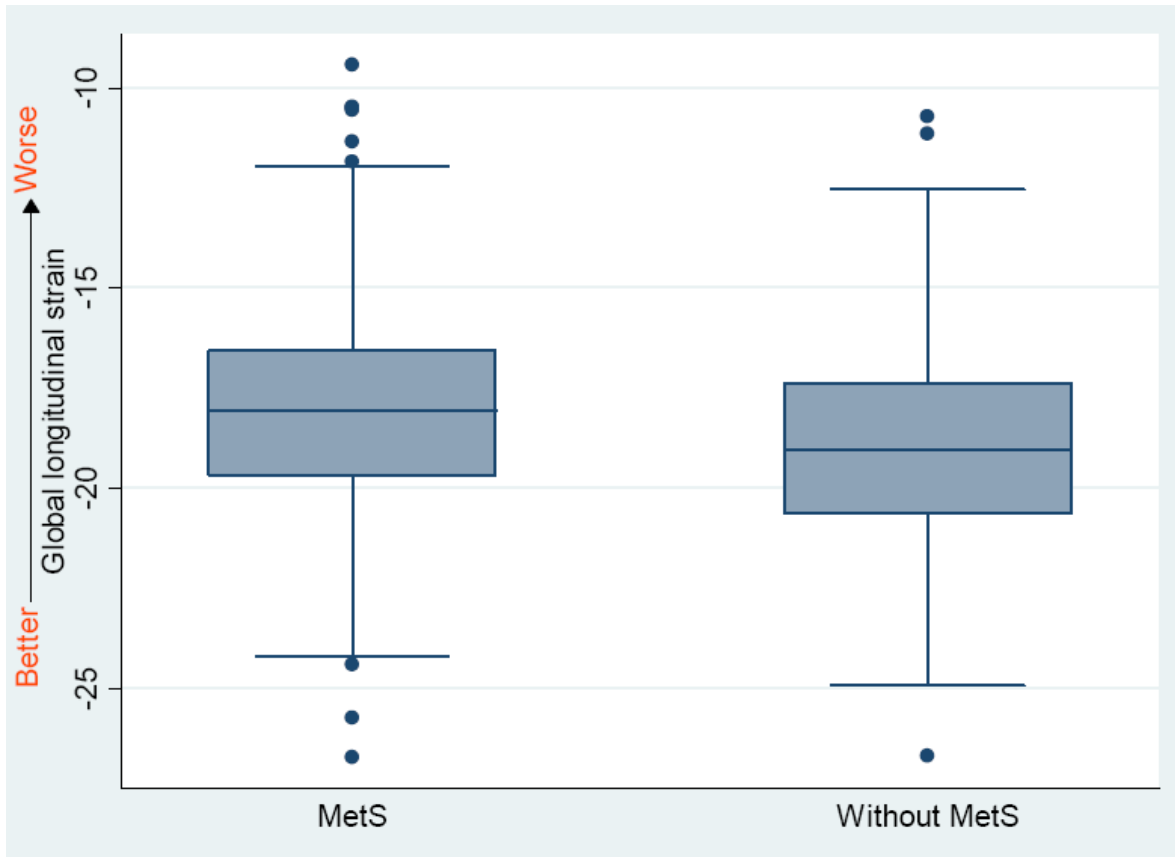


Figure 2. Global longitudinal strain according to the presence of the metabolic syndrome

In subjects with MetS, lower GLS was associated with worst values for waist circumference, systolic and diastolic blood pressures (all  $p$  values  $< 0.01$ ) (Table 2).

**Table 2. Clinical and demographic characteristics of participants presenting the metabolic syndrome according to quartiles of global longitudinal strain**

Characteristics Mean ± SD or n, %	Global longitudinal strain (GLS) ← Better → Worse				P-value
	Quartile 1 (n=113) (-26.73% to -19.71%)	Quartile 2 (n=114) (-19.70% to -18.05%)	Quartile 3 (n=114) (-18.04% to -16.57%)	Quartile 4 (n=113) (-16.56% to -9.43%)	
<b>Demographic parameters</b>					
Age (years)	53 ± 8	54 ± 9	53 ± 9	53 ± 8	0.58
Sex (female)	73, 63.5%	67, 58.3%	41, 35.3%	38, 33.0%	<0.0001
Race/color (white)	42, 37.2%	60, 52.6%	54, 46.5%	50, 43.9%	0.13
Height (cm)	163 ± 8	164 ± 9	168 ± 10	168 ± 8	<0.0001
BMI (kg/m <sup>2</sup> )	28.4 ± 3.8	28.8 ± 3.4	28.9 ± 4.1	29.9 ± 5.2	0.05
Educational level					0.17
Never attended school or incomplete elementary school	10, 8.7%	8, 7.0%	7, 6.0%	13, 11.3%	
Complete elementary school or incomplete secondary school	11, 9.6%	2, 1.7%	12, 10.3%	11, 9.6%	
Complete secondary school	36, 31.3%	39, 33.9%	42, 36.2%	42, 36.5%	
University degree	58, 50.4%	66, 57.4%	55, 47.4%	49, 42.6%	
<b>Clinical and laboratory parameters</b>					
Waist circumference (cm)*	95 ± 10	97 ± 8	100 ± 11	101 ± 12	<0.0001
Glucose (mg/dL)*	116 ± 32	117 ± 32	119 ± 33	127 ± 38	0.05
Triglycerides (mg/dL)*	177 ± 107	170 ± 95	207 ± 119	181 ± 85	0.03
HDL-cholesterol (mg/dL)*	51 ± 11	52 ± 13	51 ± 13	50 ± 11	0.84
Systolic blood pressure (mmHg)*	123 ± 15	125 ± 19	128 ± 15	130 ± 17	0.005
Diastolic blood pressure (mmHg)*	77 ± 10	78 ± 10	82 ± 10	84 ± 10	<0.0001
Hypertension*	56, 48.7%	63, 55.3%	68, 58.6%	71, 61.7%	0.22
Diabetes mellitus	34, 29.6%	30, 26.1%	31, 26.7%	48, 41.7%	0.03
Heart rate (bpm)	68 ± 10	69 ± 11	71 ± 10	73 ± 11	0.001
<b>Echocardiographic parameters</b>					
LA diameter (cm)	3.6 ± 0.4	3.6 ± 0.5	3.7 ± 0.4	3.6 ± 0.4	0.42
LA volume (ml)	50.0 ± 12.5	51.0 ± 15.4	50.9 ± 14.4	49.6 ± 14.4	0.88
LA BSA-indexed volume (ml/m <sup>2</sup> )	27.5 ± 6.7	27.7 ± 7.3	26.5 ± 6.7	25.9 ± 7.5	0.26
Mitral E to e' ratio	8.0 ± 1.9	7.9 ± 2.2	7.4 ± 1.9	7.6 ± 1.9	0.11
LV diastolic diameter (cm)	4.4 ± 0.4	4.4 ± 0.5	4.6 ± 0.4	4.6 ± 0.5	0.03
LV mass (g)	141 ± 33	145 ± 38	154 ± 37	157 ± 41	0.007
LV mass index-BSA (g/m <sup>2</sup> )	77.6 ± 15.6	78.9 ± 18.2	80.6 ± 17.3	81.2 ± 18.2	0.42
LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	37.5 ± 7.8	38.3 ± 9.2	38.0 ± 8.5	38.7 ± 9.9	0.79
LV ejection fraction - Teicholtz (%)	68 ± 7	69 ± 5	66 ± 7	65 ± 8	0.002
Relative wall thickness	0.43 ± 0.06	0.43 ± 0.07	0.43 ± 0.06	0.43 ± 0.07	0.88
<b>2D-STE parameters</b>					
LV ejection fraction - four-chamber view (%)	62.1 ± 5.8	59.5 ± 6.1	57.2 ± 6.5	51.0 ± 7.3	<0.0001
LV ejection fraction - two-chamber view (%)	64.0 ± 7.1	60.5 ± 5.9	59.3 ± 6.5	54.5 ± 5.4	<0.0001

