SÍNDROME METABÓLICA
EM DIFERENTES FASES DA VIDA
PREDIÇÃO E IMPORTÂNCIA DE SEUS COMPONENTES

SÃO LUÍS, MA
NOVEMBRO – 2024

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SÍNDROME METABÓLICA EM DIFERENTES FASES DA VIDA: PREDIÇÃO E IMPORTÂNCIA DE SEUS COMPONENTES

Tese apresentada ao Programa de Pós-Graduação em Saúde Coletiva da Universidade Federal do Maranhão como requisito parcial à obtenção do título de Doutor em Saúde Coletiva.

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Costa Júnior, Antonio.
Síndrome metabólica em diferentes fazes da vida : : predição e importância de seus componentes / Antonio Costa Júnior. - 2024.
118 f.

Coorientador(a) 1: Alcione Miranda dos Santos.
Orientador(a): Ana Karina Teixeira da Cunha França.
Tese (Doutorado) - Programa de Pós-graduação em Saúde Coletiva/ccbs, Universidade Federal do Maranhão, São Luís, 2024.

1. Síndrome Metabólica. 2. Inteligência Artificial. 3. Modelos de Redes Neurais. I. Miranda dos Santos, Alcione. II. Teixeira da Cunha França, Ana Karina. III. Título.

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À Profa. Dra. Sílvia Tereza de Jesus Rodrigues Moreira Lima (*in memoriam*).

AGRADECIMENTOS

A Deus, Pai, Filho e Espírito Santo. Alfa e ômega. Princípio e fim.

À minha Mãe Maria Santíssima!

A São José, São Giuseppe Moscati, São Lucas, São Rafael, Santo Antônio Maria Zaccaria, Santa Terezinha do Menino Jesus e da Sagrada Face, Santa Tereza de Calcutá, Santa Dulce dos Pobres, Santa Gianna, Santa Luzia, Santa Benedita da Cruz, Beato Carlo Acutis Venerável Guido Schaffer, Venerável Frei Alberto Beretta e todos os santos que intercedem por mim!

À minha amada mulher Amanda Lima Rodrigues. Ao lado de um grande homem, sempre há uma grande mulher.

À minha orientadora Profa. Dra. Ana Karina França. Ainda que eu escrevesse uma tese apenas com palavras de agradecimento, estas seriam insuficientes. Não há como tentar agradecê-la sem que lágrimas venham aos olhos ao lembrar de tanta dedicação, tanto amor ao que faz, tantas palavras de ensinamento e incentivo. Até quando precisava ser mais dura e exigente, o fazia com a delicadeza de uma mãe. Mais que uma orientadora, uma amiga, defensora, conselheira, incentivadora, torcedora, apoiadora. Uma querida mãe, que levo para sempre em minha vida!

À minha coorientadora Profa. Alcione Miranda, que nos presenteou com a ideia dos dois artigos, sempre disponível e dedicada, como muita paciência tirava minhas dúvidas nas análises e, quando precisava, as fazia junto comigo. É um grande exemplo de professora para mim, que me mostrou desde a graduação como é linda a estatística.

Ao meu amigo e colega de turma, Victor Silveira, que nos momentos mais apertados, me salvou, que me respondida sempre prontamente, independente do horário.

À minha mãe Adriane Braga e à minha avó Rosalina Santos, por doarem diariamente suas vidas por mim!

Aos meus irmãos, André Costa e Adriano Costa, pela força e companheirismo. À minha cunhada Marina Costa e ao meu sobrinho Gustavo Costa.

Aos meus sogros Fernando Lima e Ana Cláudia Lima, por torcerem e vibrarem comigo em cada conquista.

À minha filhota Maria Clara Nogueira.

À minha bisavó Haydée Cavalcante (*in memoriam*), sempre!

À minha família do outro lado do Atlântico! Vocês, mesmo longe, sempre estão tão perto!

À minha segunda mãe, Karlla Aquino, à minha tia, Solange Mendes (*in memoriam*), e ao meu tio Sérgio José Cavalcante.

Aos meus amigos e companheiros de treino de natação. Estar todos os dias com vocês me renova e me dá forças!

Aos meus amigos queridos, apoiadores, incentivadores e torcedores Érica Mendonça, Maylla Martins, Luiz Henrique Veras, Louise Serra, Janderson Saulnier, e Olívia Alencar!

Aos meus estimados amigos sacerdotes e religiosos, em especial, Pe. Guilherme Masiero, Pe. Rafael Borges, Pe. Paulo de Tarso, Pe. Ronney, Pe. Jozimar Pinheiro, e Diácono Fábio Martins (e sua esposa Camila), que me sustentam com suas palavras e suas orações.

À Universidade Federal do Maranhão, por possibilitar a realização dos meus estudos, e ao Programa de Pós-Graduação em Saúde Coletiva, aos professores que contribuíram para minha formação, e a Mailane, sempre atenciosa e prestativa.

À minha querida profa. Sílvia Tereza Moreira Lima (*in memoriam*), a quem dedico este trabalho. Nem nos meus piores pesadelos pensaria que escreveria este agradecimento com um aposto! Que falta nos faz.

Às minhas professoras do curso de Nutrição, especialmente às Profa. Dra. Isabela Calado e Profa. Dra. Helma Veloso, e às Profa. Me. Teresa Ferreira e Profa. Yara Portela, que tanto me incentivam, me motivam, me inspiram, e torcem por mim.

Ao consórcio RPS, pela disponibilização dos dados e apoio financeiro para a publicação deste trabalho.

A todos que contribuíram direta e indiretamente para a concretização dessa etapa, expresso minha gratidão.

O Senhor é quem dá a sabedoria, e da sua boca sai a prudência e a ciência.

(Pv 2:4)

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LISTA DE ABREVIATURAS E SIGLAS

ACUR - Acurácia
ATP III - *Adult Treatment Panel III*
AUC - *Area Under the Curve*
CC - Circunferência da cintura
CEP - Comitê de Ética em Pesquisa
CETP - Proteína de transferência de ésteres de colesterol
ESPEC - Especificidade
FN - Falso negativo
FP - Falso positivo
HAS - Hipertensão Arterial Sistêmica
HDL - *High-density lipoprotein*
IA - Inteligência Artificial
IQ - Intervalo interquartil
IDF - *International Diabetes Federation*
IMC - Índice de massa corporal
JIS - *Joint Interim Statement*
LDL - *Low-density lipoprotein*
ML - *Machine Learning*
NCEP - *National Cholesterol Education Program*
PAD - Pressão arterial diastólica
PAS - Pressão arterial sistólica
RNA - Rede neural artificial
RPS - Ribeirão Preto – Pelotas – São Luís
ROC - *Reciever Operator Characteristic*
SENS - Sensibilidade
SM - Síndrome metabólica
SUS - Sistema único de saúde
VLDL - *Very low density lipoprotein*
VN - Verdadeiro negativo
VP - Verdadeiro positivo

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RESUMO

Objetivos: Predizer a chance de um adolescente desenvolver Síndrome Metabólica (SM) e avaliar os componentes mais importantes na definição da SM em adultos.

Métodos: Estudo com dados provenientes de duas coortes do Consórcio RPS: a de Ribeirão Preto-SP, iniciada em 1978-1979, e a de São Luís-MA, iniciada em 1997-1998. No artigo 1 foram avaliados adolescentes de 18-19 anos pertencentes a esta coorte (n=2.064) e no artigo 2, adultos aos 23-25 anos e aos 37-39 anos pertencentes àquela coorte (n=1.098). Para diagnóstico da SM, foram empregados os critérios Cook et al. (2003), De Ferranti et al. (2004), *International Diabetes Federation - IDF* (2005) e *Joint Interim Statement* (2009). No artigo 1, Redes neurais artificiais (RNA) foram empregadas para predizer a chance de um adolescente desenvolver SM, a partir de dados clínicos e antropométricos não invasivos, e, no artigo 2, elas foram utilizadas para identificar a importância relativa dos componentes da SM.

Resultados: A prevalência de SM variou entre 5,7% e 12,3%, aos 18-19 anos, a depender do critério adotado, e foi de 12,1%, aos 23-25 anos, e de 41,6%, aos 37-39 anos. A RNA que incluiu idade, sexo, circunferência da cintura (CC), peso e pressão arterial sistólica (PAS) e diastólica (PAD) apresentou melhor desempenho e poder discriminatório na predição da SM em adolescentes (sensibilidade 89,8% e acurácia 86,8%). O componente mais importante para o diagnóstico da SM, aos 23-25 anos, foi a PAS, e aos 37-39 nos, foi o HDL. O menos relevante foi a CC, no primeiro momento, e os triglicerídeos, no segundo. Com a mudança da fase da vida, PAD, glicemia e HDL tiveram sua importância aumentada e PAS, PAD e HDL configuraram entre os componentes mais importantes para o diagnóstico da SM.

Conclusões: Predizer a SM por medidas não invasivas, de fácil e rápida obtenção, bem como conhecer a importância relativa de cada componente da SM em cada fase da vida permite o direcionamento das políticas públicas em saúde, com a concentração de recursos para controle e redução da prevalência da SM.

Palavras-chave: Síndrome metabólica. Inteligência Artificial. Modelos de Redes Neurais.

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ABSTRACT

Objectives: To propose predictive models to Metabolic Syndrome (MetS) in adolescents and to evaluate the most important MetS components in adults.

Methods: The data used were from two cohorts of the RPS Consortium: Ribeirão Preto-SP, initiated in 1978-1979, and São Luís-MA, initiated in 1997-1998. Adolescents aged 18-19 years from this cohort (n=2,064) and adults aged 23-25 years and 37-39 years from that cohort (n=1,098) were evaluated. The criteria of Cook et al. (2003), De Ferranti et al. (2004), International Diabetes Federation - IDF (2005) and Joint Interim Statement (2009) were used to diagnose MetS. Artificial neural networks (ANNs) were trained to predict MetS in adolescents, based on noninvasive clinical and anthropometric data, and also to determine the relative importance of MetS components.

Results: The prevalence of MetS in adolescents ranged from 5.7% to 12.3%, and was 12.1% at 23-25 years and 41.6% at 37-39 years. The ANN that included age, sex, waist circumference (WC), weight, and systolic and diastolic blood pressure showed better performance and discriminatory power in predicting MetS in adolescents (sensitivity 89.8% and accuracy 86.8%). The most important component for the diagnosis of MetS at 23-25 years was systolic blood pressure, and at 37-39 years of age, it was HDL. The least relevant was WC, at the first time point, and triglycerides, at the second. Therefore, systolic and diastolic blood pressure, and HDL were among the most important components for the diagnosis of MetS.

Conclusions: Predicting MetS through non-invasive, easy and quick measurements, as well as knowing the relative importance of each component of MetS in each lifetime, allows the targeting of public health policies, with the concentration of resources for controlling and reducing the prevalence of MetS.

Keywords: Metabolic syndrome. Artificial Intelligence. Neural Networks.

SUMÁRIO

1 INTRODUÇÃO

A Síndrome Metabólica (SM) se caracteriza por distúrbios no metabolismo da glicose, hipertensão arterial, dislipidemia e acúmulo de gordura abdominal. Há uma extensa lista de critérios para diagnosticá-la. Contudo, estes critérios divergem especialmente quanto aos pontos de corte dos componentes que a definem e à obrigatoriedade de determinados componentes. O consenso entre os critérios repousa apenas nas anormalidades metabólicas que constituem a síndrome (Weihe; Weihrauch-Blüher, 2019; Nagayama et al., 2022). Assim, não existem critérios diagnósticos definitivos ou considerados de referência para definir SM (Orsini et al., 2023).

Apesar de não haver consenso quanto ao diagnóstico da SM (Li et al., 2023a), é incontestável que se trata de um problema de saúde pública de escala global (Alberti et al., 2005; Carvajal, 2017; Zimmet et al., 2019; Gouveia et al., 2021; Valadares et al., 2022; Li et al., 2023a; Li et al., 2023b). No Brasil, estima-se uma prevalência de SM de 33%, com uma tendência de aumento (De Siqueira Valadares et al., 2022).

O diagnóstico e intervenção precoces na SM e em seus fatores de risco são fundamentais na evolução e desfecho da doença (Li et al., 2023a). Nesse sentido, modelos preditivos desenvolvidos a partir do aprendizado de máquina (*machine learning* - ML), construídos a partir dos componentes da SM, podem ser usados como ferramentas auxiliares na prevenção e diminuição do risco cardiometabólico, a partir da predição da SM e da identificação dos seus componentes a receberem maior atenção (Hirose et al., 2011; Hu et al., 2022; Yang et al., 2022).

Dessa forma, a alta prevalência da SM, seus desfechos desfavoráveis e a existência de diversos critérios diagnósticos sem consenso entre eles, independente da faixa etária, motivaram a elaboração desta tese.

Inicialmente, foi estudada a síndrome na população pediátrica, especificamente em adolescentes entre 18-19 anos (artigo 1). Dada a importância do diagnóstico e intervenção nessa faixa etária, foi proposto um modelo neural para predizer a SM em adolescentes, a partir de medidas não invasivas, de fácil e rápida obtenção.

Após, a SM foi estudada em duas fases da vida adulta, quais sejam 23-25 anos e 37-39 anos, e a importância relativa de cada componente da síndrome foi avaliada (artigo 2).

2 OBJETIVOS

2.1 Geral

Criar um modelo estatístico classificatório para estimar a probabilidade de um adolescente ter Síndrome Metabólica e avaliar os componentes mais importantes na definição da Síndrome Metabólica em adultos.

2.2 Específicos

- Determinar a prevalência de Síndrome Metabólica em adolescentes e adultos;
- Calcular o poder discriminatório dos modelos neurais;
- Analisar a acurácia, sensibilidade e especificidade dos modelos neurais;
- Avaliar as medidas clínicas e antropométricas não invasivas que melhor predizem a Síndrome Metabólica em adolescentes;
- Analisar a importância de cada componente da Síndrome Metabólica na sua caracterização em adultos.

3 REFERENCIAL TEÓRICO

3.1 Definição de Síndrome Metabólica

A SM se refere a um conjunto de anormalidades metabólicas, que constituem fatores de risco cardiovascular que aumentam a probabilidade de sofrer doenças cardíacas, acidente vascular encefálico e diabetes (Gutiérrez-Esparza *et al*., 2020; Trigka; Dritsas, 2023). Zimmet *et al*. (2019) simplificam sua definição ao descrevê-la como um conjunto de fatores de risco cardiovasculares inter-relacionados, de origem metabólica.

Esse grupo de anormalidades metabólicas incluem obesidade central, hipertrigliceridemia, intolerância à glicose, hipertensão e dislipidemia (Karimi-Alavijeh, Jalili e Sadeghi, 2016).

Esta síndrome foi descrita pela primeira vez em 1920 como a coexistência de hipertensão, hiperglicemia e gota. Em 1940, foi adicionado o componente da adiposidade visceral. Desde então, diversas definições foram utilizadas para descrever a síndrome (Gutiérrez-Esparza *et al*., 2020).

Diversos nomes já foram atribuídos à SM, como síndrome X, síndrome de resistência à insulina e quarteto mortal (Gutiérrez-Esparza *et al*., 2020). Também já foi chamada de Síndrome Circadiana, uma vez que uma alteração no ritmo circadiano se associa com todos os componentes metabólicos que a definem (Zimmet *et al*., 2019).

Ela se associa principalmente à mortalidade por diabetes e doenças cardíacas (Li *et al*., 2023a) mas também a distúrbios cognitivos e de humor, depressão, insônia, doença hepática gordurosa não alcóolica (Zimmet *et al*., 2019).

O primeiro critério diagnóstico foi proposto em 1999 pela Organização Mundial de Saúde e foi sendo modificado à medida que novas descobertas científicas surgiam (Alberti et al., 2005).

Apesar de mais de 40 tipos de critérios sugeridos terem sido publicados ao longo dos anos, não há uma definição globalmente aceita de SM. Consequentemente, é extremamente difícil determinar qual critério seria mais apropriado para o ambiente clínico (Piña-Aguero *et al*., 2018).

3.2 Componentes da Síndrome Metabólica

3.2.1 Obesidade

A obesidade decorre de um desbalanço energético entre a ingestão de alimentos e o gasto calórico de um indivíduo, com acumulação de lipídios no tecido adiposo. A capacidade deste tecido em responder às necessidades de acumulação de gordura é limitada. Se este limite é ultrapassado, há a hipertrofia dos adipócitos e uma resposta inflamatória subjacente (Carvajal, 2017).

A SM está associada com o aumento da massa corporal, sobrepeso, obesidade e um estilo de vida sedentário (Trigka; Dritsas, 2023), em virtude da função endócrina que o tecido adiposo apresenta (Fahed et al., 2022).

O tecido adiposo libera adipocinas, dentre as quais hormônios (leptina e adiponectina), peptídeos (inibidor do ativador do plasminogênio-1) e citocinas inflamatórias (como interleucina-6 e fator de necrose tumoral α), que desempenham um papel importante na fisiopatologia da resistência à insulina e da SM (Fahed et al., 2022).

A leptina, por exemplo, é sacietogênica e estimula o gasto de energia, além de controlar a homeostase da glicose e a sensibilidade à insulina. Na obesidade, há uma falha dos altos níveis de leptina em corrigir o desequilíbrio metabólico e os tecidos apresentam sensibilidade diminuída à leptina (resistência à leptina), que promove uma resposta pró-inflamatória. Assim, níveis mais altos de leptina se correlacionam com a inflamação e aumento do risco cardiovascular (Fahed et al., 2022).

3.2.2 Hipertrigliceridemia e Dislipidemia

As alterações no perfil lipídico são principalmente caracterizadas pelo aumento dos níveis séricos de triglicerídeos e LDL-colesterol e pela redução dos níveis de HDL-colesterol, que se relacionam com o aumento do risco de doenças cardiovasculares (Gouveia et al., 2022; Carvajal, 2017).

A elevação dos níveis séricos de triglicerídeos aumenta a atividade da proteína de transferência de ésteres de colesterol (CETP), uma enzima que catalisa a transferência de ésteres de colesterol do HDL-colesterol para lipoproteínas ricas em triglicerídeos, quais sejam, VLDL-colesterol e LDL-colesterol. Nessa troca, formam-se moléculas pequenas e

densas de HDL-colesterol e LDL-colesterol. Estas são altamente aterogênicas (Carvajal, 2017).

As moléculas menores de HDL-colesterol apresentam um maior catabolismo, o que contribui para a redução dos seus níveis séricos e consequente diminuição dos seus efeitos anti-inflamatórios e antioxidantes sistêmicos e protetor da função das células endoteliais (Carvajal, 2017; Gouveia et al., 2022). Independentemente dos níveis de triglicerídeos e LDL-colesterol, as concentrações de HDL-colesterol estão inversamente associadas ao risco cardiovascular, independentemente dos níveis de triglicerídeos e LDL-colesterol (Gouveia et al., 2022).

3.2.3 Elevação da Pressão Arterial

Alterações metabólicas se associam à elevação da pressão arterial tanto em indivíduos obesos quanto em não obesos (Da Silva et al., 2020). A hiperglicemia e a hiperinsulinemia, condições presentes na obesidade e na resistência insulínica, ativam o sistema renina-angiotensina, com o aumento da expressão da angiotensina II, cujos efeitos modulam a pressão arterial (Carvajal, 2017). Além dessas, adipocinas do tecido adiposo, microbiota intestinal anormal, ativação do sistema nervoso simpático, excesso de hormônios antinatriuréticos, deficiência de hormônios natriuréticos, e disfunção vascular e renal são fatores de mediação da hipertensão na SM, apesar dos mecanismos ainda não serem conhecidos (Da Silva et al., 2020).

3.2.4 Resistência Insulínica

A resistência insulínica caracteriza-se por uma resposta mais baixas dos tecidos insulinodependentes à ação da insulina. Sua gênese está associada ao acúmulo de lipídios em diferentes tecidos e órgãos, sobretudo fígado, músculo esquelético, pâncreas e coração, decorrente da obesidade e do estado inflamatório crônico subclínico (Carvajal, 2017). Esse acúmulo de gordura causa lipotoxicidade na célula, o que pode levar à sua apoptose. E este processo provoca estresse celular e disfunção de algumas organelas, especialmente as mitocôndrias e o retículo endoplasmático (Carvajal, 2017).

O estado de resistência insulínica pode desencadear uma hiperglicemia, mesmo na ausência de diabetes, em virtude da captação de glicose pelo músculo esquelético estar

diminuída e pela maior gliconeogénese hepática (Carvajal, 2017). A hiperglicemia aumenta os marcadores inflamatórios, que atuam de forma negativa sobre o sistema cardiovascular. O processo inflamatório crônico contribui para o desenvolvimento da resistência insulínica e para a disfunção na secreção de insulina (Da Silva et al., 2020).

3.3 Síndrome Metabólica em Crianças e Adolescentes

Na população pediátrica, a SM segue a definição geral, sendo definida como o conjunto simultâneo da presença de três ou mais dos seguintes critérios: obesidade abdominal, dislipidemia (triglicerídios elevado e/ou baixo HDL-C), resistência insulínica e/ou pressão sanguínea elevada (Piña-Aguero *et al*., 2018).

Os três critérios diagnósticos de SM mais utilizados na população pediátricas são: 1. Cook *et al*. (2003); 2. De Ferranti *et al*. (2004); e, 3. *International Diabetes Federation* (IDF) (2005). Os componentes utilizados por esses critérios consideram elevação de triglicérides, glicemia em jejum, pressão arterial sistólica (PAS) e diastólica (PAD) e circunferência da cincutra (CC) e baixos níveis de HDL-colesterol. Os critérios de Cook e De Ferranti definem ser necessária a presença de, no mínimo, três dessas alterações para diagnóstico da SM, enquanto o IDF exige, obrigatoriamente, a presença da alteração da CC, e pelo menos, mais duas alterações, conforme apresentado na Tabela 01.

Tabela 1. Critérios para definição de Síndrome Metabólica em adolescentes.

Componentes/ Critérios	**Cook et al. (2003)**	**De Ferranti et al. (2004)**	**IDF (2005)**
PAS/PAD	≥ p90	> p90 para idade e sexo	> 130/85 mmHg
Glicemia	≥ 110 mg/dL	≥ 110 mg/dL	≥ 100 mg/dL
HDL	≤ 40 mg/dL	< 50mg/dL (♀ e ♂ < 15a) < 45 mg/dL (♂ 15-19a)	< 40 mg/dL (♂) < 50 mg/dL (♀)
Triglicerídeos	≥ 110 mg/dL	≥ 100 mg/dL)	≥ 150 mg/dL
CC*	> p90 para idade e sexo	> p75 para idade e sexo	≥ 94 cm (♂) ≥ 80 cm (♀)

*Componente obrigatório para o IDF, associada a outros dois componentes.
CC: Circunferência da cintura | IDF: *International Diabetes Federation* | PAD: Pressão arterial diastólica | PAS: Pressão arterial sistólica |

3.4 Síndrome Metabólica em Adultos

Em adultos, os três principais critérios diagnósticos da SM são: 1. National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) (2001); 2. IDF (Alberti et al., 2005) e, 3. *Joint Interim Statement* (JIS) (Alberti et al., 2009).

