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Chain Mediation of the Aortic Path in the Relationship between Body Mass Index and Abdominal Aortic Diameter.

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ABSTRACT

Introduction: the aorta, sensitive to excess weight, can undergo changes associated with cardiovascular risk. Studying its segments will allow a better understanding of the relationship between BMI and distal structural alterations.

Objective: to analyze the relationship between BMI and abdominal aortic diameter, considering the thoracoabdominal aortic segments as mediators.

Materials and methods: a cross-sectional study based on secondary data from 801 adults evaluated by thoracoabdominal computed tomography. The independent variable was BMI. The dependent variable was abdominal aortic diameter at the origin of the celiac trunk. The potential mediating effect of aortic diameters was evaluated using a six-segment chain mediation model: aortic sinus of Valsalva, sinotubular junction, mid-ascending aorta, mid-aortic arch, mid-descending aorta, and aorta at the level of the diaphragm. A directed acyclic graph was developed to support the causal structure.

Results: BMI was not directly associated with abdominal aortic diameter but was associated with the aortic sinus of Valsalva (B=14.159; p<0.001) and the sinotubular junction (B=0.4686; p=0.0036). There was no relationship with the middle ascending aorta (B=-0.0715; p=0.757). A positive effect was observed on the middle descending aorta (B=0.4837; p<0.001) and the aorta at the diaphragm (B=0.6110; p<0.001), both of which were directly associated with abdominal aortic diameter (B=0.1570 and B=0.6113, respectively; p<0.001). These findings suggest a structural sequence where distal thoracic diameters progressively influence abdominal aortic caliber. Three significant indirect pathways were identified: BMI → sinus of Valsalva→ mid-descending aorta → diaphragmatic aorta → abdominal aorta (effect = 0.1807; 95% CI [0.0878–0.2778]), BMI → mid-ascending aorta → mid-aortic arch → mid-descending aorta → abdominal aorta (effect = 0.0611), and BMI → mid-descending aorta → abdominal aorta (effect = 0.0759; 95% CI [0.0306–0.1343]).

Conclusions: the findings suggest that BMI may indirectly influence abdominal aortic diameter through interconnected aortic segments. This structural pattern could have clinical implications for the early detection of vascular abnormalities associated with excess weight.

INTRODUCTION

Body mass index (BMI) is an anthropometric measure widely used to estimate nutritional state in population and clinical contexts.[1] Its simplicity has favored its adoption as a standard criterion to classify weight excess, which has allowed to establish associations consistent with multiple outcomes, among them cardiovascular, metabolic diseases and premature death.[2] However, BMI presents significant limitations: it does not differentiate fat mass from lean mass, nor does it allow to assess fat tissue distribution.[3] These limitations become relevant when we seek to understand how body weight influences the structure and function of organs and blood vessels.

The aorta, as the largest artery of the body and the main pathway to transport oxygenated blood from the heart to the rest of the body, is a structure highly sensitive to hemodynamic and metabolic changes induced by body weight excess.[4,5] It is known that aortic dimensions can change in response to factors such as hypertension, low-grade chronic inflammation and mechanical stress.[6] These alterations may lead to progressive dilatations that increase the risk of aneurysms, dissections and other major cardiovascular events.[6] For this reason, the morphological evaluation of the aorta in individuals with a different anthropometric profile has important clinical implications.

In spite of the growing interest to understand the relationship between BMI and aortic structure, a large part of the evidence available has focused on isolated segments, such as the ascending or the abdominal aorta.[7,8] This fragmented approach prevents characterizing comprehensively the possible remodeling patterns along the aortic trajectory. Likewise, although the morphological changes of the aorta can be influenced by multiple

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factors, in this study we propose the hypothesis that BMI, as a clinical marker of the cardiometabolic state, could be associated to the distal aortic morphology through its effect on the proximal segments. Although BMI does not differentiate between fat mass and lean mass, it has been associated consistently with metabolic alterations like resistance to insulin, low grade chronic inflammation, endothelial dysfunction and arterial rigidity, all of them factors that can contribute to vascular remodeling. Particularly, it is proposed to explore whether the alterations in these segments could mediate the relationship between BMI and abdominal aorta diameter, where the clinically relevant dilatations are most frequently located.[9]

In this context, the need to explore the relationship between BMI and the dimensions of the aorta are justified, considering its segments from the sinus of Valsalva. Analyzing the mediating role of the different aortic sections would allow to clarify anatomical and functional mechanisms, by which body weight may influence on distal vascular morphology.