BMI: body mass index; HDL: high-density lipoprotein; \* Metabolic syndrome component; LA: left atrium; BSA: body surface area; LV: left ventricle; 2D-STE: two-dimensional speckle-tracking echocardiography.

In multiple linear regression analysis, GLS was associated with MetS ( $\beta= 0.58$ ;  $p <0.0001$ ) even after adjusting for sex, age, race/color, educational level, study center, heart rate, and 2D speckle-tracking left ventricular ejection fraction from 4 Chamber apical view, but the effect was attenuated after adjusting for body mass index (Table 3).

**Table 3. Adjusted worsening (%) global longitudinal strain with the presence of metabolic syndrome. Random sample from ELSA-Brasil (2008-2012) (N=1076)**

Differences in Global Longitudinal Strain			
	% (SE)	P-value	R-squared (%)
Model 1	1.02 (0.15)	<0.0001	4.0
Model 2	0.90 (0.15)	<0.0001	13.0
Model 3	0.58 (0.12)	<0.0001	45.0
Model 4	0.39 (0.14)	0.004	45.0

SE: standard error.

Adjusted through multiple linear regression for the following:

Model 1: crude.

Model 2: model 1 + sex, age (years), race/color, educational level, ELSA-Brasil center.

Model 3: model 2 + heart rate (bpm), 2D speckle-tracking left ventricular ejection fraction from 4 Chamber apical view (%).

Model 4: model 3 + body mass index (kg/m<sup>2</sup>).

The adjusted prevalence of altered GLS was 45% higher in MetS compared to those without MetS for the 1.0 SD GLS cut-point (GLS=-16.1%; PR=1.45 [95% CI: 1.09 - 1.93]) and 93% higher for the 1.5 SD GLS cut-point (GLS=-14.8%; PR=1.93 [95% CI: 1.25 - 2.99]), but was not statistically significant higher for the 2.0 SD GLS cut-point (GLS=-13.5%; PR=1.63 [95% CI: 0.81 - 3.28]) (Table 4 and Figure 3).



**Table 4. Prevalence ratios (PR) for the association of metabolic syndrome with altered global longitudinal strain defined by various cut-offs. Random sample from ELSA-Brasil (2008-2012) (N=1076)**

	Association	
	PR	95% CI
<b>GLS cut-off <math>\leq</math> 1 SD (-16.1%)</b>		
Model 1	1.92	1.42 - 2.59
Model 2	1.76	1.30 - 2.39
Model 3	1.45	1.09 - 1.93
Model 4	1.21	0.89 - 1.65
<b>GLS cut-off <math>\leq</math> 1.5 SD (-14.8%)</b>		
Model 1	2.71	1.71 - 4.32
Model 2	2.44	1.52 - 3.92
Model 3	1.93	1.25 - 2.99
Model 4	1.55	0.96 - 2.52
<b>GLS cut-off <math>\leq</math> 2 SD (-13.5%)</b>		
Model 1	2.47	1.19 - 5.10
Model 2	2.18	1.05 - 4.54
Model 3	1.63	0.81 - 3.28
Model 4	1.32	0.61 - 2.88

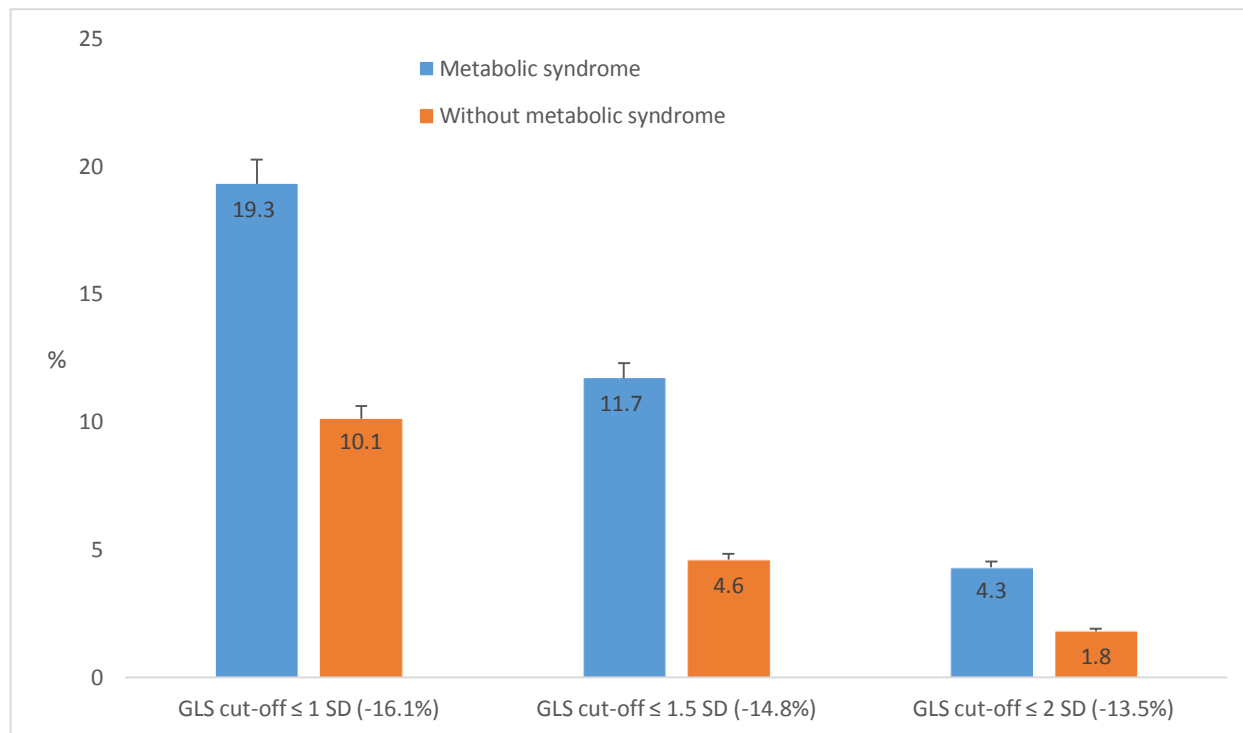
GLS: global longitudinal strain; SD: standard deviation.