As alterações metabólicas consideradas por esses critérios são a elevação da pressão arterial (PAS e/ou PAD), da glicemia em jejum, dos triglicerídeos e da CC e baixos níveis de HDL-colesterol. Os critérios do NCEP e do JIS definem ser necessária a presença de, no mínimo, três dessas alterações para diagnóstico da SM, enquanto o IDF exige, obrigatoriamente, a presença da alteração da CC, e pelo menos, mais duas alterações. A Tabela 2 apresenta detalhes e os pontos de corte utilizados em cada uma dessas classificações diagnósticas.

Tabela 2. Critérios para definição de Síndrome Metabólica em adultos.

Componentes/ Critérios	**NCEP/ATP III (2002)**	**IDF (2005)**	**JIS (2009)**
PAS/PAD	≥ 130/85 mmHg	≥ 130/85 mmHg	≥ 130/85 mmHg
Glicemia	≥ 110 mg/dL	≥ 100 mg/dL	≥ 100 mg/dL
HDL	< 40 mg/dL (♂) < 50 mg/dL (♀)	< 40 mg/dL (♂) < 50 mg/dL (♀)	< 40 mg/dL (♂) < 50 mg/dL (♀)
Triglicerídeos	≥ 150 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
CC	≥ 102 cm (♂) ≥ 88 cm (♀)	≥ 94 cm (♂) * ≥ 80 cm (♀) *	≥ 90 cm (♂) ≥ 80 cm (♀)

*Componente obrigatório para o IDF, associado a outros dois componentes.
PAS: Pressão arterial sistólica | PAD: Pressão arterial diastólica | CC: Circunferência da cintura

3.4 Inteligência Artificial

A inteligência artificial (IA) é um campo da ciência cujo objetivo é automatizar tarefas intelectuais, normalmente desempenhadas por seres humanos. Trata-se de programar computadores para pensar e raciocinar. Esse termo surgiu em 1956, quando um grupo de cientistas propôs que qualquer característica da inteligência humana e todo aspecto do processo de aprendizado podem, a princípio, ser tão precisamente descritos que uma máquina pode ser programada para copiá-los (Choi et al., 2020).

A IA se enquadra no domínio da ciência de dados e inclui programação clássica e ML. Este apresentam muitos modelos e métodos, que incluem a aprendizagem profunda (*Deep Learning*) e redes neurais artificiais (RNA) (Choi et al., 2020).

Com o advento e desenvolvimento de novas tecnologias, numa era digital, a IA tem sido usada na área da saúde para facilitar a solução de problemas em todos os níveis de assistência. Na atenção primária à saúde e na Medicina Preventiva, o emprego da IA apresenta importante potencial de transformação de desfechos em saúde (Gallardo-Ricon et al., 2023).

3.2.1 Aprendizado de Máquina

O ML é uma importante área da IA e consiste no estudo de algoritmos e modelos estatísticos empregados em sistemas computacionais para que realizem uma determinada tarefa sem ser programados, aprendendo-a a partir de dados. Assim, o ML permite a criação de algoritmos que ensinam determinada máquina a desempenhar tarefas, apresentam diversas aplicações na vida diária (Mahesh, 2018).

As técnicas de ML desempenham um papel importante na compreensão das relações não lineares e complexas entre vários fatores, extraindo informações úteis que podem ajudar na tomada de decisões (Kim et al., 2022).

As áreas de aplicações de ML são abundantes (Mahesh, 2018). Na área médica, as técnicas de aprendizado de máquina permitem a análise de dados clínicos, de imagem e genômicos para melhorar a precisão do diagnóstico e da classificação de doenças, ao mesmo tempo em que apresentam um novo paradigma no tratamento (Kim et al., 2022).

3.2.2 Redes Neurais Artificiais

A rede neural artificial (RNA) consiste numa série de algoritmos que objetivam reconhecer relações subjacentes em um conjunto de dados por meio de um processo que imita a forma como o cérebro humano funciona (Liao; Wen, 2007).

Nesse sentido, redes neurais referem-se a sistemas de neurônios, de natureza orgânica ou artificial. As redes neurais podem adaptar-se às mudanças de entrada; então a rede gera o melhor resultado possível sem a necessidade de redesenhar a saída. O conceito de redes neurais, que tem suas raízes em IA, está rapidamente ganhando (Liao; Wen, 2007).

As RNAs podem ser aplicadas a problemas de regressão, classificação e sumarização de dados, bem como em situações em que há interações não lineares entre as variáveis dependentes e independentes. Em termos de topologia, para implementar uma rede neural, as seguintes variáveis devem ser determinadas: (a) o número de nós na camada de entrada; (b) o número de camadas ocultas e o número de neurônios a serem inseridos nessas camadas; e (c) o número de neurônios na camada de saída. O número de nós na camada de entrada corresponde ao número de variáveis que serão usadas para alimentar a RNA. Essas são frequentemente as variáveis mais relevantes para o problema em estudo (Santos et al., 2005). Assim, uma RNA funciona em três camadas: a camada que recebe entrada; a camada oculta, que processa a entrada; e, finalmente, a camada de saída, que envia a saída calculada (Liao; Wen, 2007).

Além disso, as RNAs podem ser empregadas e analisadas sem pressupostos, como a normalidade, independência dos resíduos, a homogeneidade das variâncias e a colinariedade. Outras vantagens seriam reconhecer padrões lineares e não lineares com impactos de limite e efeito de contingência. Além disso, uma RNA não precisa de uma hipótese inicial para ser testada (Gholipour et al., 2018).

3.3 Aprendizado de Máquina na Predição da Síndrome Metabólica

As RNAs têm sido empregadas nas Ciências Médicas como um método para modelos preditivos capazes de predizerem relações/associações complexas, não lineares e tempo-dependentes (Gholipour et al., 2018). Karimi-Alavijeh, Jalili e Sadeghi (2016) recomendam o uso da inteligência artificial nos serviços de saúde devido ao seu sucesso no diagnóstico, prognóstico e escolha de tratamento.

Uma coorte retrospectiva com 410 japoneses adultos (entre 30 e 59 anos no início do estudo), dentre professores e trabalhadores de uma universidade, objetivou predizer a SM num acompanhamento de seis anos, a partir de RNA e modelos de regressão logística múltipla. Foram obtidos anualmente dados clínicos e bioquímicos, incluindo resistência insulínica e adiponectina sérica. A sensibilidade e a especificidade foram, respectivamente, 93% e 91% no modelo de RNAs e de 27% e 95% nos modelos de regressão logística múltipla. As variáveis empregadas que se mostraram importantes preditoras da SM foram idade, IMC, PAD, HDL-colesterol, LDL-colesterol e HOMA-IR como importantes preditores da SM e os

autores também concluíram que o emprego de sistemas de RNAs na rotina da prática médica melhoraria a qualidade do cuidado e, ainda, reduziria custos (Hirose et al., 2011).

Um estudo realizado com 2.107 iranianos entre 34 e 86 anos, participantes do *Isfahan Cohort Study*, empregou outras técnicas de aprendizado de máquinas, quais sejam: árvore de decisão e máquina de vetores de suporte, no intuito de predizer a SM num seguimento de sete anos. Variáveis demográficas, clínicas, nutricionais e bioquímicas foram utilizadas na predição da SM e o critério NCEP/ATPIII foi empregado para o diagnóstico da SM. A sensibilidade, a especificidade e a acurácia dos modelos empregados foram, respectivamente, 0,774, 0,74 e 0,757 na máquina de suporte de vetores e, 0,758 0,72 e 0,739 na árvore de decisão. Assim, os autores concluíram que o primeiro método foi mais eficiente que o primeiro e, ainda, que os triglicerídeos foram o componente definidor da SM mais importante (Karimi-Alavijeh, Jalili e Sadeghi, 2016).

No México, uma coorte desenvolvida com 2.942 indivíduos, entre 20 e 50 anos, sendo quase dois terços de mulheres, foi utilizada para identificar as variáveis prognósticas com maior poder de predizer a SM, a partir de algoritmos de aprendizado de máquina, como *random forest* e máquina de suporte de vetor. Foram empregados dados sobre estilo de vida e medidas clínicas, bioquímicas e antropométricas, totalizando 16 variáveis estudadas. O critério NCEP/ATPIII foi adotado para o diagnóstico da SM. A sensibilidade, especificidade e acurácia dos algoritmos foram obtidos, e os modelos desenvolvidos a partir do *random forest* se mostraram melhores preditores da SM. Os componentes da SM mais importantes para o seu diagnóstico foram, em ordem decrescente: glicemia, triglicerídeos e HDL-colesterol (Gutiérrez-Esparza et al., 2020).

Nos EUA, Trigka e Dritsas (2023) utilizaram a base de dados do *NHANES (National Health and Nutrition Examination Survey)* para predizer o risco do desenvolvimento da SM a partir de modelos de aprendizado de máquinas, dentre os quais regressão logística, árvore de decisão e máquina de vetores de suporte. Foram avaliados 2.009 americanos entre 20 e 80 anos. As variáveis analisadas foram glicemia, HDL, triglicerídeos, IMC, CC, ácido úrico, albuminúria, relação albumina urinária/creatinina, idade, cor, estado civil, sexo e renda; não foi avaliada PA. O IMC, a CC e relação cintura/quadril foram os melhores preditores dos componentes não relacionados a gordura corporal.

4 MÉTODOS

4.1 Base de Dados

Trata-se de um estudo transversal (artigo 1) e longitudinal (artigo 2) com dados provenientes do Consórcio RPS, o qual inclui nove coortes de nascimento de três cidades brasileiras: Ribeirão Preto-São Paulo, Pelotas-Rio Grande do Sul e São Luís-Maranhão. Maiores detalhes sobre aspectos metodológicos das coortes do Consórcio RPS estão disponíveis em Confortin et al. (2021).

O primeiro artigo utilizou dados da coorte de nascimento 1997-1998 do município de São Luís-Maranhão, em seu segundo seguimento. O artigo 2 usou dados da coorte de Ribeirão Preto-São Paulo, iniciada em 1978-1979, em seus seguimentos três (2002-2004) e quatro (2016-2017), quando os participantes estavam com 23-25 anos e 37-39 anos, respectivamente.

4.2 Amostras em Estudo

A amostra do primeiro artigo foi constituída por 2.515 adolescentes avaliados aos 18-19 anos, sendo constituída por 687 adolescentes provenientes da coorte original e 1.828 adolescentes oriundos de uma coorte aberta composta por indivíduos também nascidos em São Luís-MA no ano de 1997. A inclusão desses novos participantes teve como objetivo ampliar o tamanho da amostra. Eles foram selecionados por amostragem aleatória, a partir do Sistema de Informações sobre Nascidos Vivos, restrita a crianças nascidas em 1997, e identificados em escolas e universidades e por meio de redes sociais. Dos 2.515 adolescentes, foram excluídos do estudo 451, em virtude de informações incompletas ou inconsistências das variáveis de interesse. Assim, a amostra final foi constituída por 2.064 adolescentes de 18-19 anos de São Luís-MA.

No segundo artigo a amostra foi constituída da seguinte forma: no terceiro seguimento da coorte de Ribeirão Preto 1978-1979 foram avaliados 2.103 indivíduos, enquanto no quarto seguimento foram 1.775. Assim, foram incluídos os indivíduos que participaram dos dois seguimentos da coorte (1.113). E foram excluídos 15 participantes por

apresentarem informações incompletas ou inconsistentes nas variáveis de interesse. Assim, a amostra final do artigo 2 foi constituída por 1.098 indivíduos.

4.3 Variáveis em Estudo

No presente estudo, foram utilizadas as seguintes variáveis: idade (anos), sexo (masculino ou feminino), cor (branca, negra, parda ou outra), estado civil (com ou sem companheiro/casado), filho (sim/não), tabagismo (sim/não), prática de atividade física regular (sim/não), pressão arterial sistólica (PAS) e diastólica (PAD) (mmHg), peso (kg), altura (cm), CC (cm) e níveis séricos de glicose (mg/dl), triglicerídeos (mg/dl) e HDL-colesterol (*High-density lipoprotein cholesterol*) (mg/dl).

As variáveis sociodemográficas e de hábitos de vida foram obtidas por meio de questionários semi-estruturados aplicados na entrevista com os participantes.

Para a PAS e a PAD, foram consideradas as médias dos valores de três aferições realizadas após cinco minutos de repouso, com intervalos de 15 minutos entre elas, utilizando o aparelho Omron HEM742INT (Omnron®, São Paulo, Brasil). A média das duas últimas medidas foi calculada e utilizada como a medida correspondente à variável.

Os níveis séricos de glicemia, HDL-colesterol e triglicerídeos foram dosados pelo método colorimétrico enzimático automatizado por meio do equipamento Cobas c501 (Roche®, São Paulo, Brasil).

O peso foi aferido por meio de uma balança de alta precisão acoplada ao equipamento BOD POD Gold Standard (COSMED Metabolic Company®, Roma, Itália). A altura foi medida utilizando-se um estadiômetro portátil (AlturaExata®, Belo Horizonte, Brasil) e a CC foi obtida a partir da imagem tridimensional do corpo por meio do aparelho 3-Dimensional Photonic Scanner ([TC] Labs®, Cary, Estados Unidos). O índice de massa corporal (IMC) foi obtido por meio da razão: peso corporal (kg)/altura^2 (m^2).

Para identificação da SM em adolescentes, foram consideradas as três classificações específicas para essa faixa etária mais utilizadas: 1. Cook et al.12; 2. De Ferranti et al.13; e, 3. International Diabetes Federation (IDF)14. Os componentes utilizados por essas classificações consideram elevação de triglicérides, da glicemia em jejum, da PAS e/ou PAD e da CC e baixos níveis de HDL-colesterol, conforme apresentado na Tabela 1.

O critério para identificação da SM adotado pelo IDF requer, obrigatoriamente, a presença de obesidade central, medida pela CC, e pelo menos outros dois componentes. Os

critérios estabelecidos por Cook et al. e De Ferranti et al. definem ser necessária a presença de, no mínimo, três componentes, sem estabelecer a obrigatoriedade da obesidade central, como faz o critério IDF.

Para o diagnóstico da SM em adultos, foi empregado o critério do JIS (2009). As alterações metabólicas consideradas por esse critério são a elevação da pressão arterial (PAS ≥130mmHg e/ou PAD ≥85mmHg), da glicemia em jejum (≥100mg/dL), dos triglicerídeos (≥150mg/dL) e da CC (≥90cm em homens e ≥80cm em mulheres) e baixos níveis de HDL-colesterol (<40mg/dL em homens e <50mg/dL em mulheres). Para definição de SM, o JIS exige a presença de, no mínimo, três dessas alterações.

4.4 Análise Estatística

Primeiramente, foi realizada a análise descritiva das variáveis em estudo. As variáveis categóricas foram apresentadas por meio de frequências simples e porcentagens. Os testes Lilliefors, Cramér-von Mises e Shapiro-Wilk foram utilizados para avaliação da normalidade das variáveis numéricas. As que apresentaram distribuição normal foram apresentadas por média e desvio-padrão e as que não apresentaram e foram apresentadas por meio de mediana e intervalo interquartílico (IQ).

Para comparação entre as variáveis, foram utilizados os testes de Wilcoxon pareado, Qui-Quadrado ou Exato de Fisher.

O nível de significância adotado em todos os testes foi de 0,05.

4.4.1 Implementação da RNA

Para construção dos modelos preditivos foram implementadas diferentes RNA do tipo *feed-forward*. A técnica de RNA foi escolhida em virtude da correlação dos componentes da SM com a variável resposta (presença de SM), pois as RNA possibilitam a identificação da influência das variáveis de entrada na predição da saída (variável resposta), visto que o seu desempenho está fortemente atrelado a escolha destas variáveis. Além disso, as RNA são normalmente utilizadas em estudos de classificação ou regressão, por serem aproximadores universais de qualquer função não linear (Santos et al., 2005).

As RNAs podem ser aplicadas a problemas de regressão, classificação e sumarização de dados, bem como em situações em que há interações não lineares entre as variáveis dependentes e independentes. Em termos de topologia, para implementar uma rede neural, as seguintes variáveis devem ser determinadas: (a) o número de nós na camada de entrada; (b) o número de camadas ocultas e o número de neurônios a serem inseridos nessas camadas; e (c) o número de neurônios na camada de saída. O número de nós na camada de entrada corresponde ao número de variáveis que serão usadas para alimentar a RNA. Essas são frequentemente as variáveis mais relevantes para o problema em estudo (Santos et al., 2005).

Vários métodos para o treinamento supervisionado de RNAs têm sido propostos. No entanto, o algoritmo mais popular usado para esse tipo de treinamento é o algoritmo de retropropagação[18]. A aplicação deste algoritmo requer a escolha de um conjunto de parâmetros (número de iterações do algoritmo, critérios de parada, pesos iniciais e taxa de aprendizado), cuja influência pode ser decisiva para a capacidade de generalização da rede (Haykin, 2009).

A variável resposta de interesse considerada neste estudo foi a presença de SM, a qual assume o valor “um” se há o diagnóstico de SM e “zero”, caso contrário.

No primeiro artigo, as RNA avaliadas consideraram como variáveis de entrada, além dos componentes da SM, idade, sexo, IMC, peso e altura, e como variável de saída a presença de SM (sim/não). Foram testadas várias combinações de variáveis de entrada nas RNA, bem como o número de neurônios e de camadas ocultas. As redes implementadas que são apresentadas neste trabalho são as que mostraram melhor desempenho. No artigo 1 foram implementadas as seguintes redes:

· RNA 1: Glicemia, CC, HDL, Triglicerídeos, PAS, PAD (incluiu os mesmos componentes dos critérios utilizados neste estudo, sendo considerada apenas uma rede de referência).

· RNA 2: Idade, Sexo, Peso, Altura, PAS, PAD.

· RNA 3: Idade, Sexo, CC, PAS, PAD.

· RNA 4: Idade, Sexo, IMC, PAS, PAD.

· RNA 5: Idade, Sexo, CC, Peso, PAS, PAD.

No artigo 2, as RNA avaliadas consideraram como variáveis de entrada os componentes da SM.

Após a definição das variáveis de entrada da rede, a etapa seguinte foi a definição dos conjuntos de treino e de teste.

Entre os adolescentes, visto que se está considerando três diferentes critérios para diagnóstico de SM, foram construídas três amostras de acordo com a prevalência de SM segundo o critério adotado. Assim, em cada amostra foram incluídos todos os adolescentes com SM e a mesma quantidade de adolescentes sem SM, de forma que em cada amostra houvesse 50% de adolescentes com SM (1:1). Esse procedimento de obtenção das amostras foi considerado visto que os critérios adotados forneceram diferentes prevalências de SM. Os adolescentes sem SM foram sorteados aleatoriamente. Após a formação das amostras, cada amostra foi dividida em duas sub-amostras: 70% para treino e 30% para teste (Tabela 3).

Tabela 3. Conjuntos de treino e de teste das Redes Neurais Artificiais, segundo os critérios IDF, Cook et al. e De Ferranti et al., em adolescentes de 18-19 anos, São Luís-Maranhão, Brasil.

Critério	Total		Treino		Teste	
	Com SM	Sem SM	Com SM	Sem SM	Com SM	Sem SM
Cook et al.	118 (50%)	118 (50%)	81 (49,1%)	84 (50,9%)	37 (52,1%)	34 (47,9%)
De Ferranti et al.	253 (50%)	253 (50%)	175 (49,4%)	179 (50,6%)	78 (51,3%)	74 (48,7%)
IDF	124 (50%)	124 (50%)	88 (50,6%)	86 (49,4%)	36 (48,6%)	38 (51,4%)

SM: Síndrome metabólica

Entre os adultos, optou-se por formar uma amostra contendo todos os indivíduos com SM e selecionar aleatoriamente a mesma quantidade de indivíduos sem SM (na proporção 1:1). Essa proporção foi escolhida para balancear os dados, de forma a facilitar o aprendizado da rede, uma vez que o evento de interesse (SM) apresentou uma baixa prevalência (12,1% aos 23-25 anos e 41,6% aos 37-39 anos). Da amostra formada, foram utilizados 80% dos dados para treinamento da rede e 20% para teste do desempenho preditivo (Tabela 4).

Tabela 4. Conjuntos de treinos e teste, segundo as fases da vida adulta, Ribeirão Preto- São Paulo, Brasil (n=1.098)

Fase da vida adulta	Treino		Teste	
	Com SM	Sem SM	Com SM	Sem SM
23-25 anos	107 (50%)	107 (50%)	26 (50%)	26 (50%)
37-39 anos	366 (50%)	366 (50%)	91 (50%)	91 (50%)

SM: Síndrome metabólica

A técnica de validação cruzada (k-fold cross validation) foi aplicada no conjunto de treino com a finalidade de evitar sobreajuste (*overfitting*). O objetivo dessa técnica é dividir aleatoriamente a amostra em estudo em *k* subconjuntos de forma que cada um seja usado para treinamento e o restante para validação da rede. Neste estudo, o conjunto de treino foi dividido em 10 subconjuntos. Desses, nove foram utilizados para treinamento da rede e um subconjunto foi utilizado para testar o desempenho da rede. O processo de validação foi repetido 10 vezes, de modo que cada um dos subconjuntos foi utilizado tanto no treinamento quanto no teste.

Com relação à configuração da RNA, foram implementadas diferentes redes *feed-forward* contendo apenas uma camada oculta. A diferença entre elas estava no número de neurônios da camada de entrada e na camada oculta. O número ótimo de neurônios na camada oculta da rede foi estabelecido a partir do desempenho de diferentes redes validadas com 5, 10 e 15 neurônios ocultos. A quantidade escolhida foi aquela correspondente a que obteve o melhor desempenho da RNA. Para treinamento da rede, foi utilizado o algoritmo *back-propagation* com no máximo 10.000 iterações, taxa de aprendizado de 0,25 e três diferentes parâmetros de decaimento (0,01; 0,1 e 0,5) para evitar o *overfitting* da rede. A função de ativação utilizada na camada oculta e de saída foi a função logística sigmoidal.

No artigo 2, após a definição da rede neural, foi avaliada a importância de cada componente da SM segundo a fase da vida por meio do algoritmo de Garson.

4.4.2 Avaliação do Desempenho da Rede Neural

A capacidade de generalização das redes neurais treinadas foi avaliada a partir do conjunto de teste, considerando as seguintes métricas: acurácia (ACUR), sensibilidade (SENS), especificidade (ESPEC) e curva ROC (*Reciever Operator Characteristic*). Tais

métricas foram obtidas por meio de uma matriz de confusão (Tabela 5), calculando as seguintes medidas: VP (Verdadeiros Positivos), VN (Verdadeiros Negativos), FP (Falsos Positivos) e FN (Falsos Negativos).

Tabela 5. Matriz de confusão.