This approach is particularly pertinent within the framework of cardiovascular prevention, given that early detection of structural alterations may contribute to a better risk stratification.

For this reason, the goal of this study was to analyze the relationship between BMI and the diameter of the abdominal aorta, considering as possible mediator variables the dimensions of the different segments of the aorta along its thoracoabdominal trajectory.

MATERIALS AND METHODS

Design and population

A cross-sectional and analytical study was carried out, using a secondary database obtained from the Harvard Dataverse repository. The database included adults with and without comorbidities, evaluated between March 2018 and October 2019, by chest CT without contrast. This technique, although it does not allow to make a thorough functional or tissue characterization, offers a reliable measurement of the aortic diameters, particularly in standardized axial views, being useful for the morphological analysis of the aorta. The sample consisted of 801 adults older than 18 years, all undergoing chest CT. According to the authors of the original study, individuals with significant arterial anomalies or diseases severely affecting the structure of the arteries were not considered in the database, so individuals with history of revascularization or aortic valve replacement, stent placement, genetic syndromes related to aortic diseases (like Marfan or Turner), relevant congenital malformations, inflammatory diseases affecting the aorta, acute aortic syndromes, aneurysms, hypovolemia or severe hemodynamic instability, advanced heart failure with reduced ejection fraction and patients in hemodialysis were all ruled out. All the available data in the database were used for the analysis, not applying sampling or randomization methods.

Variables and measurements

Different variables were analyzed with the aim of understanding the relationship between BMI and the diameter of the abdominal aorta, mediated by different anatomical sections of the aorta. BMI was used as an independent variable, categorized in two groups: 0 (with no overweight or obesity) and 1 (with overweight or obesity), with the measure unit kg/m^2.

BMI was classified in two levels; without overweight or obesity (BMI <25 kg/m2) and with overweight or obesity (BMI ≥25 kg/m2). The cutoff point of BMI ≥25 kg/m2 was used following the classification established by the World Health Organization, which defines overweight as a BMI between 25 and 29.9 kg/m2 and obesity as BMI ≥30 kg/m2. This categorization allows to identify individuals with increased risk of cardiometabolic alterations and cardiovascular diseases. Although this threshold spans a wide range of conditions, it is justified in this context due to its clinical and epidemiological applicability, besides facilitating a comparative analysis with previous studies using the same classification.

The dependent variable was the diameter of the abdominal aorta, measured in millimeters (mm) by chest CT with no contrast. Besides, several anatomical sections of the aorta were considered as mediators in the relationship between BMI and the abdominal aorta diameter. These regions were sequentially modeled according to their anatomical arrangement along the aorta. The sections considered as mediators were aortic sinus of Valsalva, sinotubular junction, mid-ascending aorta, middle aortic arch, mid-descending aorta and the aorta in the diaphragm. All these sections were measured in millimeters (mm) and their role in mediation was evaluated through regression models. Likewise, as the chain mediation model of the PROCESS procedure of Hayes only admits a maximum of six mediators, the proximal aortic arch and the proximal descending thoracic aorta were excluded. This decision was based in its lower level of statistical significance in preliminary analyses. Although the exclusion of these segments could limit a full characterization of the aortic trajectory, the inclusion of those with greater contribution to the model were prioritized, so as to optimize the explicative capacity of the analysis and to fulfill the methodological requirements of the procedure.

According to the authors of the database, the aortic diameters were obtained by an automated system based on artificial intelligence (AI) for the segmentation of organs in computerized tomography (CT) imaging. The CT images were acquired using high resolution scanners (Siemens Somatom Force, Toshiba Aquilion ONE and GE CT750 HD), with matrices of 512x512 pixels and slice thickness between 0.625 and 1.5 mm. Later, the images were automatically processed by the AI-Rad Companion (Chest CT) prototype of Siemens-Healthineers, that uses deep algorithm algorithms to detect the central line of the aorta and to make a partition into nine specific anatomical regions, according to the 2010 AHA clinical guidelines. Mean diameters were estimated in a standardized manner as the root square of the product between the maximum and minimum diameters in each transverse plane. This methodology guarantees a high reproducibility in measurements, minimizes human error and allows to work with error margins within the acceptable standards in images of chest CT.[10] These measurements were treated as continuous variables for the serial or sequential mediation model.