Model 1: metabolic syndrome.

Model 2: model 1 + sex, age (years), race/color, educational level, ELSA-Brasil center.

Model 3: model 2 + heart rate (bpm), 2D speckle-tracking left ventricular ejection fraction from 4 Chamber apical view (%).

Model 4: model 3 + body mass index (kg/m<sup>2</sup>).



**Figure 3. Prevalence of altered global longitudinal strain (GLS) in participants with and without metabolic syndrome according to various cut-offs for GLS**

## DISCUSSION

In our study, one of the largest reported MetS samples of non-referred participants, the 42% individuals with MetS had worse LV function measured by GLS [ $-18.0 \pm 2.5\%$ ] compared to those without MetS [ $-19.0 \pm 2.4\%$ ],  $p < 0.0001$ . These MetS participants had about twice the prevalence of subclinical systolic dysfunction, using different GLS cut-off points. Moreover, MetS was independently associated with GLS even after adjusting for body mass index. A large body of evidence have shown the impact of obesity and cardiometabolic risk factors on myocardial dysfunction with structural and functional abnormalities as coronary dysfunction (4,5), diabetic cardiomyopathy (6), and LV hypertrophy (29). Nonetheless, the mechanisms contributing to these changes remain not completely understood with a complex interplay of hemodynamic, neurohumoral, and metabolic substrate as well as inflammation and oxidative stress, contributing to cellular apoptosis, hypertrophy, and interstitial fibrosis (4,5,30,31).

These associations of MetS with myocardial dysfunction have been previously shown using conventional echocardiography and TDI (7,8,32). Recently, 2D-STE has emerged as a more robust technique to detect subclinical LV dysfunction by quantitative assessment of myocardial deformation (10,11). 2D-STE has the advantage over TDI of angle independency, offering the possibility to examine a major component of regional myocardial performance (33,34). 2D-STE has becoming widely available, due to technological development and its inclusion in most commercially available echocardiographic systems. Crendal *et al.* (12) compared 92 MetS participants to healthy controls, and showed impaired longitudinal myocardial diastolic and systolic function in the former (35). Furthermore, in a subsample of the MESA study (14) MetS was significantly associated with worst GLS after adjustment for ethnicity, LV ejection fraction, and creatinine. More recently, Tadic *et al.* (13) and Wang *et al.* (36) found that LV function assessed by 2D-STE was significantly impaired in patients with MetS.

The lack of standardization across commercially available speckle-tracking software makes the evaluation of myocardial strain vendor-dependent (11,37,38,39). In addition, some studies showed that biological variation, as those related to age and sex, are likely to influence reference GLS values (23,25,40,41). Normal GLS values have been reported in a range between -11% and -

22% (23,24,25,26,27,28). In the Framingham Offspring Study, the 97th percentile of GLS in a normal healthy population was -14.4% in subjects  $\geq 75$  years old, and -15.0% and -16.2% in men and women 55-64 years old (25). In a recent meta-analysis (23) from 24 studies, normal values of GLS varied from -15.9% to -22.1% (mean, -19.7%; 95% CI, -18.9% to -20.4%). Our data showed a mean of GLS of  $-18.6 \pm 2.5\%$  in overall sample.

To overcome the limitation of cut-off definition of altered GLS we explored the associations of MetS with three different reference cut-offs for GLS. Our findings demonstrate a high prevalence (19.3%) of altered GLS in MetS participants compared to the remaining (10.1%) using the less conservative 1 SD cut-off. This higher prevalence was independently present after adjusting for most of relevant covariates except for BMI. As expected, prevalences were lower using stricter cut-offs, but associations were in general similar. Using this strategy, we were not able to identify a clear inflection point between MetS and increased risk of altered GLS, thus suggesting a progressive continuous risk. For the evidence known to date, this is the first echocardiography study to have reported associations between MetS and different reference cut-offs for LV GLS.

#### Study limitations

Because of the cross-sectional design of our study, a causal relationship between MetS and global longitudinal strain cannot be determined. The choice of covariates to adjust the models is also a matter of concern as most of these are intrinsically related to the MetS definition. Additionally, as previously stated, there are still some variation in GLS calculation algorithms across vendors, which may impair generalization to use the reported absolute GLS values. Prospective studies with a large number of participants are essential to evaluate the impact of impaired LV deformation on CV morbidity and mortality in MetS population.

#### Conclusions

LV function assessed by GLS was significantly impaired in MetS participants. We further found that the prevalence of impaired LV GLS was higher in MetS participants compared to controls using different GLS cut-offs. Our findings suggest the presence of an early subclinical direct cardiac impairment related to MetS. The early detection of subclinical myocardial dysfunction may allow a

better understanding of the pathophysiology of MetS, and could be tested as a CV risk stratification tool in this condition.

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**3. Association of global longitudinal strain with metabolic syndrome components: the role of abdominal obesity. (Artigo 3).**

Associação do *strain* longitudinal global com os componentes da síndrome metabólica: o papel da obesidade abdominal

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## Resumo

A síndrome metabólica (SM) é um agrupamento de fatores de risco cardiometabólicos, incluindo a obesidade abdominal, intolerância à glicose, resistência à insulina, dislipidemia e hipertensão. A disfunção sistólica subclínica avaliada pela ecocardiografia bidimensional *speckle-tracking* (2D-STE) está presente em indivíduos com SM, mas poucos estudos têm examinado o impacto dos componentes da SM na alteração do *strain* longitudinal global (GLS) do ventrículo esquerdo (VE). O objetivo do estudo foi determinar que componentes da SM são determinantes da alteração da função do VE e investigar a associação dos componentes da SM com o GLS.

A partir da amostra aleatória do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) - um estudo de coorte multicêntrico de funcionários ativos ou aposentados com idades compreendidas entre 35 a 74 anos - foi medido o GLS naqueles participantes livres de doença arterial coronariana ou insuficiência cardíaca.