Condição atual	**Predição**		**Total**
	Com SM	Sem SM	
Com SM	VP	FN	VP + FN
Sem SM	FP	VN	FP + VN
Total	VP + FP	FN + VN	VP + FP + FN + VN

SM: Síndrome metabólica

A SENS é definida como a porcentagem dos adolescentes com SM que foram classificados corretamente pela RNA e é dada pela razão: SENS = VP / (VP + FN). Já a ESPEC é a porcentagem dos adolescentes sem SM que foram classificados corretamente, dada por: ESPEC = VN / (VN + FP). Por fim, a ACUR é a porcentagem dos adolescentes com SM e sem SM que foram corretamente classificados, isto é: ACUR = (VP + VN) / (VP + VN + FP + FN).

Para avaliar o poder discriminatório das RNA, foi construída a curva ROC e determinada a área sob a curva (*Area Under the Curve* – AUC). A curva ROC demonstra como variam a SENS e a ESPEC do método, conforme se consideram diferentes pontos de corte. O valor da AUC varia de 0,0 até 1,0. Quanto maior o AUC, melhor o método avaliado.

As análises foram realizadas no programa estatístico de acesso livre R (R Core Team, 2023). Foram utilizados os pacotes NeuralNetTools, Caret, ggplot2 e pROC (R versão 4.4.0).

4.5 Aspectos éticos

Os dados analisados no presente estudo fazem parte do projeto “Determinantes ao Longo do Ciclo Vital da Obesidade, Precursores de Doenças Crônicas, Capital Humano e Saúde Mental: Uma Contribuição das Coortes de Nascimento de São Luís para o SUS”, aprovado pelo Comitê de Ética em Pesquisa do Hospital Universitário da Universidade

Federal do Maranhão pelo processo nº 1.302.489. Todos os participantes assinaram o Termo de Consentimento Livre e Esclarecido.

Este estudo foi realizado em conformidade com a Declaração de Helsinque e aos requisitos da Resolução nº 466/12 do Conselho Nacional de Saúde e suas complementares.

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5 RESULTADOS

5.1 Artigo 1

Uso de Redes Neurais Artificiais para Predição de Síndrome Metabólica, baseada em medidas não invasivas, em Adolescentes

(publicado na revista Journal of Clinical Medicine, Fator de impacto 3.0, Qualis A2)

Uso de Redes Neurais Artificiais para Predição de Síndrome Metabólica, Baseada em Medidas não Invasivas, em Adolescentes

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RESUMO

Introdução: A prevalência da Síndrome Metabólica aumenta em todos o mundo, e um crescente número de casos são diagnosticados em idades mais jovens. Assim, esse estudo objetivou propor modelos preditivos para predizer a chance de um adolescente ter Síndrome Metabólica (SM) por meio de características demográficas, antropométricas e clínicas não invasivas.

Métodos: A amostra foi composta por 2.064 adolescentes, de 18-19 anos de idade, de São Luís-MA, integrantes de uma coorte de nascimento. Foram consideradas variáveis demográficas, clínicas e antropométricas dos adolescentes e foram empregados três critérios para diagnóstico de SM: Cook *et al*. (2003), De Ferranti *et al*. (2004) e *International Diabetic Federation* (IDF, 2007). Redes neurais artificiais (RNA) do tipo *feed-forward* foram treinadas para predizer a ocorrência da SM. Para avaliação do desempenho das RNA foram calculadas acurácia, sensibilidade e especificidade. Também foi construída a Curva ROC e analisada a área sob a curva para avaliar o poder discriminatório das redes.

Resultados: A prevalência de SM nos adolescentes de 18-19 anos de São Luís-MA variou entre 5,7%; e 12,3%, sendo a maior pelo critério de De Ferranti et al. As RNAs obtiveram melhor desempenho quando a SM foi definida de acordo com o critério de Cook et al. A RNA que apresentou melhor desempenho e poder discriminatório na predição da SM em adolescentes foi a RNA 5 (sensibilidade 89,8% e acurácia 86,8%), que incluiu as variáveis: idade, sexo, circunferência da cintura, peso, pressão arterial sistólica e pressão arterial diastólica; seguida da RNA 3 (sensibilidade 89,0% e acurácia 87,0%), que considerou as mesmas variáveis, com exceção do peso.

Conclusão: A partir de medidas não invasivas é possível predizer a chance de um adolescente ter SM, orientando o fluxo de atendimento na atenção primária à saúde e otimizando a gestão de recursos públicos.

Descritores: Síndrome metabólica. Adolescente. Rastreamento. Atenção Primária à Saúde. Inteligência Artificial.

1. Introdução

Com os hábitos de vida da população atual, a Síndrome Metabólica (SM) tem sido observada em faixas etárias cada vez mais jovens, favorecendo piores cenários futuros[1-3], com o aumento da morbimortalidade associada a doenças cardiovasculares[2,4].

Essa síndrome caracteriza-se pela presença de três ou mais dos seguintes componentes: triglicerídeos elevados; lipoproteína de alta densidade (*high-density lipoprotein*: HDL-colesterol) reduzida; pressão arterial e glicemia em jejum elevadas; e deposição central de gordura, representada pela circunferência da cintura (CC), que pode ser componente obrigatório para caracterização da SM, a depender do critério adotado[5,6].

Diversos critérios são utilizados por diferentes pesquisadores e sociedades para definição da SM[1,3]. No entanto, apesar de avaliarem praticamente os mesmos componentes, o que difere esses critérios são os pontos de cortes utilizados para cada um deles e a obrigatoriedade da CC alterada para caracterização da síndrome[3,7].

Consequentemente, a prevalência estimada da SM pode variar numa mesma população, a depender do critério diagnóstico adotado[8]. Vanlanker et al[9] observaram uma variação de 2,7 a 3,8% na prevalência de SM entre adolescentes europeus de 12,5 a 17 anos.

O diagnóstico precoce da SM e de seus fatores de risco são determinantes para uma intervenção mais efetiva evoluindo com desfechos favoráveis[3,10]. Porém, para o diagnóstico pelos critérios preconizados são necessários alguns exames bioquímicos[5,6] que, por mais que não sejam dos mais complexos, são invasivos, demandam o retorno do paciente à consulta e são onerosos aos cofres públicos.

Na atenção primária à saúde, o uso da Inteligência Artificial apresenta um bom potencial de rastreio de pacientes com SM, baseando-se em exames não invasivos[4]. A construção de modelos preditivos, usando redes neurais artificiais (RNA) baseadas nos componentes da SM e outras medidas antropométricas, baseados em redes neurais artificiais (RNA), apresentam bom desempenho para predição de SM e podem ser usados como ferramentas auxiliares na identificação de risco cardiometabólico[11,12]. Contudo, os modelos preditivos até o momento desenvolvidos foram para adultos orientais[11] e com base em apenas um critério definidor da SM[4,10,11]. Ademais, esses modelos preditivos incluíram variáveis invasivas e de alto custo, que podem retardar, num nível de atenção primária, o diagnóstico e tratamento da SM.

O presente estudo teve como objetivo predizer a SM em adolescentes por meio de RNA baseadas em características demográficas, e clínicas e antropométricas não invasivas.

2. Material e métodos

Trata-se de um estudo transversal com dados dos participantes da coorte de nascimento 1997-1998 do Município de São Luís-Maranhão, Brasil. Maiores detalhes sobre aspectos metodológicos das fases desta coorte estão disponíveis em Confortin et al.[13].

A amostra foi constituída por 2.515 adolescentes avaliados aos 18-19 anos, sendo constituída por 687 adolescentes provenientes da coorte original e 1.828 adolescentes oriundos de uma coorte aberta composta por indivíduos também nascidos em São Luís-MA no ano de 1997. A inclusão desses novos participantes teve como objetivo ampliar o tamanho da amostra. Eles foram selecionados por amostragem aleatória, a partir do Sistema de Informações sobre Nascidos Vivos, restrita a crianças nascidas em 1997, e identificados em escolas e universidades e por meio de redes sociais. Dos 2.515 adolescentes, foram excluídos do estudo 451, em virtude de informações incompletas ou inconsistências das variáveis de interesse. Assim, a amostra final foi constituída por 2.064 adolescentes de 18-19 anos de São Luís-Maranhão, Brasil.

No presente estudo, foram utilizadas as seguintes variáveis: idade (anos), sexo (masculino ou feminino), pressão arterial sistólica - PAS - e diastólica - PAD - (mmHg), peso (kg), altura (cm), CC (cm) e níveis séricos de glicose (mg/dl), triglicerídeos (mg/dl) e HDL-colesterol - *High-density lipoprotein* - (mg/dl).

Para a PAS e a PAD, foram consideradas as médias dos valores de três aferições realizadas após cinco minutos de repouso, utilizando o aparelho Omron HEM742INT (Omnron®, São Paulo, Brasil). Os níveis séricos de glicemia, HDL-colesterol e triglicerídeos foram dosados pelo método colorimétrico enzimático automatizado por meio do equipamento *Cobas c501* (Roche®, São Paulo, Brasil). O peso foi aferido por meio de uma balança de alta precisão acoplada ao equipamento BOD POD *Gold Standard* (COSMED *Metabolic Company*®, Roma, Itália). A altura foi medida utilizando-se um estadiômetro portátil (AlturaExata®, Belo Horizonte, Brasil) e a CC foi obtida a partir da imagem tridimensional do corpo por meio do aparelho *3-Dimensional Photonic Scanner* ([TC] Labs®, Cary, Estados Unidos). O índice de massa corporal (IMC) foi obtido por meio da razão: peso corporal (kg)/altura^2 (m^2).

Para identificação da SM nos participantes, foram consideradas as três classificações específicas para adolescentes mais utilizadas: 1. Cook et al.[14]; 2. De Ferranti et al.[15]; e, 3. *International Diabetes Federation* (IDF)[16]. Os componentes utilizados por essas

classificações consideram elevação de triglicérides, da glicemia em jejum, da PAS e/ou PAD e da CC e baixos níveis de HDL-colesterol. O critério para identificação da SM adotado pelo IDF requer, obrigatoriamente, a presença de obesidade central, medida pela CC, e pelo menos outros dois componentes. Os critérios estabelecidos por Cook et al. e De Ferranti et al. definem ser necessária a presença de, no mínimo, três componentes, sem estabelecer a obrigatoriedade da obesidade central, como faz o critério IDF (Tabela 1).

Tabela 1. Critérios para definição de Síndrome Metabólica.

Componentes/ Critérios	Cook et al. (2003)	De Ferranti et al. (2004)	IDF (2007)
PAS/PAD	≥ p90	> p90 para idade e sexo	> 130/85 mmHg
Glicemia	≥ 110 mg/dL	≥ 110 mg/dL	≥ 100 mg/dL
HDL	≤ 40 mg/dL	< 45 mg/dL (♂ 15-19a) < 50mg/dL (♀ e ♂ < 15a)	< 40 mg/dL (♂) < 50 mg/dL (♀)
Triglicerídeos	≥ 110 mg/dL	≥ 100 mg/dL)	≥ 150 mg/dL
CC*	≥ p90 para idade e sexo	> p75 para idade e sexo	≥ 94 cm (♂) ≥ 80 cm (♀)

*Componente obrigatória para o IDF, associada a outras duas componentes.
CC: Circunferência da cintura | IDF: International Diabetes Federation | PAD: Pressão arterial diastólica | PAS: Pressão arterial sistólica | p75: percentil 75 | p90: percentil 90

Conforme apresentado, o objetivo principal deste estudo é propor um modelo estatístico capaz de predizer a chance de um adolescente ter SM. Assim, foi considerada como variável resposta de interesse a presença de SM, a qual assume o valor "um" se o adolescente apresenta SM e "zero", caso contrário.

Para construção do modelo preditivo foram implementadas diferentes RNA do tipo *feed-forward*. As RNAs podem ser aplicadas a problemas de regressão, classificação e sumarização de dados, bem como em situações em que há interações não lineares entre as variáveis dependentes e independentes. Em termos de topologia, para implementar uma rede neural, as seguintes variáveis devem ser determinadas: (a) o número de nós na camada de entrada; (b) o número de camadas ocultas e o número de neurônios a serem inseridos nessas camadas; e (c) o número de neurônios na camada de saída. O número de nós na camada de entrada corresponde ao número de variáveis que serão usadas para alimentar a RNA. Essas são frequentemente as variáveis mais relevantes para o problema em estudo[17].

Vários métodos para o treinamento supervisionado de RNAs têm sido propostos. No entanto, o algoritmo mais popular usado para esse tipo de treinamento é o algoritmo de retropropagação[18]. A aplicação deste algoritmo requer a escolha de um conjunto de parâmetros (número de iterações do algoritmo, critérios de parada, pesos iniciais e taxa de aprendizado), cuja influência pode ser decisiva para a capacidade de generalização da rede.

As RNA avaliadas neste estudo consideraram como variáveis de entrada, além dos componentes da SM, idade, sexo, IMC, peso e altura, e como variável de saída a presença de SM (sim/não). As redes implementadas no estudo foram:

- RNA 1: Glicemia, CC, HDL, Triglicerídeos, PAS, PAD.
- RNA 2: Idade, Sexo, Peso, Altura, PAS, PAD.
- RNA 3: Idade, Sexo, CC, PAS, PAD.
- RNA 4: Idade, Sexo, IMC, PAS, PAD.
- RNA 5: Idade, Sexo, CC, Peso, PAS, PAD.

A RNA 1 incluiu os mesmos componentes dos critérios utilizados neste estudo, sendo considerada apenas uma rede de referência. Após a definição das variáveis de entrada da rede, a etapa seguinte foi a definição dos conjuntos de treino e de teste. Visto que se está considerando três diferentes critérios para diagnóstico de SM, foram construídas três amostras de acordo com a prevalência de SM segundo o critério adotado. Assim, em cada amostra foram incluídos todos os adolescentes com SM e a mesma quantidade de adolescentes sem SM, de forma que em cada amostra houvesse 50% de adolescentes com SM (1:1). Esse procedimento de obtenção das amostras foi considerado visto que os critérios adotados forneceram diferentes prevalências de SM. Os adolescentes sem SM foram sorteados aleatoriamente. Após a formação das amostras, cada amostra foi dividida em duas sub-amostras: 70% para treino e 30% para teste (Tabela 2).

Tabela 2. Conjuntos de treino e de teste das Redes Neurais Artificiais, segundo os critérios IDF, Cook et al. e De Ferranti et al., em adolescentes de 18-19 anos, São Luís-Maranhão, Brasil.

Critério	Total		Treino		Teste	
	Com SM	Sem SM	Com SM	Sem SM	Com SM	Sem SM
Cook et al.	118 (50%)	118 (50%)	81 (49,1%)	84 (50,9%)	37 (52,1%)	34 (47,9%)
De Ferranti et al.	253 (50%)	253 (50%)	175 (49,4%)	179 (50,6%)	78 (51,3%)	74 (48,7%)
IDF	124 (50%)	124 (50%)	88 (50,6%)	86 (49,4%)	36 (48,6%)	38 (51,4%)

IDF: *International Diabetes Federation* | SM: Síndrome metabólica.

A técnica de validação cruzada (*k-fold cross validation*) foi aplicada no conjunto de treino com a finalidade de evitar sobreajuste (*overfitting*). O objetivo dessa técnica é dividir aleatoriamente a amostra em estudo em *k* subconjuntos de forma que cada um seja usado para treinamento e o restante para validação da rede. Neste estudo, o conjunto de treino foi dividido em 10 subconjuntos. Desses, nove foram utilizados para treinamento da rede e um subconjunto foi utilizado para testar o desempenho da rede. O processo de validação foi repetido 10 vezes, de modo que cada um dos subconjuntos foi utilizado tanto no treinamento quanto no teste.

Com relação à configuração da RNA, foram implementadas diferentes redes *feed-forward*, todas elas contendo apenas uma camada oculta. A diferença entre elas estava no número de neurônios da camada de entrada e na camada oculta. Para treinamento da rede, foi utilizado o algoritmo *back-propagation* com no máximo 10.000 iterações, taxa de aprendizado de 0,25 e três diferentes parâmetros de decaimento (0,01; 0,1 e 0,5) para evitar o *overfitting* da rede. A função de ativação utilizada na camada oculta e de saída foi a função logística sigmoidal.

A capacidade de generalização das redes neurais treinadas foi avaliada a partir do conjunto de teste, considerando as seguintes métricas: acurácia (ACUR), sensibilidade (SENS), especificidade (ESPEC) e curva ROC (*Reciever Operator Characteristic*). Tais métricas foram obtidas por meio de uma matriz de confusão (Tabela 3), calculando as seguintes medidas: VP (Verdadeiros Positivos), VN (Verdadeiros Negativos), FP (Falsos Positivos) e FN (Falsos Negativos).

Tabela 3. Matriz de confusão.

Condição atual	**Predição**		**Total**
	Com SM	Sem SM	
Com SM	VP	FN	VP + FN
Sem SM	FP	VN	FP + VN
Total	VP + FP	FN + VN	VP + FP + FN + VN

SM: Síndrome metabólica | VP: Verdadeiro positivo | VN: Verdadeiro negativo | FP: Falso positivo | FN: Falso negativo

A SENS é definida como a porcentagem dos adolescentes com SM que foram classificados corretamente pela RNA e é dada pela razão: SENS = VP / (VP + FN). Já a

ESPEC é a porcentagem dos adolescentes sem SM que foram classificados corretamente, dada por: ESPEC = VN / (VN + FP). Por fim, a ACUR é a porcentagem dos adolescentes com SM e sem SM que foram corretamente classificados, isto é: ACUR = (VP + VN) / (VP + VN + FP + FN).

Para avaliar o poder discriminatório das RNA, foi construída a curva ROC e determinada a área sob a curva (*Area Under the Curve* – AUC). A curva ROC demonstra como variam a SENS e a ESPEC do método, conforme se consideram diferentes pontos de corte. O valor da AUC varia de 0,0 até 1,0. Quanto maior o AUC, melhor o método avaliado.

As análises foram realizadas no programa estatístico de acesso livre R (R Core Team, 2023). Foram utilizados os pacotes NeuralNetTools, Caret, ggplot2 e pROC (R versão 4.4.0).

Os dados analisados no presente estudo fazem parte do projeto "Determinantes ao Longo do Ciclo Vital da Obesidade, Precursores de Doenças Crônicas, Capital Humano e Saúde Mental: Uma Contribuição das Coortes de Nascimento de São Luís para o SUS", aprovado pelo Comitê de Ética em Pesquisa do Hospital Universitário da Universidade Federal do Maranhão pelo processo nº 1.302.489.

Todos os participantes assinaram o Termo de Consentimento Livre e Esclarecido. Este estudo foi realizado em conformidade com a Declaração de Helsinque e aos requisitos da Resolução nº 466/12 do Conselho Nacional de Saúde e suas complementares.

3. Resultados

A amostra em estudo foi composta por 2.064 adolescentes de 18 e 19 anos, sendo 50,9% do sexo feminino. A Tabela 4 apresenta as principais medidas descritivas das variáveis em estudo.

A prevalência da SM variou a depender do critério diagnóstico adotado. Pelo IDF e por Cook et al., as prevalências foram bem próximas e menos da metade da obtida a partir da definição adotada por De Ferranti et al. (5,9%; 5,7%; e 12,3%, respectivamente). Independente do critério escolhido, as alterações no perfil lipídico foram as mais observadas: baixos níveis de HDL-colesterol (44,5%, 35,2% e 22,2% em De Ferranti et al., IDF. e em Cook et al., respectivamente) e hipertrigliceridemia (29,7% em De Ferranti et al. e 22,9% em Cook et al.), com exceção do IDF (8,4%). Por sua vez, pelo IDF houve maior prevalência de alteração da glicemia (19,0%) em comparação aos demais critérios (9,0% em ambos). A alteração pressórica apresentou pequena variação entre os critérios (9,4% a 11,5%), enquanto

a CC alterada foi mais prevalente de acordo com o IDF (28,1%) e De Ferranti et al. (25,1%) quando comparada a Cook et al. (10,1%) (Tabela 5).

Tabela 4. Características antropométricas e clínicas dos adolescentes de 18-19 anos, São Luís-Maranhão, Brasil (n=2.064).

Variáveis	Média±DP (♂) | (♀)	Mediana (p25-p75) (♂) | (♀)	p90 (♂) | (♀)
Peso (kg)	61,3±13,1 66,1±12,9 | 56,7±11,5	59,5 (160,0-174,0) 63,7 (57,4-72,4) | 54,8 (48,4-63,4)	77,4 81,5 | 71,5
Altura (cm)	167,0±9,1 173,5±6,9 | 160,7±6,1	166,0 (160,0-174,0) 173,0 (169,0-178,0) | 160,5 (156,5-165,0)	179,0 182,0 | 168,7
IMC (kg/m²)	21,9±3,9 21,9±3,7 | 21,9±4,1	21,2 (19,1-24,0) 21,1 (19,3-23,8) | 21,2 (18,9-24,1)	27,1 26,7 | 27,3
CC (cm)	81,7±9,0 83,6±9,0 | 79,8±8,7	80,5 (75,4-86,5) 81,8 (77,3-88,2) | 78,5 (73,5-84,9)	93,4 94,8 | 91,7
PAS (mmHg)	114,2±12,2 121,0±11,0 | 107,7±9,3	113,0 (105,0-122,0) 120,0 (113,0-128,0) | 107,0 (101,0-113,0)	131,0 136,0 | 119,0
PAD (mmHg)	70,9±7,4 71,8±7,6 | 70,0±7,1	70,0 (66,0-75,0) 71,0 (66,0-76,0) | 69,0 (65,0-74,0)	80,0 81,6 | 79,0
Glicemia (mg/dL)	92,2±16,0 93,4±17,8 | 91,1±14,0	90,0 (84,0-97,0) 91,0 (85,0-98,0) | 89,0 (83,0-96,0)	108,0 109,0 | 107,0
HDL (mg/dL)	49,4±11,8 45,6±10,3 | 53,0±12,0	48,0 (41,0-56,0) 45,0 (38,0-52,0) | 52,0 (45,0-60,0)	65,0 58,0 | 68,0
Triglicerídeos (mg/dL)	90,8±48,5 98,3±55,0 | 83,6±40,1	79,0 (61,0-106,0) 86,0 (64,0-114,0) | 73,0 (58,0-96,0)	142,7 154,0 | 130,0

DP: desvio padrão | ♂: sexo masculino | ♀: sexo feminino | IQ: intervalo interquartil | p90: percentil 90 | IMC: índice de massa corporal | CC: circunferência da cintura | PAS: pressão arterial sistólica | PAD: pressão arterial | HDL: HDL(*High-density lipoprotein)*-colesterol

A Tabela 6 mostra o desempenho das RNA nas amostras teste e total, considerando os três critérios utilizados neste estudo. De forma geral, para os três critérios, todas as RNA apresentaram bom desempenho na predição da SM nos adolescentes da amostra estudada, configurado por valores de ACUR, SENS e ESPEC acima de 70%.

Quando o critério adotado foi o de Cook et al., as RNA apresentaram melhor desempenho. Dentre elas, destacaram-se a RNA 3 e a RNA 5, que utilizaram como variáveis de entrada idade, sexo, CC, PAS, PAD; e a RNA 5 usou ainda o peso. Pelo critério de De Ferranti et al., a RNA 3 e a RNA 4 obteviveram melhor desempenho em relação às demais.