Statistical analysis

To evaluate the indirect effect of BMI, categorized in two levels (0 = no overweight or obesity, 1 = with overweight or obesity), on the diameter of the abdominal aorta through multiple anatomical aortic mediators, a chain mediation analysis was carried out using the model 6 of the PROCESS Macro for SPSS. The mediator variables included the aortic sinus of Valsalva, the sinotubular junction, the mid-ascending aorta, the middle aortic arch, the mid-descending aorta and the aorta in the diaphragm, sequentially modeled according to their anatomical arrangement.

The model 6 of mediation of Hayes is an approach used to examine how an independent variable (in this case BMI) can influence a dependent variable (abdominal aorta diameter) through a sequence of interrelated mediators. This model is known because it allows to evaluate the indirect effects through a chain of mediator variables.[11] In this study, model 6 was applied to analyze the chain relationship between BMI and the abdominal aorta, and considering how the different anatomical regions of the aorta mediate this relation, the model assumes that BMI influences the proximal sections of the aorta, which in turn, progressively affect the distal segments, ending in the abdominal aorta. This assumption is based on the structural and hemodynamic continuity of the aorta as the ground for the vascular alterations induced by weight excess being able to spread along the aortic axis.

The mediation analysis was made by linear regression models for each mediator and the dependent variable. The indirect effects were estimated by bootstrap resampling with 5000 samples and the generation of 95% confidence intervals. The effects were considered statistically significant if the confidence intervals did not include the null value. The significance threshold was set in $p < 0.05$. The IBM SPSS Statistics 25 supplemented with the PROCESS Macro (version 5.0 of Andrew F. Hayes) were used for data processing.

Finally, a directed acyclic graph (DAG) was built using the Dagitty library (www.dagitty.net) to represent the causal relationships between the variables of the study. This diagram was useful to identify the causal paths and verify the relationships between BMI, the anatomical aortic mediators and the abdominal aorta. From the DAG, it was possible to clearly visualize the possible confounding variables and the structure of the mediation model was theoretically supported.

Ethical considerations

The information used in this study comes from the open access repository Harvard Dataverse, and is found under the Creative Commons Zero (CC0) license, which allows using it without restrictions. As this is a set of completely anonymous secondary data, it was not necessary to obtain additional ethical approvals or specific permissions. The confidentiality of the data was ensured according to the ethical principles established in the Declaration of Helsinki.

The set of data is available at:
https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/C0YY9I

For specific details, it is possible to check the following link:
https://doi.org/10.3389/fcvm.2021.737161

RESULTS

In the descriptive analysis of clinical variables, a wide variability was observed in the diameters of the different sections of the aorta, from the aortic sinus of Valsalva up to the abdominal aorta, reflecting the morphological diversity of the analyzed sample. The average measures of the different aortic regions showed a progressive decrease of the diameter from the ascending aorta until the descending and abdominal aorta, matching the normal physiology of the aortic tree. In regard to BMI, a little more than half of the population presented normal ranges, while close to 44% corresponded to people with overweight or obesity *(Table 1)*.

The table summarizes the direct and indirect effects of BMI on the diameter of the abdominal aorta in a model of chain mediation, considering six sequential anatomical mediators, corresponding to the thoracoabdominal aortic segments. It is observed that the direct effect of BMI on the abdominal aorta is not statistically significant ($p = 0.7060$), suggesting the absence of a direct relationship between both variables once mediators are considered. Nonetheless, the total indirect effect is statistically significant (bootstrapped 95% confidence interval: 0.4790-1.0725), indicating a significant mediation through the anatomical structures of the aorta. These findings highlight the relevance of the anatomical mediators of the aortic segments in the association between BMI and the abdominal aorta diameter, supporting the hypothesis of an indirect influence of BMI mediated by structural changes along the aortic axis *(Table 2)*.