Entre os 1074 participantes que preencheram os critérios de inclusão [53% mulheres;  $52 \pm 9$  anos], a média de GLS foi  $-18,6 \pm 2,5\%$ . Na análise de regressão quantílica ajustada, a circunferência da cintura elevada foi o componente da SM independentemente associado com o GLS alterado (percentil 95), mesmo após o ajuste para sexo, idade, raça/cor, escolaridade, centro de investigação, frequência cardíaca e fração de ejeção do VE ( $p < 0,0001$ ), e a associação permaneceu mesmo após o ajuste para o índice de massa corporal ( $p = 0,01$ ). As associações foram semelhantes utilizando-se como ponto de corte a mediana e o percentil 75 do GLS.

A circunferência da cintura elevada é o principal componente da SM associado com o GLS do VE. Este achado destaca a importância da obesidade abdominal no contexto de consequências cardiovasculares da SM.

## **Association of Global Longitudinal Strain with Metabolic Syndrome Components: The Role of Abdominal Obesity**

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## ABSTRACT

*Background:* Metabolic syndrome (MetS) is a clustering of cardio-metabolic risk factors, including abdominal obesity, impaired glucose tolerance, insulin resistance, dyslipidemia and hypertension. Subclinical systolic dysfunction assessed by 2D speckle-tracking echocardiography (2D-STE) is present in individuals with MetS, but few studies have examined the impact of each MetS component on left ventricular (LV) global longitudinal strain (GLS) impairment.

*Objective:* To determine which components of the MetS are determinants of impaired LV function, and investigate the association of MetS components with GLS.

*Methods:* From a randomly selected sample of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) - a multicenter cohort study of civil servants aged 35 to 74 years - we measured LV GLS in those free of prevalent coronary artery disease and heart failure, and investigated its association with MetS components.

*Results:* Among the 1074 participants who fulfilled the inclusion criteria [53% women;  $52 \pm 9$  years], the mean of GLS was  $-18.6 \pm 2.5\%$ . In adjusted quantile regression analysis, only elevated waist circumference MetS criteria was independently associated with impaired GLS (95th quantile) after adjusting for sex, age, race/color, educational level, heart rate, study center and LV ejection fraction ( $p < 0.0001$ ), this association remained statistically significant even after adjusting for body mass index ( $p$ -value= 0.01). Associations were rather similar using 50th and 75th GLS quantiles.

*Conclusion:* Elevated waist circumference is the main MetS component associated with LV GLS. This finding highlights the importance of abdominal obesity in the context of cardiovascular consequences of MetS.

**Keywords:** Metabolic Syndrome; Risk Factors; Ventricular Function, Left; Myocardial Contraction; Two Dimensional Speckle Tracking Echocardiography.

## INTRODUCTION

With overweight and obesity reaching epidemic proportions (1), there are increased risks of cardiovascular (CV) morbidity and mortality related to adverse metabolic effects (2,3). Metabolic syndrome (MetS) represents the accumulation of multiple CV risk factors (abdominal obesity, impaired glucose tolerance, insulin resistance, dyslipidemia, and hypertension) (4), which may lead to left ventricular (LV) hypertrophy (5), and heart failure (6). MetS has been associated with systolic and diastolic dysfunction (7,8), however, ejection fraction, the most used parameter for evaluation of systolic function, have low sensitivity for assessment of early myocardial contractility dysfunction (9). Newer echocardiographic methods such as LV global longitudinal strain (GLS) by two-dimensional speckle-tracking echocardiography (2D-STE) has emerged as a most robust technique to detect subclinical LV dysfunction through quantitative assessment of myocardial deformation (10,11). However, there is controversy about the proper GLS cut-off to define subclinical LV dysfunction (12) and few studies have examined the impact of each MetS component on myocardial dysfunction (13,14,15). Therefore, this study aim to identify, in middle-aged adults free of prevalent heart disease, which components of the MetS are independently associated with LV GLS using different GLS impairment cut-off criteria.

## METHODS

### Study population

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a cohort study of 15,105 men and women, civil servants from universities or research institutions located in six states of Brazil (baseline assessment was carried out from August 2008 to December 2010). All active or retired employees aged 35 to 74 years were eligible for the study. The details of the study, including design, eligibility criteria, sources and methods of recruitment, and measurements obtained, have been described elsewhere (16,17). The ELSA-Brasil was approved by the Research and Ethics Committees of the institutions involved, and all participants provided written informed consent. This current study investigated a predefined randomly selected sample of participants who were submitted to 2D echocardiography. We included participants who underwent 2D-STE and were evaluated for

all MetS components. Exclusion criteria were echocardiography missing views and/or unsuitable images for 2D-STE, atrial fibrillation, clinically diagnosed coronary artery disease or heart failure and missing data on MetS definition.

#### Cardiovascular risk factors assessment

Participants completed a comprehensive set of standardized medical history questionnaires determining medication use and previous clinical diagnoses (16). Serum concentrations of triglycerides, high-density lipoprotein (HDL) and fasting glucose were measured by enzymatic colorimetric assay and hexokinase method using a validated equipment (ADVIA 1200 Chemistry, Siemens®, Deerfield, United States). Anthropometry measures were performed following a standardized protocol. Waist circumference was measured at the midpoint between lower edge of arc of the rib (excluding the floating ribs) and mid-axillary line of iliac crest, using a standard tape measure. Blood pressure was measured three times in a seated position using a validated oscillometric device (Omron HEM-705CP IntelliSense®, Bannockburn, United States). The mean of last measurements was used in the analysis (16,18). Hypertension was defined according the VII Joint National Committee criteria (19).

#### Metabolic syndrome definition

MetS was defined according to the Joint Interim Statement criteria for people of European origin (20). Participants with at least three of the following criteria were considered as having MetS: 1) fasting plasma glucose (FPG) level  $\geq 100$  mg/dL (5.5 mmol/L) or use of medication for hyperglycemia; 2) raised concentration of triglycerides  $\geq 150$  mg/dL (1.7 mmol/L) or specific treatment for this lipid anomaly; 3) reduced concentration of HDL-cholesterol  $< 40$  mg/dL (1.0 mmol/L) for men and  $< 50$  mg/dL (1.3 mmol/L) for women or specific treatment for this lipid anomaly; 4) abdominal obesity [waist circumference  $\geq 94$  cm for men and  $\geq 80$  cm for women]; 5) blood pressure  $\geq 130/85$  mmHg, or treatment for hypertension.