Tabela 5. Prevalência da Síndrome Metabólica e de seus componentes, segundo os critérios de Cook et al., De Ferranti et al. e IDF, em adolescentes de 18/19 anos, São Luís-Maranhão, Brasil (n=2.064).

SM e Componentes	Cook et al. (2003)	De Ferranti et al. (2004)	IDF (2005)
SM	5,7% (n=118)	12,3% (n=253)	5,9% (n=121)
CC*	10,1% (n=208)	25,1% (n=518)	28,1% (n=579)
PAS/PAD	11,5% (n=238)	9,4% (n=194)	11,3% (n=234)
Glicemia	9,0% (n=185)	9,0% (n=185)	19,0% (n=393)
HDL-colesterol	22,2% (n=459)	44,5% (n=918)	35,2% (n=726)
Triglicerídeos	22,9% (n=473)	29,7% (n=612)	8,4% (n=174)

IDF: *International Diabetes Federation* | SM: Síndrome metabólica | CC: circunferência da cintura | PAS: pressão arterial sistólica | PAS: pressão arterial diastólica | HDL: HDL(*High-density lipoprotein*)-colesterol
*Componente diagnóstico obrigatório no critério do IDF.

Considerando a amostra total (n=2.064), o desempenho das RNA teve uma pequena queda quando o critério diagnóstico da SM adotado foi o de Cook et al.; contudo, as RNA 3 e RNA 5 permaneceram em destaque em relação às outras. Em relação ao critério de De Ferranti et al., de maneira geral, o desempenho das RNA não sofreu grandes variações e a RNA 5 se sobressaiu, juntamente com a RNA 3. Pelo critério do IDF, o desempenho das RNA melhorou ao se utilizar toda a amostra, mas permaneceu inferior quando os outros dois critérios foram empregados. Por este critério, tomando-se a amostra total, também se sobressaíram a RNA 3 e a RNA 5 e não mais a RNA 4, como ocorreu com a amostra teste.

A Figura 1 apresenta as curvas ROC obtidas para avaliar o poder discriminatório das RNA. O critério de Cook et al. apresentou maiores valores da AUC (superior a 90%). Observa-se, ainda, que a RNA 5 apresentou bom poder discriminatório em todos os critérios diagnósticos adotados (Cook et al.: AUC = 96,7%; De Ferranti et al.: AUC = 89,0%; e IDF: AUC = 87,5%).

4. Discussão

Neste estudo, foram propostas diferentes RNA para predizer a chance de um adolescente ter SM. Para isso, diferentes critérios para o diagnóstico de SM foram considerados. As RNA, implementadas a partir do critério de Cook et al., apresentaram maior ACUR e SENS. Além disso, a RNA que incluiu apenas as variáveis idade, sexo, CC, peso, PAS e PAD (RNA 5) apresentou melhor desempenho e poder discriminatório na predição da SM, independente do critério adotado, seguida da rede que incluiu idade, sexo, CC, PAS e

PAD (RNA 3). Essas redes incluem os mesmos componentes não invasivos dos critérios definidores da SM (CC, PAS e PAD). Além disso, os componentes incluídos nas redes são valores numéricos, sem a necessidade de definição de ponto de corte para identificação do risco de desenvolver SM.

Tabela 6. Medidas de desempenho das RNA para o conjunto de teste e para a amostra total (n=2.064), segundo os critérios de Cook et al., De Ferranti et al. e IDF, em adolescentes de 18-19 anos, São Luís-Maranhão, Brasil.

RNA	Critérios de caracterização da Síndrome Metabólica								
	Cook et al. (2003)			De Ferranti et al. (2004)			IDF (2007)		
	ACUR	SENS	ESPEC	ACUR	SENS	ESPEC	ACUR	SENS	ESPEC
Conjunto teste		***n=84***			***n=166***			***n=73***	
RNA1	87,3%	97,3%	76,5%	88,2%	91,0%	85,1%	68,5%	81,1%	55,6%
RNA2	87,3%	91,9%	82,4%	82,2%	80,8%	83,8%	75,3%	75,7%	75,0%
RNA3	88,7%	89,2%	88,2%	83,6%	80,8%	86,5%	76,7%	73,0%	80,6%
RNA4	84,5%	89,2%	79,4%	80,3%	79,5%	81,1%	79,5%	81,1%	77,8%
RNA5	90,1%	91,9%	88,2%	82,2%	75,6%	89,2%	79,5%	78,4%	80,6%
Amostra total									
RNA1	87,5%	96,6%	86,9%	87,2%	88,9%	86,9%	76,2%	88,4%	75,4%
RNA2	84,3%	89,0%	84,0%	81,4%	77,9%	81,9%	78,7%	81,0%	78,5%
RNA3	87,0%	89,0%	86,9%	83,8%	80,2%	84,3%	82,5%	78,5%	82,7%
RNA4	82,4%	90,7%	81,9%	80,9%	78,7%	81,2%	77,5%	81,8%	77,3%
RNA5	86,8%	89,8%	86,6%	85,3%	76,3%	86,5%	82,3%	82,6%	82,3%

IDF: *International Diabetes Federation* | RNA: rede neural artificial | ACUR: Acurácia | SENS: sensibilidade | ESPEC: especificidade.

A medida da CC representa um método prático e de baixo custo, mas o seu modo de avaliação representa uma importante limitação, uma vez que os pontos de discriminação diagnóstica variam com o sexo e grupos étnicos[19]. Os critérios adotados neste estudo consideram diferentes pontos de cortes para a CC segundo o sexo e A idade. Quando se compara a SENS entre a RNA 3 e a RNA 5, segundo os critérios adotados, a RNA que considerou o critério de Cook et al. para diagnóstico de SM apresentou maior SENS para a amostra em estudo, mostrando que o ponto de corte da CC pode influenciar a identificação dos adolescentes com SM.

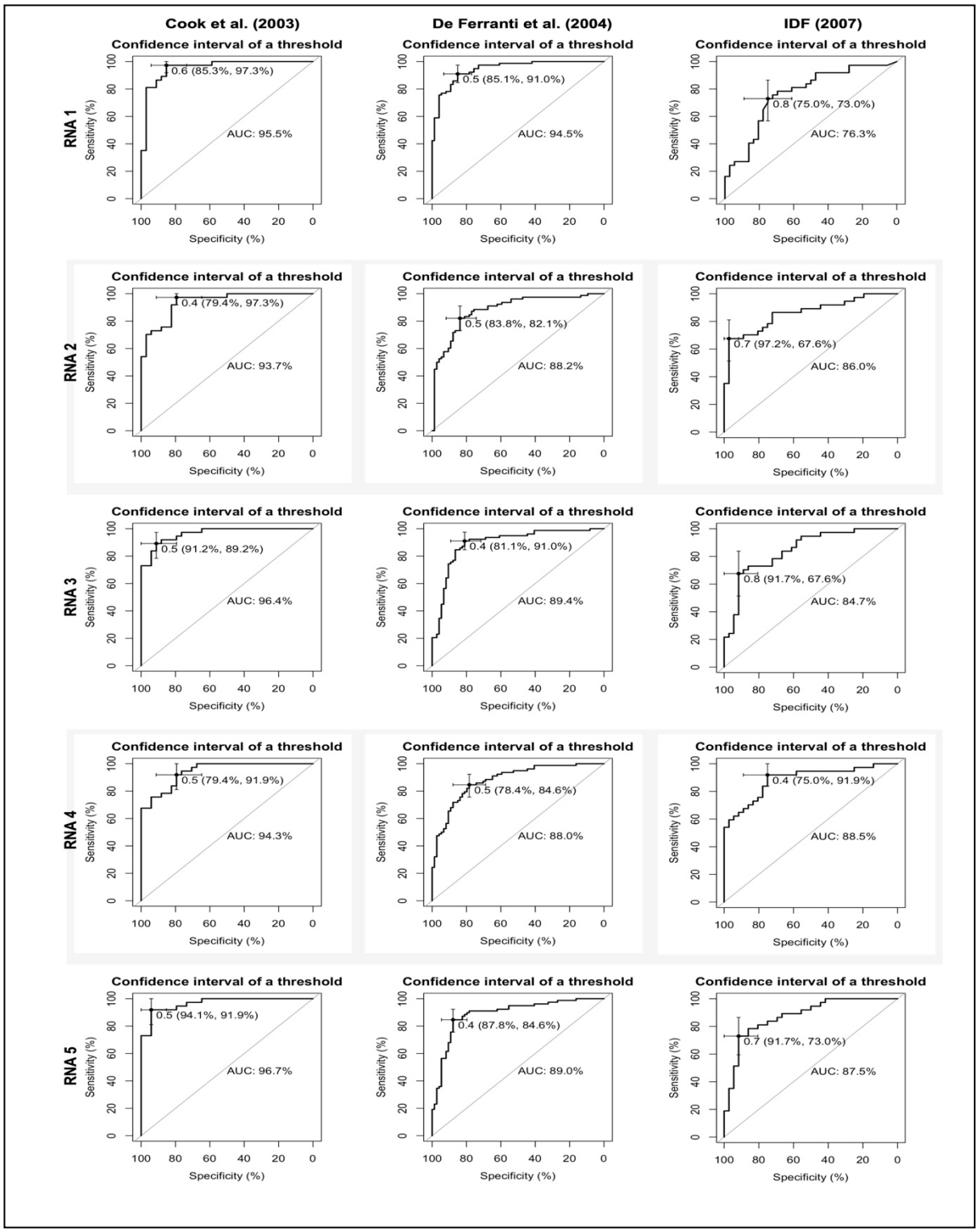

Figura 01. Poder discriminatório das Redes Neurais Artificiais na predição da Síndrome Metabólica, segundo os critérios de Cook et al., De Ferranti et al. e IDF, em adolescentes de 18-19 anos, São Luís-Maranhão, Brasil.

Embora a CC seja o indicador antropométrico mais utilizado para avaliar a gordura abdominal, que está associada às anormalidades metabólicas[7,20], talvez, em faixas etárias mais jovens, ainda não seja um componente isoladamente tão importante e

preponderante para a definição de SM. Desta forma, a inclusão de outra medida antropométrica é importante para o diagnóstico da SM nessa faixa etária. Conforme resultados da RNA 5, a inclusão do peso do adolescente, além da CC, permitiu melhor identificação dos adolescentes com SM, segundo o critério do IDF.

Os critérios adotados neste estudo utilizam os mesmos componentes metabólicos para definir SM. Todavia, seus pontos de corte e a obrigatoriedade da CC diferem, de modo a determinar grandes variações[1,21]. Nesse sentido, Weihe e Weihrauch-Blüher[6] consideram mandatório um critério unificado para definição de SM na população de crianças e adolescentes, e que considere o estágio puberal e etnia, além da idade e sexo.

No presente estudo, as RNA propostas para predição de SM em adolescentes de 18 e 19 anos apresentaram bom desempenho. Até o momento, não foram encontrados na literatura estudos que propusessem o desenvolvimento e validação de um modelo preditivo que considerasse apenas medidas não invasivas (CC, PAS e PAD) nessa população.

Alguns estudos têm aplicado, com êxito, a Inteligência Artificial no nível de atenção primária à saúde com o intuito de rastrear condições futuras e possibilitar prevenções precoces, de modo a melhorar desfechos e otimizar recursos[12,22,23]. Estes estudos demonstram que a Inteligência Artificial pode ser empregada para identificar e predizer risco cardiovascular, permitindo a implementação de estratégias precoces de intervenção. Esta abordagem pode melhorar a efetividade dos serviços de atenção primária à saúde e, consequentemente, as condições de saúde da população em geral.

No contexto de assistência primária à saúde do Brasil, o acesso a exames bioquímicos, necessários para o diagnóstico da SM, pode ser limitado, dispendioso e demorado[24]. Isto pode minar o potencial da atenção primária à saúde em diagnosticar e conduzir o tratamento da SM eficazmente.

Assim, a aplicabilidade da RNA 5 desenvolvida neste estudo permite que, a partir de medidas simples, não invasivas, obtidas na triagem de uma consulta médica de atenção primária à saúde, por meio de instrumentos acessíveis e baratos, possa ser predita a chance de um adolescente ter SM. A partir de então, é possível concentrar esforços para que haja uma intervenção precoce capaz de diminuir riscos cardiometabólicos e sobrecarga de doenças. Ao identificar o adolescente com maior chance de ter SM, o seu vínculo com o sistema de saúde pode ser melhor trabalhado para que ele, de fato, realize os exames, retorne às consultas, esteja motivado às mudanças propostas e dê seguimento ao acompanhamento médico, com maior possibilidade de sucesso na intervenção.

A construção das RNA para a predição de SM considerou apenas adolescentes de 18 e 19 anos, não incluindo outras faixas etárias inerentes a esta fase da vida, o que pode representar uma limitação. Porém, teve-se o cuidado em utilizar apenas critérios que abrangessem essas idades para o diagnóstico da SM. Recomenda-se cautela ao extrapolar os achados deste estudo para adolescentes com idades diferentes.

Em contraponto, foram utilizados três critérios diagnósticos de SM neste estudo, para também verificar por qual deles as RNA apresentavam melhor desempenho na predição da síndrome. A maioria dos estudos utilizou apenas um critério[4,10,20,21,25,26]. Também se optou por utilizar apenas variáveis de entrada que representassem medidas não invasivas, de obtenção rápida e fácil, com o intuito de ser utilizada como um instrumento de rastreamento da SM a nível de atenção primária à saúde, a despeito de estudo que incluiu apenas parâmetros bioquímicos e cardíacos mais complexos[25].

4. Conclusões

Os achados deste estudo mostram que a RNA 3, construída com as variáveis idade, sexo, PAS, PAD e CC, e a RNA 5, com a inclusão do peso, apresentaram melhor ACUR e SENS, com grande potencial para rastreio de SM em adolescentes. Assim, medidas não invasivas podem predizer a chance de um adolescente desenvolver SM, orientando o fluxo de atendimento na atenção primária à saúde e otimizando a gestão de recursos públicos.

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5.2 Artigo 2

Importância Relativa dos Componentes da Síndrome Metabólica no seu Diagnóstico

(a ser submetido à Revista Obesity, Fator de impacto 4,2, Qualis A1)

Importância Relativa dos Componentes da Síndrome Metabólica no seu Diagnóstico

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RESUMO

Objetivo: Avaliar a relevância dos componentes da Síndrome Metabólica (SM) para o seu diagnóstico em dois momentos da vida adulta. **Métodos:** Estudo longitudinal com dados de 1.098 participantes de uma coorte em Ribeirão Preto/SP, aos 23-25 anos e aos 37-39 anos. Foram utilizadas variáveis sociodemográficas, clínicas, bioquímicas, antropométrica e de hábitos de vida. Para o diagnóstico da SM, foi empregado o critério do JIS (2009). A importância de cada componente da SM foi determinada por meio de redes neurais artificiais e do algoritmo de Garson. **Resultados:** Predominaram indivíduos do sexo feminino (52,2%) e a prevalência de SM aos 23-25 anos foi de 12,1% e aos 37-39 anos, esta prevalência mais que triplicou (41,6%). O componente mais importante para o diagnóstico da SM, aos 23-25 anos, foi a pressão arterial sistólica (PAS), e aos 37-39 nos, foi o HDL. O menos relevante foi a circunferência da cintura (CC), no primeiro momento, e os triglicerídeos, no segundo. Com a mudança da fase da vida, PAD, glicemia e HDL tiveram sua importância aumentada e PAS, PAD e HDL configuraram entre os componentes mais importantes para o diagnóstico da SM. **Conclusão:** O HDL e a pressão arterial foram os componentes de maior importância e que mais ganharam relevância para diagnóstico da SM; os triglicerídeos foram de menor relevância. Realizar intervenções, em especial, no controle dos níveis de HDL e de pressão arterial, poderia contribuir com maior eficácia na prevenção e até diminuição da prevalência de SM.

Palavras-chave: Síndrome metabólica. HDL-colesterol. Pressão arterial.

INTRODUÇÃO

A Síndrome Metabólica (SM) é uma condição globalmente prevalente, que se acentua com o avanço da idade, e está associada a diversas patologias e maior mortalidade cardiovascular (1). Ela compreende um conjunto de disfunções metabólicas, que incluem

resistência insulínica, obesidade abdominal, dislipidemia e hipertensão (2). O seu diagnóstico é feito a partir de critérios que se baseiam na presença dessas alterações (3,4,5).

Existem diversos critérios para o diagnóstico da SM, que se distinguem quanto à seleção dos componentes, aos pontos de corte adotados e à obrigatoriedade da presença de determinados componentes (6,7). Entre esses critérios, o *Joint Interim Statement* (JIS) foi proposto pela *International Diabetes Federation Task Force on Epidemiology and Prevention* a partir de um consenso entre seis grandes organizações das áreas de endocrinologia, metabologia e cardiologia no intuito de unificar os critérios ora existentes. Suas principais características são a não obrigatorieadade de um componente específico e os pontos de corte para definição da obesidade abdominal variarem de acordo com características regionais e nacionais das populações (5)

Para definição de SM na população brasileira, o JIS exige a presença de, no mínimo, três das seguintes alterações: pressão arterial ≥130mmHg/85mmHg; glicemia em jejum ≥100mg/dL; triglicerídeos ≥150mg/dL; HDL-colesterol <40mg/dL em homens e <50mg/dL em mulheres; e da circunferência da cintura (CC) ≥90cm em homens e ≥80cm em mulheres (5).

Independente do critério diagnóstico a ser escolhido pelos profissionais de saúde, a escassez de estudos que demonstrem a relevância dos componentes para o diagnóstico da síndrome ao longo da vida dificulta o direcionamento das intervenções prioritárias para prevenção e controle da SM (8,9), específicas a cada fase da vida (1,10). Com o avanço da idade, há maior predisposição às mudanças metabólicas, que podem culminar em condições patológicas, como diabetes, hipertensão arterial e obesidade (11).

Considerando a importância de avaliar essas mudanças metabólicas, é necessário investigar a relevância dos componentes da SM em diferentes fases da vida. Entretanto, deve-se considerar a alta correlação existente entre os componentes da síndrome. Por

exemplo, o aumento da CC relaciona-se ao aumento da glicemia e da pressão arterial (12). Neste contexto, os modelos de regressão não são aplicados devido à colinariedade entre esses componentes (13).

Assim, estudos mais recentes na área médica têm utilizado as técnicas de Aprendizado de Máquina (14, 15, 16, 17) para avaliar a relevância dos componentes da SM. Todavia, estes estudos têm avaliado os componentes da SM numa ampla faixa de idade (14, 15, 16, 17) e considerado, além desses componentes, outros parâmetros clínicos, bioquímicos e antropométricos (14, 16, 17), que poderiam mascarar o destaque de um componente específico da SM. Ainda, nenhum desses estudos utilizou na avaliação da importância dos componentes a técnica das Redes Neurais Artificiais (RNA), que se insere no âmbito do Aprendizado de Máquina. Trata-se de uma técnica não paramétrica, que permite a correlação entre as variáveis (13) e que constitui uma potencial ferramenta para analisar a importância dos componentes dos critérios diagnósticos da SM.

Nesse contexto, o objetivo deste estudo foi utilizar a técnica de RNA para investigar a relevância dos componentes da SM para o seu diagnóstico em dois momentos da vida adulta.

MÉTODOS

Tipo de estudo

Trata-se de um estudo longitudinal, com dados provenientes do Consórcio RPS, o qual inclui nove coortes de nascimento de três cidades brasileiras: Ribeirão Preto-São Paulo, Pelotas-Rio Grande do Sul e São Luís-Maranhão.

Base de dados

Neste estudo, foram utilizados os dados dos participantes da coorte de Ribeirão

Preto-São Paulo, intitulada “Determinantes ao longo do ciclo vital da obesidade, precursores de doenças crônicas, capital humano e saúde mental”, iniciada em 1978-1979.

O município de Ribeirão Preto localiza-se no nordeste do estado de São Paulo, distante da capital 315 km. Em 1978-1979, o município de Ribeirão Preto apresentava 318.554 habitantes e em 2022, 698.642 habitantes. Em 2010, a renda *per capita* era de R$ 1.317,00 (US$ 793), o Índice Gini de 0,54 e o IDHM (Índice de Desenvolvimento Humano Municipal) era 0,8 (Atlas de Desenvolvimento Humano. Caracterização do território de Ribeirão Preto. http http://www.atlasbrasil.org.br/perfil/municipio/354340, acesso em 17/Abril/2024).

Os dados utilizados compreenderam o terceiro seguimento (2002-2004), quando os participantes estavam com 23-25 anos, e o quarto seguimento (2016-2017), tendo os participantes 37-39 anos. Maiores detalhes sobre aspectos metodológicos das coortes do Consórcio RPS estão disponíveis em Confortin et al. (18).

No terceiro seguimento da coorte foram avaliados 2.103 indivíduos, enquanto no quarto seguimento foram 1.775. Para este estudo, foram incluídos 1.113 indivíduos, que participaram dos dois seguimentos da coorte. Foram excluídos 15 participantes por apresentarem informações incompletas ou inconsistentes nas variáveis de interesse. Assim, a amostra final foi constituída por 1.098 indivíduos.

Variáveis em estudo

No presente estudo, foram utilizadas as seguintes variáveis: sexo (masculino ou feminino), idade (anos), cor (branca, negra, parda ou outra), estado civil (com ou sem companheiro/casado), filho (sim/não), tabagismo (sim/não), prática de atividade física regular (sim/não), circunferência da cintura (CC) (cm), pressão arterial sistólica (PAS) e diastólica (PAD) (mmHg), e níveis séricos de glicose (mg/dl), triglicerídeos (mg/dl) e HDL-colesterol

(*high-density lipoprotein*) (mg/dl).

As variáveis sociodemográficas e de hábitos de vida foram obtidas por meio de questionários semi-estruturados aplicados na entrevista com os participantes. A CC foi aferida com o indivíduo em pé, com o abdomen relaxado, na menor circunferência entre a última costela e a crista ilíaca, com uma trena inelástica de 0,1 cm de graduação.

Para a PAS e a PAD, as medidas foram obtidas com o paciente sentado e com o braço esquerdo na altura do coração, por meio de um esfigmomanômetro com braçadeira ajustável ao tamanho do braço. Foram obtidas três medidas das pressões arteriais, pelo mesmo avaliador, com intervalos de 15 minutos entre elas. A média das duas últimas medidas foi calculada e utilizada como a medida correspondente à variável.

Os níveis séricos de glicose, HDL-colesterol e triglicerídeos foram obtidos a partir de uma amostra de sangue coletada após 12h de jejum e dosados nos laboratórios do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo (HCFMRP-USP).

Para o diagnóstico da SM, foi empregado o critério do JIS (5). As alterações metabólicas consideradas por esse critério são a elevação da pressão arterial (PAS ≥130mmHg e/ou PAD ≥85mmHg), da glicemia em jejum (≥100mg/dL), dos triglicerídeos (≥150mg/dL) e da CC (≥90cm em homens e ≥80cm em mulheres) e baixos níveis de HDL-colesterol (<40mg/dL em homens e <50mg/dL em mulheres). Para definição de SM, o JIS exige a presença de, no mínimo, três dessas alterações.