Regression models were analyzed, relating BMI with the abdominal aorta diameter, through the different anatomical regions of the aorta as mediator variables. The results indicate that

TABLE 1.
Descriptive statistics and frequency of aortic segments and BMI

Variable (unit)	Minimum	Maximum	Mean	SD
Variable (unit)	21.4	51.1	35.23	42.53
Aortic sinus of Valsalva (mm)	23	51.8	32.98	40.45
Sinotubular juncture (mm)	23.5	53.6	37.12	47.31
Mid-ascending aorta (mm)	22	44.7	33.15	37.08
Proximal aortic arch (mm)	19.3	39.4	30.31	30.83
Middle aortic arch (mm)	19.5	40.6	28.6	32.77
Descending thoracic aorta (mm)	15.9	35.5	25.64	31.94
Mid-descending aorta (mm)	15.3	33.5	25.25	25.95
Aorta in the diaphragm (mm)	13	31.7	23.85	25.63
Abdominal aorta (mm)				
Variable	Category	Frequency	Percentage	
BMI	Normal	449	56.1	
	Elevated	352	43.9	

TABLE 2.
Mediation analysis of BMI on the abdominal aorta: direct and indirect effects

Type of effect	Coefficient	p-value	Bootstrapped confidence interval (CI)
Direct effect (BMI → abdominal aorta)	-0,0381	0,706	—
Total indirect effect (via mediators)	0,7765	—	[0,4790, 1,0725]

overweight or obesity are significantly associated to a greater size in the aortic sinus of Valsalva and in the sinotubular junction, suggesting a first impact of BMI on the initial sections of the aorta. Although the mid-ascending aorta did not show a direct association with BMI, it was indeed influenced by the previous sections, highlighting their role as mediators in transmitting the effect. Instead, in the mid-descending aorta, a significant direct relationship was observed with BMI, besides the accumulated effect of the ascending and arch sections, showing a structural continuity in the expansion of the aortic diameter. In the region of the diaphragm, BMI did not have a direct effect, but it did have an effect on the mid-descending aorta, consolidating as a key link in the chain mediation. Finally, the abdominal aorta diameter was not directly associated to BMI, but was strongly influenced by the dimensions of the mid-descending aorta and the region of the diaphragm, reinforcing the role of these two zones as essential mediators in the relationship between nutritional state and aortic morphology. These findings reveal a structured sequence, where the effects of overweight or obesity are progressively transmitted along the aorta, particularly toward the inferior sections, which may have clinical implications in the identification of anatomical modifications associated to cardiovascular risk *(Table 3)*.

Chain mediation of BMI on the abdominal aorta diameter by different anatomical aortic structures was evaluated, revealing 63 trajectories, of which 4 were selected, that were more significant in the transmission of the effect. The trajectory, that includes the sinus of Valsalva, the mid-descending aorta and the diaphragm region showed the greater indirect impact, reflecting a central

TABLE 3
Regression models for mediator variables and the result (abdominal aorta)

Dependent variable	Predictors	B	SE	t	p	95% CI
Aortic sinus of Valsalva	**BMI**	14.159	0.2988	4.739	<0.001	[0.8294. 2.0024]
Sinotubular junction	**BMI**	0.4686	0.1605	2.921	0.0036	[0.1537. 0.7836]
	Aortic sinus of Valsalva	0.7841	0.0187	41.847	<0.001	[0.7473. 0.8209]
Mid-descending aorta	**BMI**	-0.0715	0.2310	-0.310	0.757	[-0.5249. 0.3819]
	Aortic sinus of Valsalva	0.1703	0.0480	3.551	<0.001	[0.0762. 0.2644]
	Sinotubular junction	0.7132	0.0507	14.071	<0.001	[0.6137. 0.8127]
Middle aortic arch	**BMI**	0.0982	0.1307	0.752	0.452	[-0.1582. 0.3547]
	Aortic sinus of Valsalva	0.0376	0.0273	1.376	0.169	[-0.0160. 0.0913]
	Sinotubular junction	0.0968	0.0320	3.021	0.0026	[0.0339. 0.1596]
	Mid-ascending aorta	0.4392	0.0200	21.925	<0.001	[0.3999. 0.4786]
Mid-descending aorta	**BMI**	0.4837	0.1262	3.832	<0.001	[0.2359. 0.7315]
	Aortic sinus of Valsalva	0.0426	0.0264	1.611	0.108	[-0.0093. 0.0945]
	Sinotubular junction	-0.0344	0.0311	-1.105	0.270	[-0.0954. 0.0267]
	Mid-descending aorta	0.2065	0.0245	8.425	<0.001	[0.1584. 0.2546]
	Middle aortic arch	0.5732	0.0342	16.743	<0.001	[0.5060. 0.6404]
Aorta in the diaphragm	**BMI**	-0.0200	0.1046	-0.191	0.848	[-0.2253. 0.1853]
	Aortic sinus of Valsalva	0.0336	0.0217	1.548	0.122	[-0.0090. 0.0763]
	Sinotubular junction	0.0172	0.0256	0.674	0.501	[-0.0330. 0.0674]
	Mid-ascending aorta	-0.0214	0.0210	-1.022	0.307	[-0.0627. 0.0198]
	Middle aortic arch	0.0660	0.0327	2.020	0.044	[0.0019. 0.1302]
	Mid-descending aorta	0.6110	0.0291	20.991	<0.001	[0.5539. 0.6682]
Abdominal aorta (final section)	**BMI**	-0.0381	0.1010	-0.377	0.706	[-0.2363. 0.1601]
	Mid-descending aorta	0.1570	0.0350	4.480	<0.001	[0.0882. 0.2258]
	Aorta in the diaphragm	0.6113	0.0343	17.839	<0.001	[0.5440. 0.6786]