## 2D echocardiography and speckle-tracking analysis

All echocardiograms were performed by trained cardiologists following recommendations by the European and North American Cardiology Societies (21,22). All studies were obtained using identical equipment (Aplio XG, Toshiba Corporation, Tshigi, Japan) with a 2.5 MHz sector transducer. Sequences of three consecutive heartbeats in each echocardiographic window were selected and recorded in digital format and then transferred to the ELSA echocardiography reading center, together with an image acquisition form reporting image quality and preliminary findings assessment. All studies were blindly read at the reading center, under a pre-specified protocol in a dedicated workstation (ComPACS Review Station 10.5, Medimatic Solutions Srl, Italy) (18).

## Left ventricular global longitudinal strain and reproducibility

The quantitative assessment of myocardial deformation followed current procedures and guidelines for speckle-tracking echocardiography (11,23), using a commercially available software (2D Cardiac Performance Analysis©, TomTec-Arena™ 1.2 Imaging Systems, Unterschleißheim, Germany).

For analysis, endocardial borders were traced at the end-diastolic frame in the apical two and four chamber views. End-diastole was delimited by the QRS complex, or as the frame after mitral valve closure. The 2D-STE software tracks speckles patterns along the endocardial border throughout the cardiac cycle. Subsequently, GLS was measured and computed automatically (in 6 segments from each view) and presented as peak average in %. Intra and inter-observer variability for GLS measures were assessed in a sample of 20 randomly selected participants. Coefficient of variation was 5.6% and 8.7%, respectively. Intraclass correlation coefficients were 0.77 (95% CI: 0.59 to 0.95) and 0.68 (95% CI: 0.44 to 0.91), respectively.

## Statistical analysis


Data are presented as mean  $\pm$  standard deviation (SD) for continuous variables and as a total number and proportions for categorical variables. Differences in clinical and demographic

characteristics were tested for trend in GLS quartiles. We estimated 50th, 75th and 95th quantile thresholds for GLS measures using quantile regression analysis (24), and multivariable models were adjusted for clinically relevant covariates. All tests were two-sided and  $p$ -values  $< 0.05$  were considered statistically significant. Statistical analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

Of the 1,204 participants with echocardiography, 2D-STE was not measurable in 60 (5%) due to missing views or inadequate image quality, 3 participants had atrial fibrillation and were not measured, 53 participants were excluded due to prevalent coronary artery disease or clinically diagnosed heart failure, and 14 additional participants were excluded due to missing data on MetS definition. The final study population consisted of 1,074 participants (53% women;  $52 \pm 9$  years). In overall sample, the mean of GLS was  $-18.6 \pm 2.5\%$ . [Table 1](#) shows the clinical and demographic characteristics of all participants according to quartiles of GLS. Worst GLS (less negative values) was associated with most of MetS components (all  $p$  values  $< 0.01$ ).

**Table 1. Clinical and demographic characteristics of participants according to quartiles of global longitudinal strain. Random sample from ELSA-Brasil (2008-2012) (N=1074)**

Characteristics Mean ± SD or n, %	Global longitudinal strain (GLS) 					P-value
	Overall (n=1074)	Quartile 1 (n=268)	Quartile 2 (n=269)	Quartile 3 (n=269)	Quartile 4 (n=268)	
Global longitudinal strain, %	-18.6 ± 2.5	-26.73% to -20.27%	-20.26% to -18.61%	-18.60% to -17.08%	-17.07% to -9.43%	
<b>Demographic parameters</b>						
Age (years)	52 ± 9	51 ± 8	52 ± 9	52 ± 9	52 ± 8	0.43
Sex (female)	573, 53%	189, 70.5%	158, 58.7%	125, 46.5%	101, 37.7%	<0.0001
Race/color (white)	538, 50.1%	134, 50.0%	137, 50.9%	135, 50.2%	132, 49.2%	0.98
Height (cm)	165 ± 9	163 ± 8	164 ± 9	166 ± 10	167 ± 9	<0.0001
BMI (kg/m <sup>2</sup> )	26.6 ± 4.4	25.8 ± 4.0	26.0 ± 3.9	26.9 ± 4.5	27.6 ± 4.8	<0.0001
<b>Educational level</b>						
Never attended school or incomplete elementary school	59, 5.5%	13, 4.8%	12, 4.5%	15, 5.6%	19, 7.1%	0.34
Complete elementary school or incomplete secondary school	61, 5.7%	14, 5.2%	14, 5.2%	11, 4.1%	22, 8.2%	
Complete secondary school	360, 33.5%	84, 31.3%	86, 32.0%	96, 35.7%	94, 35.1%	
University degree	594, 55.3%	157, 58.6%	157, 58.4%	147, 54.6%	133, 49.6%	
<b>Clinical and laboratory parameters</b>						
Elevated waist circumference*	645, 60.1%	142, 53.0%	151, 56.1%	171, 63.6%	181, 67.5%	0.002
Elevated glucose and/or diabetes treatment	766, 71.3%	179, 66.8%	179, 66.5%	194, 72.1%	214, 79.8%	0.002
Elevated triglycerides and/or hypolipemic medication use	334, 31.1%	61, 22.8%	68, 25.3%	97, 36.1%	108, 40.3%	<0.0001
Reduced HDL-cholesterol and/or hypolipemic medication use	205, 19.1%	46, 17.2%	57, 21.2%	54, 20.1%	48, 17.9%	0.61
Elevated blood pressure and/or hypertension treatment	459, 42.7%	94, 35.1%	101, 37.5%	125, 46.5%	139, 51.9%	0.0002
Heart rate (bpm)	69 ± 10	66 ± 9	68 ± 10	69 ± 10	71 ± 11	<0.0001
<b>Echocardiographic parameters</b>						
LA diameter (cm)	3.5 ± 0.4	3.5 ± 0.4	3.5 ± 0.4	3.5 ± 0.4	3.5 ± 0.5	0.09
LA volume (ml)	48.0 ± 13.3	48.4 ± 12.3	46.9 ± 12.1	48.1 ± 13.6	48.9 ± 15.4	0.42
LA BSA-indexed volume (ml/m <sup>2</sup> )	26.7 ± 6.6	27.7 ± 6.4	26.5 ± 6.0	26.4 ± 6.6	26.2 ± 7.4	0.07
Mitral E to e' ratio	7.2 ± 1.9	7.4 ± 1.9	7.2 ± 1.9	7.0 ± 1.9	7.3 ± 2.0	0.30
LV diastolic diameter (cm)	4.5 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.5 ± 0.4	4.5 ± 0.5	0.001
LV mass (g)	134 ± 37	126 ± 31	128 ± 33	138 ± 39	146 ± 40	<0.0001
LV mass index-BSA (g/m <sup>2</sup> )	74.4 ± 16.4	71.9 ± 14.7	72.0 ± 15.3	75.6 ± 17.3	78.4 ± 17.7	<0.0001
LV mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	34.5 ± 8.4	33.4 ± 7.4	33.3 ± 8.0	35.0 ± 8.7	36.4 ± 9.2	<0.0001
LV ejection fraction - Teicholtz (%)	67 ± 7	68 ± 6	67 ± 7	66 ± 6	65 ± 8	<0.0001
Relative wall thickness	0.41 ± 0.07	0.40 ± 0.06	0.40 ± 0.07	0.41 ± 0.07	0.42 ± 0.07	0.02
<b>2D-STE parameters</b>						
LV ejection fraction - four-chamber view (%)	58.2 ± 7.3	63.2 ± 6.0	60.0 ± 5.5	57.6 ± 6.1	52.0 ± 6.7	<0.0001
LV ejection fraction - two-chamber view (%)	60.5 ± 7.6	66.0 ± 7.5	61.8 ± 6.4	58.9 ± 6.1	55.4 ± 6.4	<0.0001