Análise estatística

Primeiramente, foi realizada a análise descritiva das variáveis em estudo. As variáveis categóricas foram apresentadas por meio de frequências simples e porcentagens. Os testes Lilliefors, Cramér-von Mises e Shapiro-Wilk foram utilizados para avaliação da

normalidade das variáveis numéricas, as quais não apresentaram distribuição normal e foram apresentadas por meio de mediana e intervalo interquartílico (IQ).

Para comparar os componentes da SM aos 23-25 anos e aos 37-39 anos, foi utilizado o teste de Wilcoxon. As prevalências de SM e das anormalidades metabólicas que a compõe foram comparadas por meio do teste Qui-Quadrado ou Exato de Fisher. O nível de significância adotado em todos os testes foi de 0,05.

Para avaliar a importância relativa da cada componente para predição de SM, foi usada a técnica de redes neurais artificiais (RNA). Esta técnica foi escolhida em virtude da correlação dos componentes da SM com a variável resposta (presença de SM), pois as RNA possibilitam a identificação da influência das variáveis de entrada na predição da saída (variável resposta), visto que o seu desempenho está fortemente atrelado a escolha destas variáveis. Além disso, as RNA são normalmente utilizadas em estudos de classificação ou regressão, por serem aproximadores universais de qualquer função não linear (13).

Para o aprendizado das RNA, foram formados os conjuntos de treino e de teste, considerando as prevalências de SM de acordo com as fases da vida adulta. Em seguida, optou-se por formar uma amostra contendo todos os indivíduos com SM e selecionar aleatoriamente a mesma quantidade de indivíduos sem SM (na proporção 1:1). Essa proporção foi escolhida para balancear os dados, de forma a facilitar o aprendizado da rede, uma vez que o evento de interesse (SM) apresentou uma baixa prevalência (12,1% aos 23-25 anos e 41,6% aos 37-39 anos). Da amostra formada, foram utilizados 80% dos dados para treinamento da rede e 20% para teste do desempenho preditivo (Tabela 1).

A arquitetura da RNA utilizada foi *feedfoward*. O número ótimo de neurônios na camada oculta da rede foi estabelecido a partir do desempenho de diferentes redes validadas com 5, 10 e 15 neurônios ocultos. A quantidade escolhida foi aquela correspondente a que

obteve o melhor desempenho da RNA. Para treinamento da rede, foi utilizado o algoritmo *back-propagation.*

Definida a rede neural, foi avaliada a importância de cada componente da SM segundo a fase da vida por meio do algoritmo de Garson. Para avaliar a capacidade de generalização das redes neurais treinadas, do conjunto teste e da população estudada, foram utilizadas as métricas da acurácia (ACUR), sensibilidade (SENS), especificidade (ESPEC), obtidas por meio de uma matriz de confusão, calculando os valores dos verdadeiros positivos, verdadeiros negativos, falsos positivos e falsos negativos.

As análises foram conduzidas na linguagem R, utilizando-se o software R Studio. Para a implementação da RNA foi empregado o pacote *CARET* e para avaliação da importância dos componentes da SM foi usado o pacote *NeuralNetTools*.

Considerações éticas

Os dados utilizados neste trabalho fazem parte do projeto "Determinantes ao longo do ciclo vital da obesidade, precursores de doenças crônicas, capital humano e saúde mental", aprovado pelo Comitê de Ética em Pesquisa (CEP) do HCFMRP-SP. O terceiro seguimento (2002-2004) foi aprovado sob o número HCRP 7606/99 e o quarto seguimento (2016-2017) foi aprovado sob o Parecer Consubstanciado 1.282.710. Todos os participantes assinaram um termo de consentimento livre e esclarecido.

Este estudo atendeu a todas as determinações da Resolução 466/2012 e da Norma Operacional 001/2013, ambas do Conselho Nacional de Saúde, Ministério da Saúde, vigentes na época.

RESULTADOS

Neste estudo, predominaram participantes do sexo feminino (52,2%) e que se autodeclararam da cor branca (64,7%). Quando comparados os seguimentos três e quatro, aos 37-39 anos observou-se aumento da prevalência de indivíduos com companheiro/casado (30,0% *vs* 69,9%), com filhos (27,6% *vs* 70,7%) e praticantes de atividade física regular (57,4% *vs* 77,7%), e redução da frequência de fumantes (16,7% *vs* 12,1%) (Tabela 2).

Todos os componentes metabólicos definidores da SM variaram significativamente entre os dois seguimentos avaliados. A mediana da CC, dos níveis pressóricos e dos níveis séricos de triglicerídeos e de glicose aumentou, enquanto a mediana dos níveis séricos de HDL-colesterol diminuiu, em ambos os momentos analisados (Tabela 3).

A prevalência de SM aos 23-25 anos foi de 12,1% (n=133) e aos 37-39 anos, esta prevalência mais que triplicou, chegando a 41,6% (n=457). Essa variação foi estatisticamente significativa. Da mesma forma, as prevalências de todas as anormalidades metabólicas definidoras da SM também aumentaram significativamente. A prevalência de glicemia alterada apresentou o maior aumento percentual, crescendo de 3,8% (n=42) para 25,9% (n=284). Aos 23-25 anos, já se observava uma considerável prevalência de alteração pressórica (21,6%; n=237) e de baixos níveis de HDL-colesterol (42,3%; n=465). A CC inadequada apresentou expressivo aumento com a mudança da fase da vida, mais que duplicando a prevalência (32,9% *vs* 73,0%, respectivamente) (Tabela 4).

A evolução da presença de SM nos dois momentos estudados é apresentada na Tabela 5. Dos 1.098 indivíduos, 8,5% (n=93) já tinham SM aos 23-25 anos e permaneceram doentes aos 37-39 anos, enquanto 3,6% (n=40) deles apresentavam SM aos 23-25 anos e conseguiram reverter essa condição aos 37-39 anos. Evoluíram com diagnóstico de SM aos

37-39 anos 33,2% (n=364). Um total de 57,4% (n=601) não apresentaram SM em nenhum momento estudado.

A Tabela 6 apresenta a evolução dos componentes da SM segundo o diagnóstico da síndrome e a fase da vida. Os indivíduos com diagnóstico de SM nos dois momentos apresentam pequena variação na prevalência dos componentes, com exceção da glicemia alterada, cujo aumento foi significativo (18,3% *vs* 57,0%; p<0,001). Entre aqueles que apresentaram diagnóstico de SM apenas aos 23-25 anos, houve uma redução significativa para HAS (70,0% *vs* 32,5%; p<0,001), HDL (80,0% *vs* 32,5%; p<0,001) e triglicerídeos (55,0% *vs* 20,0%; p<0,05). Para aqueles que tiveram diagnóstico de SM aos 37-39 anos, houve um aumento significativo na prevalência de todos os componentes da SM (p<0,001). Os indivíduos sem diagnóstico de SM nos dois momentos, apresentaram um aumento significativo para os componentes glicemia (1,8% *vs* 7,2%; p<0,001), triglicerídeos (3,3% *vs* 13,1%; p<0,001) e CC (19,6% *vs* 54,9%; p<0,001).

A partir da análise das RNA, o componente mais importante para o diagnóstico da SMfoi a PAS, aos 23-25 anos, e o HDL, aos 37-39 nos. O menos relevante foi a CC, no primeiro momento, e os triglicerídeos, no segundo. Com a mudança da fase da vida, PAD, glicemia e HDL tiveram sua importância aumentada e PAS, PAD e HDL configuraram entre os componentes mais importantes para o diagnóstico da SM (Figura 1).

Os modelos preditivos desenvolvidos neste estudo apresentaram valores de ACUR igual ou superior a 85% no conjunto teste e a 90% na população estudada. De modo semelhante, a SENS e a ESPEC também demonstraram bom desempenho das RNA, com exceção da SENS para a população aos 23-25 anos (Tabela 7).

DISCUSSÃO

Neste trabalho, a RNA apresentou bom desempenho para identificar a relevância dos componentes da SM para seu diagnóstico em dois momentos da vida adulta: aos 23-25 anos e aos 37-39 anos. Os componentes PAS, PAD e HDL configuraram os mais importantes para o diagnóstico da SM, sendo a PAS no primeiro momento e o HDL no segundo.

A pressão arterial é afetada por fatores nutricionais, comportamentais e ambientais ao longo da vida. Quando elevada, relaciona-se a maior mortalidade, por representar um importante fator de risco para doenças cardiovasculares, especialmente infarto e acidente vascular encefálico, e doença renal crônica (19). No contexto da SM, a resistência insulínica e a maior ação da leptina contribuem para a ativação do sistema nervoso simpático, que reduz a síntese de óxido nítrico, e conduz ao aumento da pressão arterial (20). No presente estudo, a prevalência de pressão arterial aumentada foi considerável, especialmente entre os indivíduos com diagnóstico de SM. A sua elevação ou manutenção em níveis inadequados mostrou-se determinante para o diagnóstico da SM, configurando um dos seus componentes mais importantes.

De modo semelhante, o HDL foi um componente relevante para o diagnóstico da SM. O HDL é uma fração do colesterol com propriedades antioxidantes, antitrombóticas, antiinflamatórias e vasodilatadora (21). Entretanto, tem-se observado uma dificuldade dos indivíduos, desde jovens, em manter essa fração do colesterol em níveis adequados, possivelmente em virtude do stress e do estilo de vida adotado, com sedentarismo e alimentação inadequada, baseada principalmente no consumo de ultraprocessados (21,22).

Baixos níveis de HDL se relacionam a maior risco de distúrbios inflamatórios, como obesidade e SM, e diabetes, decorrente de suas funções de transporte reverso do colesterol, de inibidor da inflamação e da oxidação, e de agente antidiabetogênico (23). Este contexto pode justificar a importância que o HDL apresenta no desenvolvimento da SM.

A relevância identificada pela RNA para os níveis de pressão arterial e de HDL é corroborada ao se observar que os indivíduos com diagnóstico de SM apenas aos 23-25 anos apresentaram uma redução altamente significativa das prevalências de HAS e inadequação do HDL aos 37-39 anos. Além disso, entre aqueles indivíduos com diagnóstico de SM nos dois momentos, a prevalência de níveis de pressão arterial e de HDL alterados não mostrou uma redução significativa. A inda, nos indivíduos que não apresentaram diagnóstico de SM nos dois momentos, quando houve um aumento significativo nas prevalências de alteração de glicemia, triglicerídeos e CC aos 37-39 anos, e não houve alteração nos níveis de pressão arterial e de HDL, não houve uma mudança de diagnóstico de SM, o que reforça que os componentes glicemia, triglicerídeos e CC não são tão relevantes para a SM, quanto os níveis de PAS, PAD e HDL. Diante disso, priorizar medidas que promovam a adequação dos níveis pressóricos e de HDL na vida adulta pode contribuir com maior eficácia na diminuição da prevalência de SM.

Com menor significância, a prevalência da hipertrigliceridemia diminuiu entre os indivíduos que apresentavam a SM aos 23-25 anos, mas que aos 37-39 anos não tinham mais esse diagnóstico. Por outro lado, apresentou um aumento altamente significante aos 37-39 anos entre os indivíduos que não tinham diagnóstico de SM nos dois momentos. Tais resultados reforçam que a hipertrigliceridemia tem menor impacto no diagnóstico da SM, o que ratifica os achados da RNA acerca da relevância dos componentes da SM. Assim, apesar da prevalência de triglicerídeos alterado ter triplicado aos 37-39 anos na população estudada, os modelos identificaram esse componente como um dos de menor importância. A despeito de outros estudos terem mostrado os triglicerídeos entre os componentes mais importantes para definição da SM (14, 15, 16, 17), essa divergência pode ser atribuída às metodologias distintas utilizadas nos estudos para análise da relevância dos componentes e às características específicas das populações avaliadas, como faixa etária, sexo e presença de

comorbidades.

A glicemia alterada foi o componente que apresentou maior crescimento percentual no intervalo de 14 anos. Entretanto, não houve impacto na importância relativa desse componente. Da mesma forma, embora tenha havido aumento da prevalência da inadequação da CC aos 37-39 anos, observa-se a redução da sua relevância para diagnóstico da SM entre os dois momentos avaliados, o que pode ser atribuído à mudança da expressão da gordura visceral para a subcutânea com o avançar da idade (24). Apesar do crescimento nas prevalências da alteração da glicemia e da CC, ainda que tenha ocorrido entre indivíduos sem SM, este não foi determinante para que chegassem ao diagnóstico da síndrome.

Assim, a alta prevalência de um componente da SM, bem como significativos aumento ou diminuição nessa prevalência, não necessariamente se relacionam com a importância que esse componente exerce no diagnóstico da SM. Esse achado corrobora a necessidade de estudos como o presente, que possam identificar os componentes mais relevantes, de modo a orientar as políticas públicas de enfrentamento mais eficaz à SM, que, portanto, devem concentrar mais esforços nos componentes mais relevantes da SM.

Para essa população específica, investir em medidas que combatam a elevação da PAS, da PAD e níveis inadequados de HDL, antes mesmo da vida adulta, contribuiria para uma menor prevalência de SM na fase adulta, de forma mais eficaz se as medidas fossem direcionadas, na mesma proporção, às inadequações da CC, triglicerídeos e glicemia. Dessa forma, determinar a importância relativa de cada componente da SM possibilita o direcionamento de recursos financeiros e de políticas públicas, com o fim último de redução da prevalência da SM, e todo seu impacto na mortalidade cardiovascular.

Recomenda-se cautela ao extrapolar os dados obtidos neste estudo por ter sido realizado em apenas num local. Além disso, foram investigadas as fases inicial e intermediária da vida adulta. Todavia, trata-se de um estudo de coorte e a amostra estudada

ainda não chegou na fase final da vida adulta. Sabendo que as anormalidades metabólicas se acentuam com o processo de envelhecimento (24), torna-se importante a continuidade dos estudos que avaliem a relevância dos componentes da SM nas fases seguintes.

O presente estudo apresenta como diferencial ter avaliado a relevância dos componentes da SM em dois momentos da vida (23-25 anos e 37-39 anos), enquanto os estudos que se dedicaram a avaliar esta relevância o fizeram em apenas um momento, com uma população com ampla variação de idade. Ainda, pode-se destacar como diferencial, o uso de RNA para a predição da SM, em virtude da correlação das variáveis metabólicas que a compõem, não obstante a limitação quanto ao balanceamento dos dados, que foi enfrentada com a formação dos conjuntos treino e teste na proporção 1:1.

CONCLUSÕES

Nesse estudo, apesar dos componentes para o diagnóstico da SM manterem os pontos de corte durante a vida adulta, identificou-se uma variação na relevância desses componentes entre os dois momentos avaliados. Numa fase mais jovem, a PAS mostrou-se o componente da SM mais importante para diagnóstico da SM e a CC o de menor relevância. Aos 37-39 anos, o HDL foi o componente de maior importância e os triglicerídeos apresentaram menor relevância.

Conhecer a importância relativa de cada componente da SM em cada fase da vida permite o direcionamento das políticas públicas em saúde, com a concentração de recursos para controle dos componentes mais relevantes e que terão maior impacto na redução da prevalência da SM.

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Tabela 1. Conjuntos de treinos e teste, segundo as fases da vida adulta, Ribeirão Preto-São Paulo (n=1.098)

Fase da vida adulta	Treino		Teste	
	Com SM	**Sem SM**	**Com SM**	**Sem SM**
23-25 anos	107 (50%)	107 (50%)	26 (50%)	26 (50%)
37-39 anos	366 (50%)	366 (50%)	91 (50%)	91 (50%)

SM: Síndrome metabólica

Tabela 2. Características sociodemográficas e hábitos de vida dos participantes, aos 23-25 anos e aos 37-39 anos, Ribeirão Preto-São Paulo (n=1.098).

Variáveis	23-25 anos	37-39 anos
Sexo		
Masculino	47,8% (525)	
Feminino	52,2% (573)	
Cor		
Branca	64,7% (711)	
Negra	5,4% (59)	
Parda	28,6% (314)	
Outra	1,3% (14)	
Estado civil		
Sem companheiro/casado	70,0% (769)	30,1% (330)
Com companheiro/casado	30,0% (329)	69,9% (765)
Filhos		
Sim	27,6% (303)	70,7% (776)
Tabagismo		
Sim	16,7% (183)	12,1% (132)
Atividade física regular		
Sim	57,4% (630)	77,7% (853)

Tabela 3. Análise dos componentes da Síndrome Metabólica, segundo o critério do JIS, aos 23-25 anos e aos 37-39 anos, Ribeirão Preto-São Paulo (n=1.098).

Variáveis	23-25 anos Mediana (IQ)	37-39 anos Mediana (IQ)	p-valor
Pressão arterial sistólica (mmHg)	116,0 (107,0-127,0)	121,0 (112,0-131,5)	< 0,001
Pressão arterial diastólica (mmHg)	70,0 (64,0-76,0)	77,0 (70,5-84,4)	< 0,001
Circunferência da cintura (cm)	♂ 86,0 (80,0-93,0) ♀ 74,0 (69,0-82,0)	♂ 97,0 (90,0-105,0) ♀ 86,0 (78,0-97,0)	< 0,001 < 0,001
HDL-colesterol (m g/dL)	♂ 43,0 (36,0-50,0) ♀ 51,0 (42,0-60,0)	♂ 41,6 (35,0-47,0) ♀ 48,0 (40,4-56,5)	< 0,001 < 0,001
Triglicerídeos (mg/dL)	77,5 (56,0-113,0)	124,5 (82,9-191,0)	< 0,001
Glicemia (mg/dL)	83,0 (78,0-89,0)	89,0 (80,0-100,0)	< 0,001

Tabela 4. Prevalência de Síndrome Metabólica e seus componentes, segundo os critério do JIS, aos 23-25 anos e aos 37-39 anos, Ribeirão Preto-São Paulo (n=1.098).

Variáveis	23-25 anos	37-39 anos	p-valor
Síndrome metabólica	12,1% (133)	41,6% (457)	< 0,001
Pressão arterial	21,6% (237)	34,7% (381)	< 0,001
Glicemia	3,8% (42)	25,9% (284)	0,043
HDL-colesterol	42,3% (465)	49,6% (545)	< 0,001
Triglicerídeos	11,6% (127)	38,0% (417)	< 0,001
Circunferência da cintura	32,9% (361)	73,0% (802)	< 0,001

Tabela 5. Evolução da presença de Síndrome Metabólica em duas fases da vida adulta, Ribeirão Preto-São Paulo (n=1.098).

23-25 anos/ 37-39 anos	Com SM	Sem SM
Com SM	8,5% (93)	3,6% (40)
Sem SM	33,2% (364)	54,7% (601)

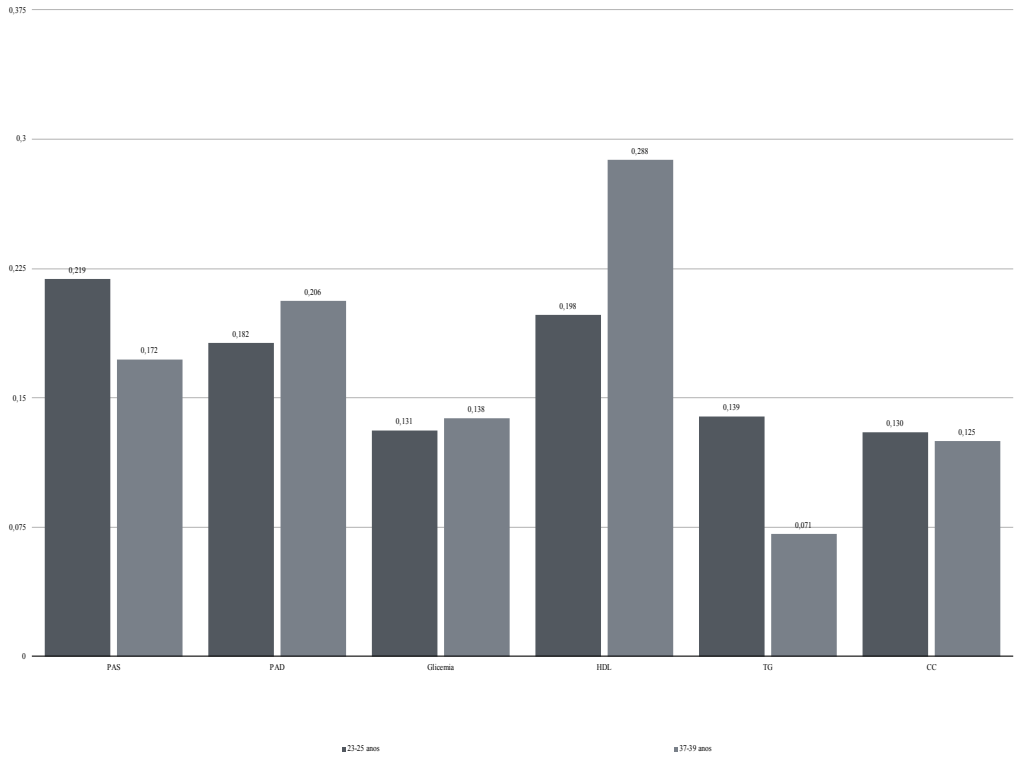
SM: Síndrome metabólica

Tabela 6. Evolução da prevalência dos componentes da Síndrome metabólica, segundo o diagnóstico da síndrome e a fase da vida adulta, Ribeirão Preto-São Paulo (n=1.098).

Variáveis	SM nos 2 momentos		SM aos 23-25 anos		SM aos 37-39 anos		Sem SM nos 2 momentos	
	23-25 anos	37-39 anos	23-25 anos	37-39 anos	23-25 anos	37-39 anos	23-25 anos	37-39 anos
Síndrome metabólica	100,0%	100,0%	100,0%	0,0%	0,0%	100,0%	0,0%	0,0%
Hipertensão Arterial Sistêmica	72,0%	78,5%	70,0%	32,5%#	18,7%	58,2%#	12,3%	13,8%
HDL-colesterol	81,7%	72,0%	80,0%	32,5%#	44,0%	72,3%#	32,8%	33,6%
Glicemia	18,3%	57,0%#	15,0%	5,0%	2,2%	51,1%#	1,8%	7,2%#
Triglicerídeos	65,6%	76,3%	55,0%	20,0%*	6,6%	71,2%#	3,3%	13,1%#
Circunferência da Cintura	96,8%	97,8%	92,5%	80,0%	31,9%	95,9%#	19,6%	54,9%#

SM: Síndrome metabólica
*p-valor <0,05 | #p-valor<0,001

Figura 1. Importância relativa dos componentes da Síndrome Metabólica, segundo o critério do JIS, aos 23-25 anos e aos 37-39 anos, Ribeirão Preto-São Paulo (n=1.098).