All p values are for quartiles of GLS; GLS: global longitudinal strain; BMI: body mass index; \* European origin cut-off waist circumference ≥ 94 cm for men and ≥ 80 cm for women; HDL: high-density lipoprotein; LA: left atrium; BSA: body surface area; LV: left ventricle; 2D-STE: two-dimensional speckle-tracking echocardiography.



In adjusted quantile regression analysis (Table 2), elevated waist circumference was the MetS component independently associated with impaired GLS (95th quantile), even after adjusting for sex, age, race/color, educational level, heart rate, study center and LV ejection fraction ( $p < 0.0001$ ), and the association remained significant even after adjust for body mass index ( $p = 0.01$ ). Most of the unadjusted and adjusted associations were rather similar using 50th and 75th quantiles of GLS distribution. However, in the fully adjusted model for the 75th quantile GLS cut-off, the hypertriglyceridemia criteria was independently associated with GLS ( $p = 0.03$ ) while waist circumference was only borderline significant ( $p = 0.06$ ).

**Table 2. Quantile regression for the association of metabolic syndrome components with global longitudinal strain. Random sample from ELSA-Brasil (2008-2012) (N=1074)**

	Model 1		Model 2		Model 3		Model 4		Model 5	
	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value	Beta (SE)	P-value
<b>50th Quantile GLS</b>										
Elevated waist circumference*	0.73 (0.19)	0.0001	0.32 (0.17)	0.07	0.85 (0.17)	<0.0001	0.42 (0.13)	0.002	0.39 (0.19)	0.04
Elevated glucose and/or diabetes treatment	0.77 (0.20)	0.0001	0.35 (0.21)	0.09	-0.21 (0.20)	0.30	0.04 (0.12)	0.71	0.02 (0.14)	0.90
Elevated triglycerides and/or hypolipemic medication use	1.02 (0.17)	<0.0001	0.69 (0.19)	0.0003	0.55 (0.21)	0.01	0.24 (0.17)	0.16	0.27 (0.16)	0.10
Reduced HDL-cholesterol and/or hypolipemic medication use	-0.02 (0.27)	0.94	-0.19 (0.18)	0.29	-0.24 (0.20)	0.22	0.14 (0.19)	0.45	0.15 (0.18)	0.40
Elevated blood pressure and/or hypertension treatment	0.75 (0.19)	<0.0001	0.42 (0.18)	0.02	0.27 (0.17)	0.12	0.07 (0.14)	0.59	0.09 (0.15)	0.53
<b>75th Quantile GLS</b>										
Elevated waist circumference*	0.56 (0.19)	0.004	0.42 (0.19)	0.03	0.81 (0.19)	<0.0001	0.42 (0.15)	0.004	0.40 (0.21)	0.06
Elevated glucose and/or diabetes treatment	0.71 (0.19)	0.0002	0.38 (0.24)	0.12	0.14 (0.21)	0.49	0.02 (0.16)	0.91	0.01 (0.17)	0.95
Elevated triglycerides and/or hypolipemic medication use	0.76 (0.24)	0.001	0.66 (0.25)	0.008	0.65 (0.21)	0.002	0.39 (0.18)	0.03	0.33 (0.16)	0.03
Reduced HDL-cholesterol and/or hypolipemic medication use	-0.08 (0.20)	0.69	-0.35 (0.35)	0.31	-0.35 (0.23)	0.13	-0.22 (0.19)	0.25	-0.26 (0.18)	0.13
Elevated blood pressure and/or hypertension treatment	0.70 (0.20)	0.0006	0.36 (0.23)	0.12	0.23 (0.21)	0.26	0.11 (0.17)	0.49	0.05 (0.17)	0.78
<b>95th Quantile GLS</b>										
Elevated waist circumference*	1.11 (0.38)	0.004	1.08 (0.44)	0.01	0.96 (0.31)	0.002	0.94 (0.20)	<0.0001	0.68 (0.27)	0.01
Elevated glucose and/or diabetes treatment	1.72 (0.32)	<0.0001	0.66 (0.44)	0.14	0.91 (0.29)	0.001	0.26 (0.26)	0.32	0.27 (0.27)	0.31
Elevated triglycerides and/or hypolipemic medication use	0.87 (0.50)	0.08	0.41 (0.56)	0.46	0.45 (0.33)	0.18	0.11 (0.23)	0.64	0.03 (0.23)	0.90
Reduced HDL-cholesterol and/or hypolipemic medication use	-0.03 (0.49)	0.95	0.04 (0.52)	0.93	-0.35 (0.35)	0.31	-0.11 (0.27)	0.69	-0.29 (0.28)	0.31
Elevated blood pressure and/or hypertension treatment	1.00 (0.38)	0.008	1.12 (0.41)	0.006	0.49 (0.30)	0.10	0.27 (0.24)	0.26	0.24 (0.24)	0.32

GLS: global longitudinal strain; SE: standard error; HDL: high-density lipoprotein; \* European origin cut-off waist circumference  $\geq 94$  cm for men and  $\geq 80$  cm for women.

Model 1: specific metabolic syndrome component.

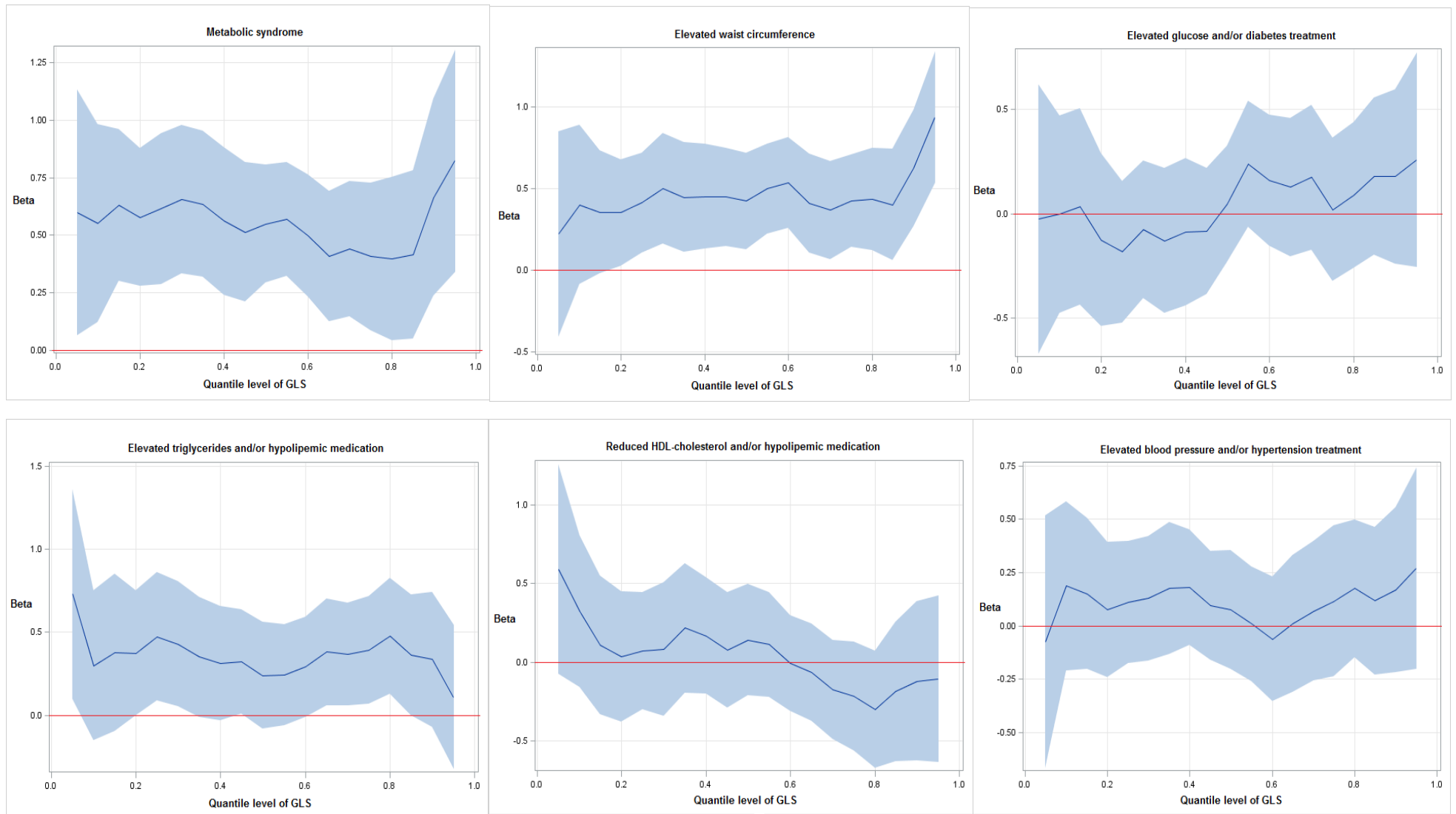
Model 2: adjusted for all metabolic syndrome components.

Model 3: model 2 + sex, age (years), race/color, educational level, ELSA-Brasil center.

Model 4: model 3 + heart rate (bpm), 2D speckle-tracking left ventricular ejection fraction from 4 Chamber apical view (%).

Model 5: model 4 + body mass index (kg/m<sup>2</sup>).

Figure 1 shows the quantile regression estimates for the associations of each MetS component with GLS analysed linearly. In this figure, elevated waist circumference reflects most of the association seen for MetS. This association remained significant throughout GLS distribution.



**Figure 1. Quantile regression estimates for the association of metabolic syndrome components with global longitudinal strain**

All plots adjusted for elevated waist circumference, elevated glucose and/or diabetes treatment, elevated triglycerides and/or hypolipemic medication use, reduced HDL-cholesterol and/or hypolipemic medication use, elevated blood pressure and/or hypertension treatment, sex, age (years), race/color, educational level, ELSA-Brasil center, heart rate (bpm), and 2D speckle-tracking left ventricular ejection fraction from 4 Chamber apical view (%).

## DISCUSSION

In this study, we investigated the association of GLS - an indicator of subclinical systolic dysfunction - with currently recommended MetS components in a multicenter cohort of middle-aged individuals. We showed that elevated waist circumference is the main MetS component associated with systolic function as measured by GLS.

In 2009, important health organizations met to construct a Joint Interim Statement intended to harmonize the diagnosis of MetS worldwide (20). This current definition of MetS proposed common operational criteria for the clinical diagnosis of MetS, but it is not clear whether these criteria depict the association of etiological factors that characterize the syndrome. Under this perspective, it makes more sense to identify the association of GLS with MetS components that with the syndrome itself.

It is known that MetS is associated with systolic and diastolic dysfunction identified by tissue Doppler imaging (TDI) (7,8), and speckle-tracking echocardiography (13,14,15), however, few studies using 2D-STE have examined which components of the MetS explain the impairment of systolic function. Previous studies demonstrated the unfavorable influence of different MetS risk factors on LV deformation such as arterial hypertension (25,26), diabetes (27,28), obesity (29,30) and dyslipidemia (31,32). Ivanovic *et al.* (33) using TDI, found that systolic blood pressure and fasting glucose were independently associated with the LV global function. In another report from the same study, systolic blood pressure was the only MetS criterion associated with LV structure and function (34).

On the other hand, some evidences support the existence of associations between components of MetS and myocardial dysfunction with increased number of risk factors for MetS. Tadic *et al.* (35) showed that increasing number of MetS criteria is associated with cardiac diastolic dysfunction. In the Multiethnic Study of Atherosclerosis (15), waist circumference and fasting glucose were significantly associated with LV impairment of circumferential and longitudinal strain, respectively. Authors also showed that GLS changed from -14.2% in participants with  $\leq$  one MetS component, to -13.4%, in participants with two, and to -12.1% in those with  $\geq$  three MetS criteria ( $p < 0.01$ ). Recently, Tadic *et al.* (14) and Wang *et al.* (36) found that among all MetS components, blood

pressure, waist circumference and fasting plasma glucose are the most associated with LV deformation indices.