CC: Circunferência da cintura
PAS: Pressão arterial sistólica
PAD: Pressão arterial diastólica
TG: Triglicerídeos

Tabela 7. Desempenho das redes neurais treinadas, no conjunto teste e na população estudada, aos 23-25 anos e aos 37-39 anos, Ribeirão Preto-São Paulo (n=1.098).

	Acurácia	**Sensibilidade**	**Especificidade**
Conjunto teste			
23-25 anos	87%	94%	88%
37-39 anos	85%	86%	85%
População			
23-25 anos	93%	50%	98%
37-39 anos	92%	90%	93%

6 CONSIDERAÇÕES FINAIS

Neste estudo, foram propostas diferentes RNA para predizer a SM em adolescentes e a importância relativa dos componentes da síndrome em adultos. Diferentes critérios para o diagnóstico de SM em adolescentes foram usados. Nos adultos, optou-se pelo critério do JIS.

As RNA, implementadas a partir do critério de Cook et al., apresentaram maior ACUR e SENS. A RNA que incluiu as variáveis idade, sexo, CC, peso, PAS e PAD apresentou melhor desempenho e poder discriminatório na predição da SM em adolescentes, independente do critério adotado, seguida da rede que incluiu idade, sexo, CC, PAS e PAD. Essas redes incluem os mesmos componentes não invasivos dos critérios definidores da SM (CC, PAS e PAD).

Além disso, os componentes incluídos nas redes são valores numéricos, sem a necessidade de definição de ponto de corte para identificação do risco de desenvolver SM. Assim, a partir de medidas não invasivas é possível predizer a chance de um adolescente ter SM, orientando o fluxo de atendimento na atenção primária à saúde e otimizando a gestão de recursos públicos.

Em adultos, o HDL e a pressão arterial foram os componentes de maior importância e que mais ganharam relevância para diagnóstico da SM; os triglicerídeos foram de menor relevância. Realizar intervenções, em especial, no controle dos níveis de HDL e de pressão arterial, poderia contribuir com maior eficácia na prevenção e até diminuição da prevalência de SM.

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ANEXO A – ARTIGO 1 PUBLICADO

Journal of
Clinical Medicine

MDPI

Article

Artificial Neural Networks to Predict Metabolic Syndrome without Invasive Methods in Adolescents

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Abstract: Background/Objectives: The prevalence of metabolic syndrome (MetS) is increasing worldwide, and an increasing number of cases are diagnosed in younger age groups. This study aimed to propose predictive models based on demographic, anthropometric, and non-invasive clinical variables to predict MetS in adolescents. **Methods**: A total of 2064 adolescents aged 18–19 from São Luís-Maranhão, Brazil were enrolled. Demographic, anthropometric, and clinical variables were considered, and three criteria for diagnosing MetS were employed: Cook et al., De Ferranti et al. and the International Diabetes Federation (IDF). A feed-forward artificial neural network (ANN) was trained to predict MetS. Accuracy, sensitivity, and specificity were calculated to assess the ANN's performance. The ROC curve was constructed, and the area under the curve was analyzed to assess the discriminatory power of the networks. **Results**: The prevalence of MetS in adolescents ranged from 5.7% to 12.3%. The ANN that used the Cook et al. criterion performed best in predicting MetS. ANN 5, which included age, sex, waist circumference, weight, and systolic and diastolic blood pressure, showed the best performance and discriminatory power (sensitivity, 89.8%; accuracy, 86.8%). ANN 3 considered the same variables, except for weight, and exhibited good sensitivity (89.0%) and accuracy (87.0%). **Conclusions**: Using non-invasive measures allows for predicting MetS in adolescents, thereby guiding the flow of care in primary healthcare and optimizing the management of public resources.

Keywords: metabolic syndrome; adolescents; screening; primary health care; artificial intelligence

Citation: Júnior, A.C.; França, A.K.; Santos, E.d.; Silveira, V.; Santos, A.d. Artificial Neural Networks to Predict Metabolic Syndrome without Invasive Methods in Adolescents. *J. Clin. Med.* **2024**, *13*, 5914. https://doi.org/10.3390/jcm13195914

Academic Editor: Angelo Scuteri

Received: 4 August 2024
Revised: 7 September 2024
Accepted: 11 September 2024
Published: 3 October 2024

1. Introduction

The prevalence of metabolic syndrome (MetS) is increasing in younger age groups, with adverse future outcomes [1–3] including increased morbidity and mortality associated with cardiovascular disease [2,4].

MetS is defined as the presence of three or more of the following components: elevated triglycerides, blood pressure, and fasting glucose, reduced high-density lipoprotein (HDL) cholesterol, and central fat deposition represented by waist circumference (WC), which may be a mandatory component for MetS, depending on the criteria adopted [5,6].

Researchers and societies use different criteria to define MetS [1,3]. Nevertheless, despite evaluating the same components, the criteria differ in two key aspects: the cut-off points used for each component, and an abnormal WC being mandatory for a diagnosis of MetS [3,7].

Consequently, the estimated prevalence of MetS may vary within the same population, depending on the diagnostic criteria adopted [8]. Vanlanker et al. [9] observed a variation ranging between 2.7 and 3.8% among European adolescents aged 12.5 to 17.0 years.

Early diagnosis of MetS and its risk factors is essential for more effective interventions that lead to favorable outcomes [3,10]. However, some biochemical tests are required regardless of the criteria to diagnose MetS [5,6]. Although these are not particularly complex, they are invasive, require patients to return for medical appointments, and are costly to the public healthcare system.

In primary healthcare, applying Artificial Intelligence has the potential to screen patients likely to have MetS, based on non-invasive measurements [4]. The construction of predictive models, using artificial neural networks (ANN) based on metabolic abnormalities that define MetS and other anthropometric measurements, has demonstrated satisfactory performance in predicting MetS. These models can be used as supplementary tools to identify cardiometabolic risk [11,12]. However, the predictive models developed to date are for Asian adults [11] and are based on a single defining criterion for MetS [4,10,11]. Moreover, these predictive models include invasive and costly variables, which may delay diagnosis and treatment.

Thus, this study aims to predict MetS in adolescents using ANNs based on non-invasive demographic, clinical, and anthropometric variables.

2. Materials and Methods

This is a cross-sectional study with a dataset from the 1997–1998 birth cohort in São Luís-Maranhão, Brazil. Further details on the methodological approaches of this cohort can be found in Confortin et al. [13].

The sample consisted of 2515 adolescents assessed at 18–19 years old, of whom 687 were from the original cohort and 1828 from an open cohort composed of people born in São Luís-MA in 1997. The purpose of including new participants was to increase the sample size. They were randomly selected from the Live Birth Information System (Sistema de Informações de Nascidos Vivos), including children born in 1997, and identified at schools and universities and through social networks. A total of 451 participants were excluded due to incomplete information or inconsistencies in the variables of interest. The final sample included 2064 adolescents aged 18–19 from São Luís-Maranhão, Brazil.

The following variables were used in this study: age (years), sex (male or female), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), weight (kg), height (cm), WC (cm), serum glucose (mmol/L), triglycerides (mmol/L), and HDL cholesterol (mmol/L).

For SBP and DBP, the mean value of three measurements was considered, taken after five minutes of rest, using the Omron HEM742INT device (Omron®, São Paulo, Brazil). Glycemia and serum levels of HDL cholesterol and triglycerides were measured using the automated enzymatic colorimetric method using the Cobas c501 device (Roche®, São Paulo, Brazil). Weight was measured using a high-precision scale integrated with BOD POD Gold Standard equipment (COSMED Metabolic Company®, Rome, Italy). Height was measured using a portable stadiometer (AlturaExata®, Belo Horizonte, Brazil). WC was obtained from a three-dimensional image of the body using a 3-Dimensional Photonic Scanner ([TC] Labs®, Cary, NC, USA). Body mass index (BMI) was calculated as follows: body weight (kg) divided by height squared (m^2).

To identify MetS in participants, the three most widely used specific criteria for adolescents were considered: 1. Cook et al. [14]; 2. De Ferranti et al. [15]; and 3. International Diabetes Federation (IDF) [16]. These classifications considered elevated triglycerides, fasting glucose, SBP and/or DBP, WC, and low HDL cholesterol levels. The IDF criteria for identifying MetS require the presence of central obesity, as measured by WC, in addition to at least two metabolic abnormalities. The criteria established by Cook et al. and De Ferranti et al. require at least three of the five metabolic abnormalities, and central obesity is not mandatory as in the IDF criteria (Table 1).

Table 1. Criteria for defining Metabolic Syndrome.

Components/ Criteria	Cook et al. (2003) [14]	De Ferranti et al. (2004) [15]	IDF (2007) [16]
SBP/DBP	≥p90	>p90 for age and sex	≥130/85 mmHg
Glycemia	≥110 mmol/L	≥110 mmol/L	≥100 mmol/L
HDL	≤40 mmol/L	<45 mmol/L (♂ 15–19 y) <50 mmol/L (♀ and ♂< 15 y)	<40 mmol/L (♂) <50 mmol/L (♀)
Triglycerides	≥110 mmol/L	≥100 mmol/L	≥150 mmol/L
WC	≥p90 for age and sex	>p75 for age and sex	≥94 cm (♂) * ≥80 cm (♀) *

* Mandatory component for the criteria of IDF, associated with two other components. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WC: Waist circumference; p75: 75th percentile; p90: 90th percentile.

The primary objective of this study is to propose a statistical model capable of predicting the probability of an adolescent developing MetS. The response variable of interest y was the presence of MetS, which takes the value "$y = 1$" if the adolescent has MetS and "$y = 0$" otherwise.

Different feed-forward ANNs were used to build the predictive model. ANNs can be applied to regression, classification, and data summarization problems, as well as in situations where there are nonlinear interactions between the dependent and independent variables. In terms of topology, to implement a neural network, we must determine the following variables: (a) the number of nodes in the input layer, (b) the number of hidden layers and the number of neurons to be inserted in these layers, and (c) the number of neurons in the output layer. The number of nodes in the input layer corresponds to the number of variables that will be used to feed the neural network. These are often the most relevant variables for the problem under study [17].

Various methods for the supervised training of ANNs have been proposed. However, the most popular algorithm used for this type of training is the backpropagation algorithm [18]. The application of the backpropagation algorithm requires the choice of a set of parameters (number of iterations of the algorithm, stopping criteria, initial weights, and learning rate), the influence of which can be decisive for the network's ability to generalize.

The ANNs considered in this study considered the following input variables: age, sex, BMI, weight, and height. The output variable was the presence or absence of MetS (yes/no). The ANNs implemented in this study are as follows:

- ANN 1: Glycemia, WC, HDL, Triglycerides, SBP, DBP.
- ANN 2: Age, Sex, Weight, Height, SBP, DBP.
- ANN 3: Age, Sex, WC, SBP, DBP.
- ANN 4: Age, Sex, BMI, SBP, DBP.
- ANN 5: Age, Sex, WC, Weight, SBP, DBP.

ANN 1 included the same components as the criteria used in this study and was considered only as a reference network. Once the input variables were defined, the next step was to define the training and test sets. Given that three different criteria were considered for diagnosing MetS, three samples were constructed based on the prevalence of MetS according to the criterion adopted. Therefore, each sample included an equal number of adolescents with and without MetS (1:1). This sampling procedure was adopted because the criteria yielded disparate MetS prevalence rates. Adolescents without MetS were randomly selected. Each sample was divided into two subsamples: 70% for training and 30% for testing (Table 2).

Table 2. Training and testing sets of Artificial Neural Networks, according to the IDF, Cook et al., and De Ferranti et al. criteria, in adolescents aged 18–19 from São Luís-Maranhão, Brazil.

Criteria	Total		Training		Test	
	MetS	No MetS	MetS	No MetS	MetS	No MetS
Cook et al.	118 (50%)	118 (50%)	81 (49.1%)	84 (50.9%)	37 (52.1%)	34 (47.9%)
De Ferranti et al.	253 (50%)	253 (50%)	175 (49.4%)	179 (50.6%)	78 (51.3%)	74 (48.7%)
IDF	124 (50%)	124 (50%)	88 (50.6%)	86 (49.4%)	36 (48.6%)	38 (51.4%)

IDF: International Diabetes Federation; MetS: Metabolic Syndrome.

To avoid overfitting, k-fold cross-validation was applied to the training set. The objective of this technique is to randomly divide the sample under study into k subsets, where each subset serves as a training set, and the remaining subsets serve as validation sets for the network. In this study, the training set was divided into ten subsets. Nine of these were used to train the network, and one subset was employed to evaluate the network's performance. The validation process was repeated ten times. Each subset was used as both training and testing sets.

Different feed-forward networks containing only one hidden layer were implemented. The distinguishing factor was the number of neurons in the input and hidden layers. To train the network, a backpropagation algorithm was employed with a maximum of 10,000 iterations, a learning rate of 0.25, and three distinct decay parameters (0.01, 0.1, and 0.5) to prevent overfitting. The activation function used in the hidden and output layers is a sigmoidal logistic function.

To avoid overfitting, k-fold cross-validation was applied to the training set. The objective of this technique is to randomly divide the sample under study into k subsets, where each subset serves as a training set, and the remaining subsets serve as validation sets for the network. In this study, the training set was divided into ten subsets. Nine of these were used to train the network.

The generalization capacity of the trained ANN was evaluated using a test set with the following metrics: accuracy (ACUR), sensitivity (SENS), specificity (SPEC), and receiver operating characteristic (ROC) curve. These metrics were derived from a confusion matrix (Table 3) that calculated the following measures: True Positives (TP), True Negatives (TN), False Positives (FP), and False Negatives (FN).

Table 3. Confusion matrix.

Real	Prediction		Total
	MetS	No MetS	
MetS	TP	FN	TP + FN
No MetS	FP	TN	FP + TN
Total	TP + FP	FN + TN	TP + FP + FN + TN

MetS: Metabolic Syndrome; TP: True Positive; TN: True Negative; FP: False Positive; FN: False Negative.

The SENS was defined as the percentage of adolescents with MetS correctly classified by the ANN. It was calculated using SENS = TP/(TP + FN). SPEC is the percentage of adolescents without MetS correctly classified. SPEC was calculated as follows: SPEC = TN/(TN + FP). The ACUR was defined as the percentage of adolescents with and without MetS correctly classified. This was calculated using ACUR = (TP + TN)/(TP + TN + FP + FN).

A ROC curve was constructed, and the Area Under the Curve (AUC) was determined to assess the discriminatory power of the ANN. The ROC curve illustrates how the SENS

and SPEC values of the method vary when different cut-off points are considered. The AUC ranges from 0 to 1. The higher the AUC, the more effective the evaluated method.

Analyses were performed in the open-access statistical program R (R Core Team, 2023). The *NeuralNetTools*, *caret*, *ggplot2*, and *pROC* packages were used (R version 4.4.0).

The data analyzed in this study are part of a larger project, Determinants throughout the Life Cycle of Obesity, Precursors of Chronic Diseases, Human Capital and Mental Health: A Contribution of the São Luís Birth Cohorts to the Unified Health System (SUS), which was approved on 29 October 2015 by the Research Ethics Committee of the University Hospital of the Federal University of Maranhão (Process n° 1.302.489).

All the participants signed an Informed Consent Form. This study was conducted in accordance with the Declaration of Helsinki and Resolution n° 466/2012 requirements of the Conselho Nacional de Saúde (National Health Council) and its complementary provisions.

3. Results

The study sample comprised 2064 adolescents aged 18–19, 50.9% of whom were female. Table 4 presents the descriptive measures of the study variables.

Table 4. Anthropometric and clinical characteristics of adolescents aged 18–19 from São Luís-Maranhão, Brazil (n = 2064).

Variables	Mean ± SD (♂) | (♀)	Median (p25–p75) (♂) | (♀)	p90 (♂) | (♀)
Weight (kg)	61.3 ± 13.1 66.1 ± 12.9 | 56.7 ± 11.5	59.5 (160.0–174.0) 63.7 (57.4–72.4) | 54.8 (48.4–63.4)	77.4 81.5 | 71.5
Height (cm)	167.0 ± 9.1 17.5 ± 6.9 | 160.7 ± 6.1	166.0 (160.0–174.0) 173.0 (169.0–178.0) | 160.5 (156.5–165.0)	179.0 182.0 | 168.7
BMI (kg/m^2)	21.9 ± 3.9 21.9 ± 3.7 | 21.9 ± 4.1	21.2 (19.1–24.0) 21.1 (19.3–23.8) | 21.2 (18.9–24.1)	27.1 26.7 | 27.3
WC (cm)	81.7 ± 9.0 83.6 ± 9.0 | 79.8 ± 8.7	80.5 (75.4–86.5) 81.8 (77.3–88.2) | 78.5 (73.5–84.9)	93.4 94.8 | 91.7
SBP (mmHg)	114.2 ± 12.2 121.0 ± 11.0 | 107.7 ± 9.3	113.0 (105.0–122.0) 120.0 (113.0–128.0) | 107.0 (101.0–113.0)	131.0 136.0 | 119.0
DBP (mmHg)	70.9 ± 7.4 71.8 ± 7.6 | 70.0 ± 7.1	70.0 (66.0–75.0) 71.0 (66.0–76.0) | 69.0 (65.0–74.0)	80.0 81.6 | 79.0
Glycemia (mmol/L)	92.2 ± 16.0 93.4 ± 17.8 | 91.1 ± 14.0	90.0 (84.0–97.0) 91.0 (85.0–98.0) | 89.0 (83.0–96.0)	108.0 109.0 | 107.0
HDL (mmol/L)	49.4 ± 11.8 45.6 ± 10.3 | 53.0 ± 12.0	48.0 (41.0–56.0) 45.0 (38.0–52.0) | 52.0 (45.0–60.0)	65.0 58.0 | 68.0
Triglycerides (mmol/L)	90.8 ± 48.5 98.3 ± 55.0 | 83.6 ± 40.1	79.0 (61.0–106.0) 86.0 (64.0–114.0) | 73.0 (58.0–96.0)	14.7 154.0 | 130.0

SD: standard deviation; ♂: male; ♀: female; p25: 25th percentile; p75: 75th percentile; p90: 90th percentile; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure.

The prevalence of MetS varies depending on the diagnostic criteria used. According to the IDF and Cook et al. criteria, the prevalence rates were very similar and less than half of those obtained from the definition adopted by De Ferranti et al. (6.0%, 5.7%, and

12.3%, respectively). Regardless of the criteria chosen, lipid profile inadequacy was the most common: low HDL cholesterol levels (44.5%, 35.2%, and 22.2% in De Ferranti et al., IDF, and Cook et al., respectively) and hypertriglyceridemia (29.7% in De Ferranti et al. and 22.9% in Cook et al.), except IDF (8.4%). The IDF showed a higher prevalence of abnormal blood glucose levels (19.0%) than the other criteria (9.0% for both). Altered blood pressure showed slight variation between the criteria (9.4% to 12.6%), whereas abnormal WC was more prevalent according to the IDF (28.1%) and De Ferranti et al. (25.1%) criteria than according to the Cook et al. criteria (10.1%) (Table 5).

Table 5. Prevalence of Metabolic Syndrome and metabolic abnormalities, according to the IDF, Cook et al., and De Ferranti et al. criteria, in adolescents aged 18–19 from São Luís-Maranhão, Brazil (n = 2064).

MetS and Metabolic Abnormalities	Cook et al. (2003) [14]	De Ferranti et al. (2004) [15]	IDF (2005) [16]
MetS	5.7% (n = 118)	12.3% (n = 253)	6.0% (n = 124)
Waist circumference	10.1% (n = 208)	25.1% (n = 518)	28.1% (n = 579) *
SBP/DBP	11.5% (n = 238)	9.4% (n = 194)	12.6% (n = 261)
Glycemia	9.0% (n = 185)	9.0% (n = 185)	19.0% (n = 393)
HDL	22.2% (n = 459)	44.5% (n = 918)	35.2% (n = 726)
Triglycerides	22.9% (n = 473)	29.7% (n = 612)	8.4% (n = 174)

* Mandatory diagnostic component in IDF criteria. IDF: International Diabetes Federation; MetS: Metabolic Syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 6 presents the ANN performance for the test and total samples, as evaluated using the three criteria employed in this study. Overall, all ANNs demonstrated satisfactory performance in predicting MetS in the adolescent sample, with the ACUR, SENS, and ESPEC values exceeding 70%.

Table 6. Artificial neural network performance for the testing set and for the total sample (n = 2064), according to the IDF, Cook et al., and De Ferranti et al. criteria, in adolescents aged 18–19 from São Luís-Maranhão, Brazil.

ANN	Metabolic Syndrome Criteria								
	Cook et al. (2003) [14]			De Ferranti et al. (2004) [15]			IDF (2007) [16]		
	ACUR	SENS	SPEC	ACUR	SENS	SPEC	ACUR	SENS	SPEC
Test set		n = 84			n = 166			n = 73	
ANN 1	87.3%	97.3%	76.5%	88.2%	91.0%	85.1%	85.1%	88.9%	81.9%
ANN 2	87.3%	91.9%	82.4%	82.2%	80.8%	83.8%	85.1%	88.9%	81.6%
ANN 3	88.7%	89.2%	88.2%	83.6%	80.8%	86.5%	87.8%	91.7%	84.2%
ANN 4	84.5%	89.2%	79.4%	80.3%	79.5%	81.1%	87.8%	91.7%	84.2%
ANN 5	90.1%	91.9%	88.2%	82.2%	75.6%	89.2%	80.1%	87.9%	79.6%
Total sample									
ANN 1	87.5%	96.6%	86.9%	87.2%	88.9%	86.9%	76.1%	93.5%	75.0%
ANN 2	84.3%	89.0%	84.0%	81.4%	77.9%	81.9%	72.8%	90.3%	71.7%
ANN 3	87.0%	89.0%	86.9%	83.8%	80.2%	84.3%	81.4%	90.3%	80.9%
ANN 4	82.4%	90.7%	81.9%	80.9%	78.7%	81.2%	77.3%	88.7%	80.9%
ANN 5	86.8%	89.8%	86.6%	85.3%	76.3%	86.5%	80.1%	87.9%	79.63%

ANN: artificial neural network; IDF: International Diabetes Federation; ACUR: accuracy; SENS: sensitivity; SPEC: specificity.

When the criteria of Cook et al. were adopted, the ANNs performed better. Among them, ANN 3 and 5 demonstrated the best performance. They used age, sex, WC, SBP, and DBP as input variables, and ANN 5 also used weight. According to the criteria of the IDF and De Ferranti, ANN 3 and ANN 4 performed better than the others.

Considering the total sample size (n = 2064), ANN performance slightly declined when the criteria of Cook et al. were used. However, ANN 3 and ANN 5 still demonstrated superior performance compared to the others. According to the criteria IDF, ANN 3 and ANN 5 also performed better than the others. When the criteria of De Ferranti et al. were used, ANN 3 exhibited superior performance, outperforming ANN 4, which performed better on the testing set.

Figure 1 shows the ROC curves generated to assess the discriminatory power of the ANNs. The criteria of Cook et al. exhibited the highest AUC value, exceeding 90%. Additionally, ANN 5 demonstrated robust discriminatory power across all diagnostic criteria: Cook et al. (AUC = 96.7%), De Ferranti et al. (AUC = 89.0%), and IDF (AUC = 87.5%).