There is evidence showing the impact of obesity and cardiometabolic risk factors on myocardial dysfunction with structural and functional abnormalities (37,38,39). Nonetheless, the mechanisms contributing to these changes remain not completely understood. Furthermore, in terms of obesity, there is increasing recognition that 'unhealthy metabolically obese' are more prone for complications compared to 'metabolically healthy obese'. The last are individuals with obesity who are free of chronic disease or its metabolic disturbances precursors and this condition is characterized by preserved insulin sensitivity, relatively low visceral fat mass, normal adipose tissue function, favorable cholesterol levels, and normal blood pressure (40,41). In this respect, recent studies showed that obesity was associated with subclinical differences in both systolic and diastolic function regardless of the presence or absence of MetS (42,43).

Interestingly, in the present study, all the parameters of the MetS, except reduced HDL-cholesterol, were individually associated with worse GLS (all p values <0.01). In addition, we demonstrated using adjusted quantile regression, that only elevated waist circumference was the MetS component independently associated with impaired GLS (95th quantile) after adjusting for most of confounders, including body mass index. Using this strategy, we were able to identify the associations of each MetS component with GLS analysed linearly. The findings showed that elevated waist circumference reflects most of the association seen for MetS, and the association is likely stronger after the GLS 90th quantile, thus suggesting an inflection point where GLS is more susceptible for the effects of elevated waist circumference.

#### Strengths and limitations

The strengths of our study are the large number of subjects randomly selected from a multicenter cohort, use of advanced imaging techniques, and wide range of CV risk profiles present in our study population. However, our study also has limitations. Because of the cross-sectional design of our study, a causal relationship between MetS components and GLS cannot be determined. Prospective studies with a large number of participants are essential to evaluate the impact of

impaired LV deformation on CV morbidity and mortality in MetS population. Although we accounted for several confounders and performed multivariate analyses adjusting for established CV risk factors, we cannot rule out the possibility of unmeasured confounders playing a role in the observed associations. Finally, it is still unclear what is the appropriate GLS cut-off to define abnormality. For this reason, we transformed a theoretical limitation in a methodological strength, using an approach to test GLS continuously.

## Conclusions

In middle-aged adults with normal ejection fraction and free of prevalent heart disease, the use of 2D-STE allowed identifying that elevated waist circumference is the main MetS component associated with LV GLS. This finding highlights the importance of abdominal obesity in the context of cardiovascular consequences of MetS.

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#### 4. CONCLUSÕES E CONSIDERAÇÕES FINAIS

A presente tese de doutorado investigou a associação entre a síndrome metabólica e seus componentes com o *strain* longitudinal global (GLS) medido pela ecocardiografia bidimensional *speckle-tracking* em adultos de meia idade no contexto brasileiro. Os dados do ELSA-Brasil aqui apresentados mostram a associação entre síndrome metabólica e seus componentes com disfunção ventricular esquerda subclínica no cenário brasileiro, abrangendo indivíduos da população urbana das regiões Nordeste, Sul e Sudeste do país, contemplando suas diversidades étnicas e sociais.

Os dados avaliados neste estudo revelaram que a síndrome metabólica é independentemente associada com a alteração da função sistólica do ventrículo esquerdo. Além disso, demonstrou-se que a circunferência da cintura elevada é o principal componente, dentre os critérios atualmente propostos para o diagnóstico de síndrome metabólica, associado a alteração do *strain* miocárdico. Neste sentido, os resultados evidenciados neste trabalho indicam que a disfunção sistólica na síndrome metabólica é fundamentalmente determinada pela obesidade abdominal.

Os achados do presente estudo sugerem a presença de uma alteração subclínica da contratilidade miocárdica relacionada com obesidade abdominal e síndrome metabólica. Acredita-se que investigações de tais alterações precoces de disfunção miocárdica subclínica relacionadas à síndrome metabólica, utilizando técnicas de ecocardiografia mais robustas, poderão permitir uma melhor compreensão da fisiopatologia desta síndrome.

Embora as técnicas ecocardiográficas de *strain* miocárdico, ainda não sejam suficientemente usadas como rotina na prática clínica, esses métodos podem oferecer informações mais completas, precisas e sensíveis ao desempenho da função miocárdica no

longo prazo. Nesta perspectiva, é importante determinar se as medidas de deformação miocárdica como o GLS fornecem informação prognóstica adicional além de parâmetros convencionais, para a predição de desfechos clínicos relevantes. Recentemente os estudos NOMAS (*Northern Manhattan Study*) e CABL (*Cardiovascular Abnormalities and Brain Lesions*) têm identificado que o GLS é um predictor independente de casos incidentes de fibrilação atrial, doença cerebral subclínica, insuficiência cardíaca e, do desfecho combinado de infarto do miocárdio, acidente vascular cerebral isquêmico e morte vascular. Além disso, uma metanálise de 16 estudos mostrou que o GLS tem um valor prognóstico superior que a fração de ejeção para predizer eventos cardíacos maiores e toda causa de mortalidade.

## 5. ANEXOS

### a. Aprovação do estudo ELSA-Brasil pelo Comitê de Ética em Pesquisa (HCPA)



**HCPA - HOSPITAL DE CLÍNICAS DE PORTO ALEGRE**  
**Grupo de Pesquisa e Pós-Graduação**  
COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

A Comissão Científica e a Comissão de Pesquisa e Ética em Saúde, que é reconhecida pela Comissão Nacional de Ética em Pesquisa (CONEP)/MS como Comitê de Ética em Pesquisa do HCPA e pelo Office For Human Research Protections (OHRP)/USDHHS, como Institutional Review Board (IRB0000921) analisaram o projeto:

**Projeto:** 06-194

**Versão do Projeto:** 15/05/2006

**Versão do TCLE:** 15/05/2006

**Pesquisadores:**

MARIA INES SCHMIDT

ALVARO VIGO

BRUCE BARTOLOW DUNCAN

FLAVIO DANNI FUCHS

MURILO FOPPA


SANDRA CRISTINA COSTA FUCHS

SOTERO SERRATE MENGUE

**Título:** ESTUDO LONGITUDINAL DE SAÚDE DO ADULTO - ELSA

Este projeto foi Aprovado em seus aspectos éticos e metodológicos, inclusive quanto ao seu Termo de Consentimento Livre e Esclarecido, de acordo com as Diretrizes e Normas Internacionais e Nacionais, especialmente as Resoluções 196/96 e complementares do Conselho Nacional de Saúde. Os membros do CEP/HCPA não participaram do processo de avaliação dos projetos onde constam como pesquisadores. Toda e qualquer alteração do Projeto, assim como os eventos adversos graves, deverão ser comunicados imediatamente ao CEP/HCPA. Somente poderão ser utilizados os Termos de Consentimento onde conste a aprovação do GPPG/HCPA.

Porto Alegre, 18 de agosto de 2006.

  
Prof. Nadine Clausell  
Coordenadora do GPPG e CEP-HCPA