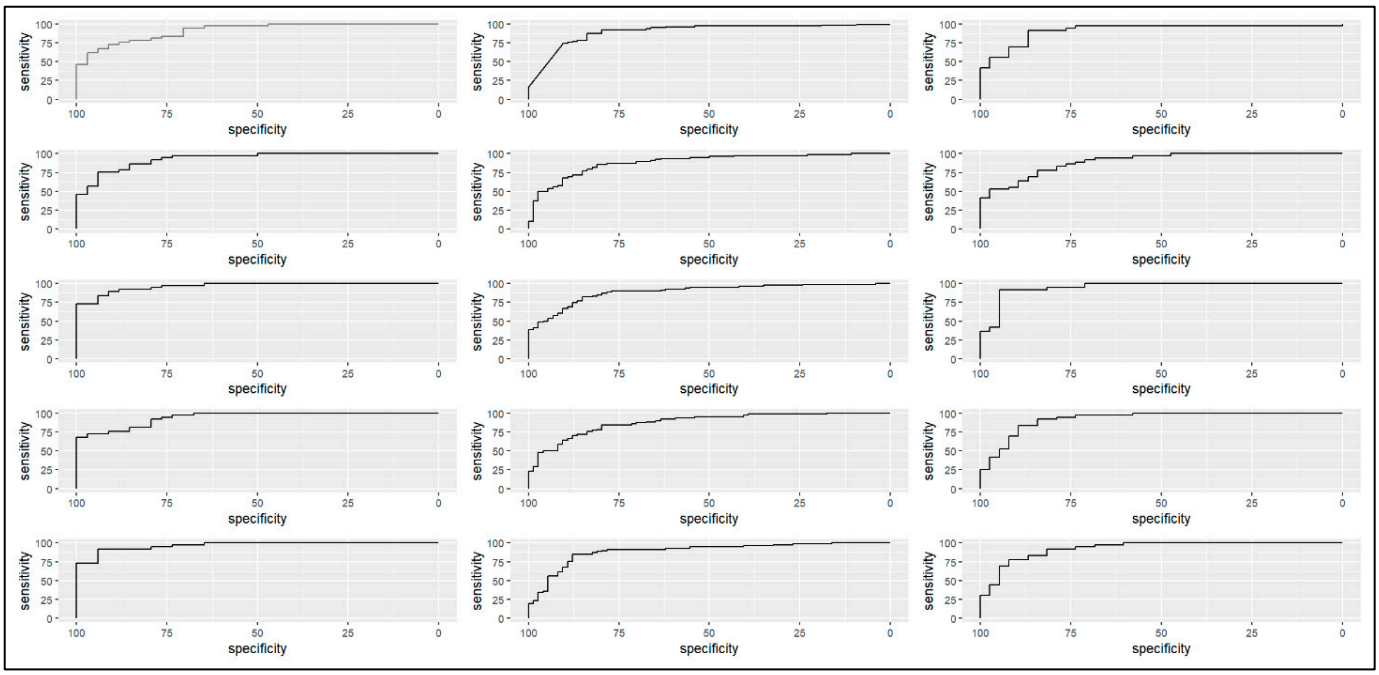

Figure 1. The discriminatory power of Artificial Neural Networks in predicting Metabolic Syndrome, according to the IDF, Cook et al., and De Ferranti et al. criteria, in adolescents aged 18–19. From left to right: Cook et al. (2003) [14]; De Ferranti et al. (2004) [15]; and IDF (2007) [16]. From top to bottom: ANN1; ANN2; ANN3; ANN4; and ANN5, São Luís-Maranhão, Brazil.

4. Discussion

This study proposed some ANNs to predict the chance of developing MetS in adolescents. Different criteria have been considered for the diagnosis of MetS. The ANN implemented using the criteria of Cook et al. demonstrated superior ACUR and SENS. Furthermore, the ANN that included only age, sex, WC, weight, SBP, and DBP (ANN 5) demonstrated superior performance and discriminatory power in predicting MetS, regardless of the criteria employed. This was followed by a network that included age, sex, WC, SBP, and DBP (ANN 3). These ANNs include the same non-invasive components used to define MetS (WC, SBP, and DBP). Moreover, the ANN used numerical values, thereby obviating the necessity of defining a cut-off point for identifying the risk of developing MetS.

WC is a practical and cost-effective anthropometric method like BMI. Nevertheless, WC exhibits an important limitation, as the diagnostic cut-off points vary according to sex and ethnic group [19]. Considering this, the criteria employed in this study considered different cut-off points for WC according to sex and age. A comparison of the SENS between ANN 3 and 5 according to the adopted criteria revealed that for ANN 3, the IDF criteria for diagnosing MetS exhibited a higher SENS for the sample under study, and for ANN 5, it was the criteria of Cook et al. This suggests that the WC cut-off point can influence identifying adolescents with MetS.

Although WC is the most used anthropometric indicator for assessing abdominal fat associated with metabolic abnormalities [7,20], it may not be a significant and predominant metabolic abnormality for defining MetS in younger people. Therefore, including other anthropometric measurements is relevant for diagnosing MetS in this age group. ANN 5's good performance shows that incorporating weight measurement in addition to WC enables a more precise identification of MetS in adolescents when the criteria of the IDF are used.

The criteria adopted in this study use the same metabolic abnormalities to define MetS. However, their cut-off points and the necessity of WC differ in such a way as to determine significant variations [1,21]. Weihe and Weihrauch-Blüher [6] argued that it is imperative to have a unified criterion for defining MetS in children and adolescents that considers pubertal stage, ethnicity, age, and sex.

In this study, the proposed ANN for predicting MetS in adolescents aged 18–19 demonstrated satisfactory performance. To date, no studies have been identified in the literature that propose developing and validating a predictive model that considers only non-invasive measurements (WC, SBP, and DBP) in this population.

Some studies have successfully applied artificial intelligence at the primary healthcare level to track future conditions and enable early prevention to improve outcomes and optimize resources [12,22,23]. These studies demonstrated that artificial intelligence can be used to identify and predict future cardiovascular risks, allowing for implementation of early prevention strategies. This approach can potentially enhance the effectiveness of primary healthcare services and improve the population's overall health.

In primary healthcare, an important challenge is limited access to the biochemical tests necessary for diagnosing MetS. In Brazil, access to these tests is limited, expensive, and time-consuming [24]. This can hinder the ability of primary healthcare providers to diagnose and manage MetS effectively.

Furthermore, in clinical practice, a significant number of patients either do not return for follow-up appointments or do not provide laboratory test results in a timely manner, which can delay the diagnosis of MetS. Developing an ANN to predict the chance of a patient exhibiting MetS at the initial appointment would optimize the intervention flow and contribute to managing public resources (financial, human, and material), prioritizing and guiding patients who require biochemical tests to confirm the diagnosis of MetS.

Thus, ANN 5 allows predicting the chance of an adolescent exhibiting MetS using simple and non-invasive measurements obtained during screening at a primary healthcare center with accessible and inexpensive instruments. After that, it is possible to direct efforts towards early intervention to reduce cardiometabolic risks and disease burden. The healthcare system can better manage their care by identifying adolescents who are more likely to develop MetS. This will facilitate effective interventions, including undergoing the necessary tests, attending scheduled appointments, motivation to embrace the proposed changes, and follow-up medical care. This approach is likely to result in higher intervention success rates.

The construction of an ANN for predicting MetS only considered adolescents aged 18–19. This may be a limitation because other age groups were not included in this life stage. However, the diagnostic criteria employed for MetS are limited to those applicable to this specified age range. Therefore, caution should be exercised when extrapolating the findings of this study to adolescents of various ages.

In contrast, this study used three diagnostic criteria for MetS to verify which criteria exhibited the most efficacious performance in predicting MetS. Most studies have utilized only a single criterion [4,10,20,21,25,26]. It was also determined that only input variables representing non-invasive measures that were fast and easy to obtain should be employed to serve as screening tools for MetS at the primary healthcare level. There is one study that included only complex biochemical and cardiac parameters [25].

5. Conclusions

The findings of this study demonstrate that ANN 3, based on age, sex, SBP, DBP, and WC, and ANN 5, with the inclusion of weight, presented better ACUR and SENS, showing great potential for screening MetS in adolescents. Therefore, non-invasive measures enable predicting the chance of an adolescent developing MetS, thereby guiding the flow of care in primary healthcare and optimizing the management of public resources.

Author Contributions: Conceptualization, A.C.J., A.K.F., V.S. and A.d.S.; methodology, A.C.J., A.K.F., V.S. and A.d.S.; formal analysis, A.C.J., A.d.S. and V.S.; investigation, A.C.J., E.d.S. and V.S.; data curation, A.C.J., E.d.S. and V.S.; writing—original draft preparation, A.C.J. and A.K.F.; writing—review and editing, A.K.F., E.d.S. and A.d.S.; supervision, A.K.F. and A.d.S.; project administration, A.K.F. and A.d.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by CAPES (Coordination for the Improvement of Higher Education Personnel) [finance code No: 001], the Brazilian National Research Council (CNPq; process 471923/2011-7 and 561058/2015-5), the Foundation for Scientific Research and Development of Maranhão (FAPEMA; process 0035/2008), and the São Paulo Research Foundation (FAPESP; process 2008-53593-0).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the or Ethics Committee of University Hospital of the Federal University of Maranhão (Protocol n° 1.302.489, approved on 29 October 2015).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Restrictions apply to the availability of these data. Data were obtained from RPS Cohort Consortium and are available from RPS Cohort Consortium with the permission of RPS Cohort Consortium.

Conflicts of Interest: The authors declare no conflicts of interest.

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• Research Involving Human Subjects

Institutional Review Board Statement

When reporting on research that involves human subjects, human material, human tissues, or human data, authors must declare that the investigations were carried out following the rules of the **Declaration of Helsinki of 1975**, which was revised in 2013. According to point 23 of this declaration, approval from the local Institutional Review Board (IRB) or another appropriate ethics committee must be obtained before undertaking the research to confirm that the study meets national and international guidelines. As a minimum, a statement including the project identification code, date of approval, and name of the ethics committee or institutional review board must be stated in the 'Institutional Review Board Statement' Section of the article.

Example of an Institutional review board statement: “The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of XXX (Project identification code) on [date of approval].”

For non-interventional studies (e.g. surveys, questionnaires, social media research), all participants must be fully informed whether their anonymity is assured, why the research is being conducted, how their data will be used, and if there are any risks involved in participating. As with all research involving humans, ethical approval from an appropriate ethics committee must be obtained prior to conducting the study. If ethical approval is not required, authors must either provide an exemption from the ethics committee or cite the local or national legislation that indicates ethics approval is not required for this type of study. When a study has been granted exemption, the name of the ethics committee that provided this should be stated in the ‘Institutional Review Board Statement’ Section with a full explanation for the rejection of ethical approval.

Informed Consent Statement

Manuscripts reporting studies involving human participants, human data, or human tissue must include a **statement of informed consent for participation** in research. Verbal informed consent to participate in a study can be acceptable under some circumstances (such as in ethnographic studies). The authors must explain the rationale for using this kind of consent in the “Informed Consent Statement” Section. For verbal informed consent, a copy of the script used must be provided during the submission stage.

For all manuscripts that include identifying patient/participant information (personal details, images, or videos relating to an individual person), written **informed consent for the publication** of these details must be obtained from patients/participants (or their relatives/guardians) before submitting to an MDPI journal. A blank version of the form used to obtain permission (without the patient/participant names or signature) should be provided upon submission. You may refer to our **template permission form** and provide an appropriate form after consulting with your affiliated institution.

For the purposes of publishing in MDPI journals, a consent, permission, or release form should include unlimited permission for publication in all formats (including print, electronic, and online), in sublicensed and reprinted versions (including translations and derived works), and in other works and products under open access license. To respect patients’/participants’ and any other individuals’ privacy, please do not send signed forms.

Private information identifying participants need not be included unless the identifiable materials are of relevance to the research (e.g., photographs of participants’ faces that show a particular symptom). Patients’/participants’ initials or other personal identifiers must not appear in any images. Patient/participant details must be anonymized as much as possible, e.g., do not mention specific age, ethnicity, or occupation where they are not relevant to the conclusions. Steps necessary to protect privacy may include de-identifying data, adding noise, or blocking portions of the database. Editors reserve the right to reject any submission that does not meet these requirements.

The Editorial Office reserves the right to request further documentation when necessary. The submitted manuscript will be scrutinized by the Editorial Office, and upon request, documentary evidence (signed consent forms and any related discussion documents from the ethics board) must be provided.

Example of an Informed Consent Statement: “Informed consent for participation was obtained from all subjects involved in the study.” OR “Informed consent for participation is not required as per local legislation [provide local legislation].” OR “Verbal informed consent was obtained from the participants. Verbal consent was obtained rather than written because [state the reason]”, OR “Informed consent for publication was obtained from all identifiable human participants.”

Requirements for Studies on Vulnerable Groups and Organ Transplants

If a study involves vulnerable groups, the manuscript will undergo an additional review by the editorial office. If requested, the author must provide documentary evidence, including blank consent forms and any related discussion documents from the ethics board or other relevant bodies. Additionally, when studies describe groups by race, ethnicity, gender, disability, disease, etc., an explanation regarding why such categorization was needed must be clearly stated in the article.

Articles describing human organ transplantation studies are subject to all policies for research involving human subjects. Additionally, the authors must specify the institution(s), clinic(s), or department(s) from which the organs or tissues were sourced. MDPI does not accept manuscripts that report data on organs and/or other materials obtained from illegal commercial activity, executed prisoners, or other unethical practices relating to organ donations. Manuscripts addressing this practice, such as editorials or reports on its secondary consequences, may be considered at the discretion of the Editor-in-Chief but require a written appeal to the editorial office before submission. For further resources on organ transplantation, MDPI follows the glossary

maintained by the Organ Procurement and Transplantation Network (**https://optn.transplant.hrsa.gov/patients/glossary/**).

- **Ethical Guidelines for the Use of Animals in Research**

The editors will require that the benefits potentially derived from any research causing harm to animals are significant in relation to any cost endured by animals, and that procedures followed are unlikely to cause offense to the majority of readers. Authors should particularly ensure that their research complies with the commonly-accepted '3Rs [1]':

- Replacement of animals by alternatives wherever possible,
- Reduction in number of animals used, and
- Refinement of experimental conditions and procedures to minimize the harm to animals.

Authors must include details on housing, husbandry and pain management in their manuscript.

MDPI endorses the ARRIVE guidelines (**arriveguidelines.org/**) for reporting experiments using live animals. Authors and reviewers must use the ARRIVE guidelines as a checklist, which can be found at **https://arriveguidelines.org/sites/arrive/files/documents/Author%20Checklist%20-%20Full.pdf**. The journal *JCM* requires authors to submit the completed checklist at submission, and it will be made available to reviewers. Editors reserve the right to reject submissions that do not adhere to these guidelines based on ethical or animal welfare concerns, or if the procedure described does not appear to be justified by the value of the work presented.

For further guidance authors should refer to the Code of Practice for the Housing and Care of Animals Used in Scientific Procedures [2], American Association for Laboratory Animal Science [3] or European Animal Research Association [4].

If national legislation requires it, studies involving vertebrates or higher invertebrates must only be carried out after obtaining approval from the appropriate ethics committee. As a minimum, the project identification code, date of approval and name of the ethics committee or institutional review board should be stated in Section 'Institutional Review Board Statement'. Research procedures must be carried out in accordance with national and institutional regulations. Statements on animal welfare should confirm that the study complied with all relevant legislation. Clinical studies involving animals and interventions outside of routine care require ethics committee oversight as per the American Veterinary Medical Association. If the study involved client-owned animals, informed client consent must be obtained and certified in the manuscript report of the research. Owners must be fully informed if there are any risks associated with the procedures and that the research will be published. If available, a high standard of veterinary care must be provided. Authors are responsible for correctness of the statements provided in the manuscript.

If ethical approval is not required by national laws, authors must provide an exemption from the ethics committee, if one is available. Where a study has been granted exemption, the name of the ethics committee that provided this should be stated in Section 'Institutional Review Board Statement' with a full explanation on why the ethical approval was not required.

If no animal ethics committee is available to review applications, authors should be aware that the ethics of their research will be evaluated by reviewers and editors. Authors should provide a statement justifying the work from an ethical perspective, using the same utilitarian framework that is used by ethics committees. Authors may be asked to provide this even if they have received ethical approval.

1. NSW Department of Primary Industries and Animal Research Review Panel. Three Rs. Available online: **https://www.dpi.nsw.gov.au/dpi/animals/animal-ethics-infolink/three-rs**
2. Home Office. Animals (Scientific Procedures) Act 1986. Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes. Available online: **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/388535/CoPanimalsWeb.pdf**
3. American Association for Laboratory Animal Science. The Scientific Basis for Regulation of Animal Care and Use. Available online: **https://www.aalas.org/about-aalas/position-papers/scientific-basis-for-regulation-of-animal-care-and-use**

4. European Animal Research Association. EU regulations on animal research. Available online: **https://www.eara.eu/animal-research-law**

• Research Involving Cell Lines

Methods sections for submissions reporting on research with cell lines should state the origin of any cell lines. For established cell lines the provenance should be stated and references must also be given to either a published paper or to a commercial source. If previously unpublished *de novo* cell lines were used, including those gifted from another laboratory, details of institutional review board or ethics committee approval must be given, and confirmation of written informed consent must be provided if the line is of human origin.

An example of Ethical Statements:

The HCT116 cell line was obtained from XXXX. The $MLH1^{+}$ cell line was provided by XXXXX, Ltd. The DLD-1 cell line was obtained from Dr. XXXX. The DR-GFP and SA-GFP reporter plasmids were obtained from Dr. XXX and the Rad51K133A expression vector was obtained from Dr. XXXX.

• Research Involving Plants

Experimental research on plants (either cultivated or wild) including collection of plant material, must comply with institutional, national, or international guidelines. We recommend that authors comply with the **Convention on Biological Diversity** and the **Convention on the Trade in Endangered Species of Wild Fauna and Flora**.

For each submitted manuscript supporting genetic information and origin must be provided. For research manuscripts involving rare and non-model plants (other than, e.g., *Arabidopsis thaliana, Nicotiana benthamiana, Oryza sativa*, or many other typical model plants), voucher specimens must be deposited in an accessible herbarium or museum. Vouchers may be requested for review by future investigators to verify the identity of the material used in the study (especially if taxonomic rearrangements occur in the future). They should include details of the populations sampled on the site of collection (GPS coordinates), date of collection, and document the part(s) used in the study where appropriate. For rare, threatened or endangered species this can be waived but it is necessary for the author to describe this in the cover letter.

Editors reserve the rights to reject any submission that does not meet these requirements.

An example of Ethical Statements:

Torenia fournieri plants were used in this study. White-flowered Crown White (CrW) and violet-flowered Crown Violet (CrV) cultivars selected from 'Crown Mix' (XXX Company, City, Country) were kindly provided by Dr. XXX (XXX Institute, City, Country).

Arabidopis mutant lines (SALKxxxx, SAILxxxx,…) were kindly provided by Dr. XXX, institute, city, country).

• Clinical Trials Registration

Registration

MDPI follows the International Committee of Medical Journal Editors (ICMJE) **guidelines** which require and recommend registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication.

Purely observational studies do not require registration. A clinical trial not only refers to studies that take place in a hospital or involve pharmaceuticals, but also refer to all studies which involve participant randomization and group classification in the context of the intervention under assessment.

Authors are strongly encouraged to pre-register clinical trials with an international clinical trials register and cite a reference to the registration in the Methods section. Suitable databases include **clinicaltrials.gov**, **the EU Clinical Trials Register** and those listed by the World Health Organisation **International Clinical Trials Registry Platform**.

Approval to conduct a study from an independent local, regional, or national review body is not equivalent to prospective clinical trial registration. MDPI reserves the right to decline any paper without trial registration for further peer review. However, if the study protocol has been published before the enrolment, the registration can be waived with correct citation of the published protocol.

CONSORT Statement

MDPI requires a completed CONSORT 2010 **checklist** and **flow diagram** as a condition of submission when reporting the results of a randomized trial. Templates for these can be found here or on the CONSORT website (**http://www.consort-statement.org**) which also describes several CONSORT checklist extensions for different designs and types of data beyond two group parallel trials. At minimum, your article should report the content addressed by each item of the checklist.

- ## Dual Use Research of Concern

MDPI follows the practical framework defined in **Guidance for Editors: Research, Audit and Service Evaluations** and introduced by the Committee on Publication Ethics (COPE). Research that could pose a significant threat, with broad potential consequences to public health or national security, should be clearly indicated in the manuscript, and potential dual-use research of concern should be explained in the cover letter upon submission. Potential areas of concern include but are not limited to biosecurity, nuclear and chemical threats, and research with a military purpose or application, etc. For these manuscripts to be considered for peer review, the benefits to the general public or public health must outweigh the risks. The authors have a responsibility to comply with relevant national and international laws.

- ## Sex and Gender in Research

We encourage our authors to follow the **'Sex and Gender Equity in Research – SAGER – guidelines'** and to include sex and gender considerations where relevant. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Article titles and/or abstracts should indicate clearly what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the Discussion. We suggest that our authors consult the full **guidelines** before submission.

- ## Borders and Territories

Potential disputes over borders and territories may have particular relevance for authors in describing their research or in an author or editor correspondence address, and should be respected. Content decisions are an editorial matter and where there is a potential or perceived dispute or complaint, the editorial team will attempt to find a resolution that satisfies parties involved.

MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

- ## Publication Ethics Statement

JCM is a member of the Committee on Publication Ethics (**COPE**). We fully adhere to its **Code of Conduct** and to its **Best Practice Guidelines**.

The editors of this journal enforce a rigorous peer review process together with strict ethical policies and standards to ensure to add high quality scientific works to the field of scholarly publication. Unfortunately, cases of plagiarism, data falsification, image manipulation, inappropriate authorship credit, and the like, do arise. The editors of *JCM* take such publishing ethics issues very seriously and are trained to proceed in such cases with a zero tolerance policy.

Authors wishing to publish their papers in *JCM* must abide to the following:

- Any facts that might be perceived as a possible conflict of interest of the author(s) must be disclosed in the paper prior to submission.
- Authors should accurately present their research findings and include an objective discussion of the significance of their findings.
- Data and methods used in the research need to be presented in sufficient detail in the paper, so that other researchers can replicate the work.

- Raw data should preferably be publicly deposited by the authors before submission of their manuscript. Authors need to at least have the raw data readily available for presentation to the referees and the editors of the journal, if requested. Authors need to ensure appropriate measures are taken so that raw data is retained in full for a reasonable time after publication.
- Simultaneous submission of manuscripts to more than one journal is not tolerated.
- The journal accepts exact translations of previously published work. All submissions of translations must conform with our **policies on translations**.
- If errors and inaccuracies are found by the authors after publication of their paper, they need to be promptly communicated to the editors of this journal so that appropriate actions can be taken. Please refer to our **policy regarding Updating Published Papers**.
- Your manuscript should not contain any information that has already been published. If you include already published figures or images, please obtain the necessary permission from the copyright holder to publish under the CC-BY license. For further information, see the **Rights and Permissions** page.
- Plagiarism, data fabrication and image manipulation are not tolerated.
    - **Plagiarism is not acceptable** in *JCM* submissions.

      Plagiarism includes copying text, ideas, images, or data from another source, even from your own publications, without giving any credit to the original source.

      Reuse of text that is copied from another source must be between quotes and the original source must be cited. If a study's design or the manuscript's structure or language has been inspired by previous works, these works must be explicitly cited.

      All MDPI submissions are checked for plagiarism using the industry standard software iThenticate. If plagiarism is detected during the peer review process, the manuscript may be rejected. If plagiarism is detected after publication, an investigation will take place and action taken in accordance with our policies.
    - **Image files must not be manipulated or adjusted in any way** that could lead to misinterpretation of the information provided by the original image.

      Irregular manipulation includes: 1) introduction, enhancement, moving, or removing features from the original image; 2) grouping of images that should obviously be presented separately (e.g., from different parts of the same gel, or from different gels); or 3) modifying the contrast, brightness or color balance to obscure, eliminate or enhance some information.

      If irregular image manipulation is identified and confirmed during the peer review process, we may reject the manuscript. If irregular image manipulation is identified and confirmed after publication, we may correct or retract the paper.

  Our in-house editors will investigate any allegations of publication misconduct and may contact the authors' institutions or funders if necessary. If evidence of misconduct is found, appropriate action will be taken to correct or retract the publication. Authors are expected to comply with the best ethical publication practices when publishing with MDPI.

- ## Citation Policy

Authors should ensure that where material is taken from other sources (including their own published writing) the source is clearly cited and that where appropriate permission is obtained.

Authors should not engage in excessive self-citation of their own work.

Authors should not copy references from other publications if they have not read the cited work.

Authors should not preferentially cite their own or their friends', peers', or institution's publications.

Authors should not cite advertisements or advertorial material.

In accordance with COPE guidelines, we expect that "original wording taken directly from publications by other researchers should appear in quotation marks with the appropriate citations." This condition also applies to an

author's own work. COPE have produced a discussion document on **citation manipulation** with recommendations for best practice.

• Reviewer Suggestions

During the submission process, please suggest three potential reviewers with the appropriate expertise to review the manuscript. The editors will not necessarily approach these referees. Please provide detailed contact information (address, homepage, phone, e-mail address). The proposed referees should neither be current collaborators of the co-authors nor have published with any of the co-authors of the manuscript within the last three years. Proposed reviewers should be from different institutions to the authors. You may identify appropriate Editorial Board members of the journal as potential reviewers. You may suggest reviewers from among the authors that you frequently cite in your paper. For detailed information regarding the qualifications and responsibilities of the reviewers, please visit **https://www.mdpi.com/reviewers**.

• Extensive English Editing

It is the authors' responsibility to submit their work in correct English. The APC includes only minor English editing, conducted by native English speakers. The APC does not include extensive English editing. If extensive editing is required, your paper could be returned to you at the English editing stage of the publication process. This could delay the publication of your work. You may have your work reviewed by an experienced English-speaking colleague or use a paid language-editing service before submitting your paper for publication. We offer rapid English editing, completed in 1 day, here: **Author Services**.

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• Preprints and Conference Papers

JCM accepts submissions that have previously been made available as preprints provided that they have not undergone peer review. A preprint is a draft version of a paper made available online before submission to a journal.

MDPI operates ***Preprints***, a preprint server to which submitted papers can be uploaded directly after completing journal submission. Note that *Preprints* operates independently of the journal and posting a preprint does not affect the peer review process. Check the *Preprints* **instructions for authors** for further information.

Expanded and high-quality conference papers can be considered as articles if they fulfill the following requirements: (1) the paper should be expanded to the size of a research article; (2) the conference paper should be cited and noted on the first page of the paper; (3) if the authors do not hold the copyright of the published conference paper, authors should seek the appropriate permission from the copyright holder; (4) authors are asked to disclose that it is conference paper in their cover letter and include a statement on what has been changed compared to the original conference paper.

Unpublished conference papers that do not meet the above conditions are recommended to be submitted to the **Proceedings Series journals**.

• Authorship

MDPI follows the International Committee of Medical Journal Editors (**ICMJE**) guidelines which state that, in order to qualify for authorship of a manuscript, the following criteria should be observed:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or reviewing it critically for important intellectual content; AND
- Final approval of the version to be published; AND

- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who contributed to the work but do not qualify for authorship should be listed in the acknowledgments. More detailed guidance on authorship is given by the **International Committee of Medical Journal Editors (ICMJE)**.

Any change to the author list should be approved by all authors including any who have been removed from the list. The corresponding author should act as a point of contact between the editor and the other authors and should keep co-authors informed and involve them in major decisions about the publication. We reserve the right to request confirmation that all authors meet the authorship conditions.

For more details about authorship please check **MDPI ethics website**.

Editorial Independence

Lack of Interference with Editorial Decisions

Editorial independence is of utmost importance and MDPI does not interfere with editorial decisions. All articles published by MDPI are peer reviewed and assessed by our independent editorial boards, and MDPI staff are not involved in decisions to accept manuscripts. When making an editorial decision, we expect the academic editor to make their decision based only upon:

- The suitability of selected reviewers;
- Adequacy of reviewer comments and author response;
- Overall scientific quality of the paper.

In all of our journals, in every aspect of operation, MDPI policies are informed by the mission to make science and research findings open and accessible as widely and rapidly as possible.

Editors and Editorial Staff as Authors

Editorial staff or editors shall not be involved in processing their own academic work. Submissions authored by editorial staff/editors will be assigned to at least two independent outside reviewers. Decisions will be made by other Editorial Board Members who do not have a conflict of interest with the author. Journal staff are not involved in the processing of their own work submitted to any MDPI journals.

Conflicts of Interest

According to The International Committee of Medical Journal Editors, “Authors should avoid entering into agreements with study sponsors, both for-profit and non-profit, that interfere with authors’ access to all of the study’s data or that interfere with their ability to analyze and interpret the data and to prepare and publish manuscripts independently when and where they choose.”

All authors must disclose all relationships or interests that could inappropriately influence or bias their work. Examples of potential conflicts of interest include but are not limited to financial interests (such as membership, employment, consultancies, stocks/shares ownership, honoraria, grants or other funding, paid expert testimonies and patent-licensing arrangements) and non-financial interests (such as personal or professional relationships, affiliations, personal beliefs).

Authors can disclose potential conflicts of interest via the online submission system during the submission process. Declarations regarding conflicts of interest can also be collected via the **MDPI disclosure form**. The corresponding author must include a summary statement in the manuscript in a separate section “Conflicts of Interest” placed just before the reference list. The statement should reflect all the collected potential conflicts of interest disclosures in the form.

See below for examples of disclosures:

Conflicts of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stocks in Company Y. Author C has been involved as a consultant and expert witness in Company Z. Author D is the inventor of patent X.

If no conflicts exist, the authors should state:

Conflicts of Interest: The authors declare no conflicts of interest.

• Editorial Procedures and Peer Review

Pre-check

Immediately after submission, the journal's Managing Editor will perform the technical pre-check to assess:

- Overall suitability of the manuscript to the journal/section/Special Issue;
- Manuscript adherence to high-quality research and ethical standards;
- Standards of rigor to qualify for further review.

The academic editor (i.e., the Editor-in-Chief in the case of regular submissions, the Guest Editor in the case of Special Issue submissions, or an Editorial Board member in the case of a conflict of interest and of regular submissions if the Editor-in-Chief allows) will be notified of the submission and invited to perform an editorial pre-check. During the editorial pre-check phase, the academic editor will assess the suitability of the submission with respect to the scope of the journal, as well as the overall scientific soundness of the manuscript, including the relevance of the references and the correctness of the applied methodology. Academic editors can decide to reject the manuscript, request revisions before peer review, or continue with the peer review process and recommend suitable reviewers.

Peer Review

Once a manuscript passes the initial checks, it will be assigned to at least two independent experts for peer review. A single-blind review is applied, where authors' identities are known to reviewers. Peer review comments are confidential and will only be disclosed with the express agreement of the reviewer.

In the case of regular submissions, in-house assistant editors will invite experts, including recommendations by an academic editor. These experts may also include *Editorial Board Members* and Guest Editors of the journal. Potential reviewers suggested by the authors may also be considered. Reviewers should not have published with any of the co-authors during the past three years and should not currently work or collaborate with any of the institutions of the co-authors of the submitted manuscript. For more details about potential conflicts of interest, please check here, **https://www.mdpi.com/reviewers#_bookmark9**.

Optional Open Peer Review

The journal operates optional open peer review: *Authors are given the option for all review reports and editorial decisions to be published alongside their manuscript. In addition, reviewers can sign their review, i.e., identify themselves in the published review reports.* Authors can alter their choice for open peer review at any time before publication, but once the paper has been published changes will only be made at the discretion of the *Publisher* and *Editor-in-Chief*. We encourage authors to take advantage of this opportunity as proof of the rigorous process employed in publishing their research. To guarantee impartial refereeing, the names of referees will be revealed only if the referees agree to do so, and after a paper has been accepted for publication.

Editorial Decision and Revision

All the articles, reviews and communications published in MDPI journals go through the peer review process and receive at least two reviews. The in-house editor will communicate the decision of the academic editor, which will be one of the following:

- *Accept after Minor Revisions*:
  The paper is in principle accepted after revision based on the reviewer's comments. Authors are given five days for minor revisions.
- *Reconsider after Major Revisions*:
  The acceptance of the manuscript would depend on the revisions. The author needs to provide a point by point response or provide a rebuttal if some of the reviewer's comments cannot be revised. A

maximum of two rounds of major revision per manuscript is normally provided. Authors will be asked to resubmit the revised paper within a suitable time frame, and the revised version will be returned to the reviewer for further comments. If the required revision time is estimated to be longer than 2 months, we will recommend that authors withdraw their manuscript before resubmitting so as to avoid unnecessary time pressure and to ensure that all manuscripts are sufficiently revised.

- *Reject and Encourage Resubmission*:
  If additional experiments are needed to support the conclusions, the manuscript will be rejected and the authors will be encouraged to re-submit the paper once further experiments have been conducted.

- *Reject*:
  The article has serious flaws, and/or makes no original significant contribution. No offer of resubmission to the journal is provided.

All reviewer comments should be responded to in a point-by-point fashion. Where the authors disagree with a reviewer, they must provide a clear response.

Author Appeals

Authors may appeal a rejection by sending an e-mail to the Editorial Office of the journal. The appeal must provide a detailed justification, including point-by-point responses to the reviewers' and/or Editor's comments using an **appeal form**. Appeals can only be submitted following a “reject and decline resubmission” decision and should be submitted within three months from the decision date. Failure to meet these criteria will result in the appeal not being considered further. The *Managing Editor* will forward the manuscript and related information (including the identities of the referees) to a designated *Editorial Board Member*. The Academic Editor being consulted will be asked to provide an advisory recommendation on the manuscript and may recommend acceptance, further peer review, or uphold the original rejection decision. This decision will then be validated by the *Editor-in-Chief*. A reject decision at this stage is final and cannot be reversed.

Production and Publication

Once accepted, the manuscript will undergo professional copy-editing, English editing, proofreading by the authors, final corrections, pagination, and, publication on the **www.mdpi.com** website.

ANEXO C – NORMAS DE PUBLICAÇÃO DA REVISTA OBESITY

AUTHOR GUIDELINES

Everything you need to know about publishing your research in *Obesity*

For a summary of requirements, please see Submission Checklist

CONTENTS

AIMS AND SCOPE

The Obesity Society's official research journal, *Obesity*, was launched in 1993 as *Obesity Research*. Three decades later, *Obesity* has become the premier source of information for increasing knowledge, fostering translational research from basic to population science, and promoting better treatment for people with obesity. *Obesity* is published 12 times per year and is a forum where knowledge on the cutting edge of discovery can be disseminated to medical and health professionals and researchers whose expertise spans a wide swath of disciplines.

Manuscripts should have a central theme of improving the understanding of obesity, including nutrition, exercise/physical activity, diabetes, obesity pharmacotherapy, bariatric surgery, public health, pediatrics, basic science, eating disorders, psychology, and genetics. Confirmatory findings and incremental

advances will take second place to new observations, scientific excellence being equal. Epidemiological studies will be expected to provide insights into causes or potential treatments of obesity and related diseases. Studies identifying new pathways or first-in-human observations are encouraged. Most published papers are quantitative; however, very high-quality qualitative studies will be considered if they provide novel information that improves obesity treatment.

Article Categories

Articles will be published under one of four categories. Your study may overlap categories, but select the type that best describes your manuscript.

- Obesity Biology and Integrated Physiology
- Clinical Trials and Investigations
- Pediatric Obesity
- Epidemiology/Genetics

Article Types

Manuscripts published by *Obesity* include:

- Original Articles
- Brief Cutting Edge Reports
- Reviews and Invited Reviews
- Meeting Reports
- Perspectives
- Commentaries
- Letters to the Editor
- Editorials

Articles (in English) should be submitted via our electronic system at: http://mc.manuscriptcentral.com/obesity. Please review "How to Prepare Your Manuscript for Submission" (below) before uploading your documents.

For step-by-step guidance on how to submit your manuscript, please see the ScholarOne Manuscripts Author Guide.

EDITORIAL POLICIES

Manuscript submissions are considered on the following conditions:

- Your manuscript must be original and not be published or submitted for publication elsewhere in any language. Submission as an abstract or on a community preprint server is not considered to constitute previous publication.
- All coauthors have fulfilled each of the following criteria—(1) have made a substantial contribution to research design or the acquisition, analysis, or interpretation of data; (2) have drafted the paper or revised it critically; and (3) have approved the submitted and final versions.
- All coauthors have declared all competing interests.
- All work complies with the Ethical Policies of *Obesity* and has been conducted under internationally accepted ethical standards after relevant ethical review. It is imperative that authors read this policy and complete any necessary documentation prior to submission.

The journal operates a stringent peer-review process. All manuscripts will be reviewed by the Editors, members of the Editorial Team, or other expert reviewers. At the discretion of the Editors, the manuscript may be returned immediately without full review if deemed not competitive (not within the top 50% for originality and quality) or outside the realm of interests of the majority of the readership of the journal. Acceptance of papers is based on the originality of the observation or investigation; the

quality of the work described; the clarity of presentation; and the relevance to our readership. All manuscripts are judged in relation to other submissions currently under consideration. The decision (reject, invite revision, accept) letter will be conveyed through the *Obesity* Manuscript Central (ScholarOne Manuscripts) system, coming directly from the Editors responsible for the manuscript's review. On average, manuscripts submitted in 2023 that were sent for external peer review took an average of 34.8 days to reach a decision.

This journal employs a plagiarism detection system. By submitting your manuscript, you accept that your manuscript may be screened for plagiarism against previously published works.

Most obesity-related topics are suitable for submission if they fall within the scope outlined above. Occasionally, authors inquire whether they should submit their manuscript. It is not possible for the Editorial Office to speculate on whether an article is likely to be accepted or not. The only way to know is to submit your manuscript, which can be done at no charge to you. The editors at *Obesity* are committed to providing a fast, but thorough, review of your submission.

Cost of Publication

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All authors are required to sign the ICMJE Form for Disclosure of Potential Conflicts of Interest and provide a copy to the corresponding author before submission. The corresponding author must then compile a full Conflict of Interest Statement that accurately reflects what each author has disclosed and include this statement on the Title Page of the Main Document. It is the corresponding author's responsibility to store the ICMJE forms and to provide them to the Editorial Office if requested at any time. ***Do not send these forms to the Editorial Office and do not upload them to the ScholarOne submission site.***

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The Obesity Society's policy is that journal content must not use potentially pejorative adjectives or adverbs when describing individuals with overweight or obesity, as well as language that directly or indirectly attributes moral judgments or character flaws to this population. **Importantly, authors should not use "obese" as an adjective or noun to describe an individual person or group of people, but instead use terms such as "people with obesity" (not "obese people" or "people who are obese").** This also includes language and images that could be interpreted as stereotyping, biased, or prejudiced.

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Obesity will consider for review articles previously available as preprints on noncommercial servers. Authors may also post the submitted version of a manuscript to noncommercial servers at any time. The details of the preprint server and any accession numbers should be included in your cover letter. Authors are also requested to update any prepublication versions with a link to the final published article.

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STANDARDS OF REPORTING FOR RIGOR AND REPRODUCIBILITY

Clinical Trials

For more information on clinical trial policies, please see the ICMJE recommendations.

Clinical trial registration – All clinical trials, regardless of when they were completed, must be pre-registered. A clinical trial is defined as any research project that prospectively assigns human participants to one or more health-related interventions to evaluate the effects on health outcomes. Health-related interventions include any intervention used to modify a biomedical or health-related outcome, including but not limited to drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and dietary changes. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.

PLEASE NOTE: For clinical trials starting participant enrollment after July 2005, trials must have been registered before onset of patient enrollment. For trials that began before July 2005 but that were not registered before September 13, 2005, trials must have been registered before journal submission.

Acceptable registries must be accessible to the public at no charge, open to all prospective registrants, managed by a not-for-profit organization, and electronically searchable, and they must have a mechanism to ensure the validity of the registration data. The trial registry name, registration identification number, and URL for the registry should be included on the article Title Page. Examples of acceptable trial registries include the following:
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http://isrctn.org
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Flow diagram – Include the participant flowchart either as part of the full paper or as part of the online Supporting Material. For randomized trials, publication of the CONSORT diagram as one of the article figures may be required at the discretion of the Editorial Team (for trials with >50 participants.

Data sharing statement – All manuscripts reporting the results of clinical trials must include a data sharing plan in the *Acknowledgments* section of the manuscript. The following must be specified:

- Will individual deidentified participant data be available (including data dictionaries)? If so, what data in particular will be shared and when (start and end dates)?
- What other documents will be available (e.g., study protocol, statistical analysis plan)?
- With whom will data be shared, for what types of analyses, and by what mechanism?

Please see the ICMJE recommendations (table) for examples of data sharing statements meeting these requirements.

Required Checklists

Depending on the design of the study, one of the health research reporting checklists referenced at the EQUATOR Network (http://www.equator-network.org/reporting-guidelines/) must accompany the first version of each manuscript as a "supplementary file" in the online manuscript submission system. Page or line numbers must be included to indicate where the checklist items are located in your paper. Flow diagrams also should be included whenever possible, especially with manuscripts that require the CONSORT, STROBE, PRISMA, or ARRIVE checklists

If none of the checklists apply to your study, ***please explain in your cover letter why none is needed.***

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Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (e.g., confidence intervals, SDs, or SEs), even for differences that were not significant. Report the numbers of observations. Specify any general-use computer programs used, including the version number and the manufacturer's name and location. Include general descriptions of statistical methods in the *Methods* section and specific descriptions in each table and figure legend. Indicate whether variables were transformed for analysis. Provide details about what hypotheses were tested, what statistical tests were used, and what the outcome and explanatory variables were, Indicate the level of significance used in tests if different from the conventional two-sided 5% alpha error and whether or what type of adjustment is made for multiple comparisons.

Physiological Modeling

Papers involving mathematical modeling must (a) include all model assumptions in list form, (b) define all variables used, with units, and (c) provide the actual model and model code.

Energy Expenditure Data

Comparisons of animal or human metabolic rates and/or energy intakes in groups of differing body size must avoid using ratios of metabolic rate or energy intake per unit of body mass. Instead, authors are encouraged to plot individual data and analyze group and body size effects using ANCOVA (Tschöp et al. *Nat Methods* 2011;9:57-63).

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Original Articles should focus on substantial novel research, findings, and developments from human or animal studies in all areas relevant to the science of obesity (including clinical trials). The following features are essential: hypothesis testing, suitable controls, appropriate statistical methods, clear reporting of results, and conclusions supported by the results.

(2) Brief Cutting Edge Report
Brief Cutting Edge Reports are short reports on "hot" research questions that present important novel results. Please note that preliminary or pilot results should not be submitted in this category.

(3) Review, including Systematic Reviews and Meta-Analyses
If you are submitting an unsolicited review, you may choose to first submit your Review Proposal (cover letter, title page, study importance questions, and abstract only), instead of the full paper, to the ScholarOne submission site. The Editorial Team will determine whether the proposed subject falls within the guidelines and interests of the journal and that a similar Review is not currently in press or under preparation by another author. Please note

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Conclusions based on personal viewpoints and suggestions for practical applications are welcome in Reviews.

(4) Perspective
Perspectives can provide new ideas on an old problem or commentary/opinion on a hot topic.

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Manuscript Type	Word Limit *(excluding cover page, abstract, references, tables, and figures)*	Max Number of References	Max Number of Combined Figures/Tables
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Brief Cutting Edge Report	1500	20	3
Letter to the Editor	500	5	1
Perspective	1000	10	2
Commentary	750	5	1
Editorial	800 to 1600	5	1

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OR
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Text subdivided into titled sections
Discussion and/or Conclusion
Acknowledgments (if needed)
References

Acknowledgments

This section should be used to thank study participants, those who did not meet the authorship criteria (see Ethical Policies) but who provided some type of support, and others who may have some way helped with your study. This section should also include a data sharing statement (see pg. 3). Please see the ICMJE recommendations (table) for examples of data sharing statements meeting these requirements.

References

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Examples of journal references:

- Stunkard AJ, Allison KC, Geliebter A, Lundgren JD, Gluck ME, O'Reardon JP. Development of criteria for a diagnosis: lessons from the night eating syndrome. *Compr Psychiatry.* 2009;50(5):391-399.
- Fukushima H, Cureoglu S, Schachern P, et al. Cochlear changes in patients with type 1 diabetes mellitus. *Otolaryngol Head Neck Surg.* 2005;133(1):100-106.

Examples of book references:

- Lissner L, Bengtsson C, Lapidus L, Larson B, Bengtsson B, Brownell KD. Body weight variability and mortality in the Gothenburg Prospective Studies on men and women. In: Bjorntorp P, Rossner S, eds. *Obesity in Europe 88: Proceedings of the First European Congress on Obesity.* Libbey; 1989: 55-60.
- Paul AA, Southgate DAT, eds. *McCance and Widdowson's The Composition of Foods.* 4th ed. HMSO; 1978.

Example of a Web reference:

- Centers for Disease Control and Prevention. Rubella in Japan. Updated March 11, 2019. Accessed July 25, 2019. https://wwwnc.cdc.gov/travel/notices/alert/rubella-japan

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- **DISCLOSURE: List all potential conflicts of interest on the Title Page, based on ALL author**s' responses to the ICMJE form. If none exist, please include the statement: "The authors declared no conflict of interest." Note that the completed forms should ***not*** be uploaded to ScholarOne. For guidance, please see the Ethical Policies of *Obesity*
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For **Original Articles, Brief Cutting Edge Reports, and Review Proposals/Reviews,** following the Title Page, provide no more than 2 short bullet-point answers to these 3 study importance questions:

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