SS: standard error.

TABLE 4
Indirect effects of BMI on the abdominal aorta through aortic anatomical mediators (model 6 of PROCESS of Hayes)

Indirect effect	Effect (coefficient B)	Standard error	95% CI
BMI → aortic sinus of Valsalva → mid-descending aorta → aorta in the diaphragm → abdominal aorta	0,1807	0,0484	[0,0878, 0,2778]
BMI → mid-ascending aorta → middle aortic arch → mid-descending aorta → abdominal aorta	0,0611	0,0169	[0,0319, 0,0981]
BMI → mid-descending aorta → abdominal aorta	0,0759	0,0268	[0,0306, 0,1343]
BMI → mid-ascending aorta → middle aortic arch → abdominal aorta	0,0108	0,0049	[0,0029, 0,0218]

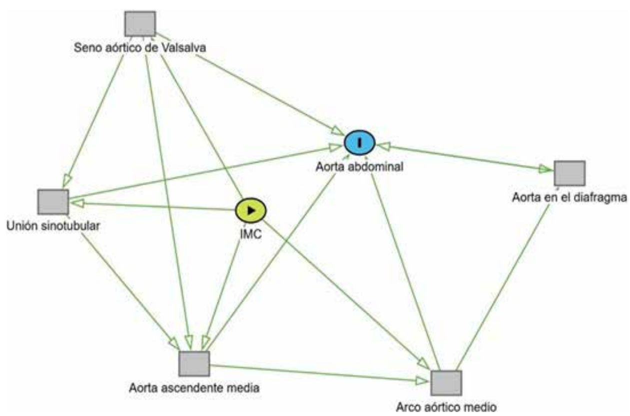

FIGURE 1.
Relationship between BMI and abdominal aorta diameter mediated by anatomical segments of aorta: directed acyclic graph model

role of these sections in the propagation of the effect of the nutritional state toward the abdominal aorta. Likewise, the sequence that involves the mid-ascending aorta, the middle aortic arch and the mid-descending aorta also showed a statistically robust mediation. Other shorter paths, although with effects of less magnitude, were significant and contributed to a comprehensive understanding of the mechanism. These findings highlight the structural relevance of the aortic anatomy as a transmission path for BMI effects, reinforcing the importance of considering complex physiological paths in the evaluation of cardiovascular risks associated to overweight and obesity *(Table 4)*.

In the DAG, the relationship between BMI and the abdominal aorta diameter was evaluated, considering different anatomical segments of the aorta as possible mediators. BMI was defined as the variable of exposition, with the aim of evaluating its indirect impact on the abdominal aorta diameter, through intermediate anatomical structures. The mediators were the aortic sinus of Valsalva, the sinotubular junction, the mid-ascending aorta, the proximal aortic arch, the middle aortic arch, the proximal descending thoracic aorta, the mid-descending aorta and the aorta in the diaphragm. These segments played an essential role in the configuration of the causal trajectories that explain how body fat may induce structural modifications in the distal aorta. Likewise, the existence of possible unobserved variables is acknowledged, such as diet habits, physical activity and blood pressure, which may influence both body composition and vascular architecture, without being explicitly included in the model *(Figure 1)*.

DISCUSSION

The findings of the study suggest the existence of a complex network of associations between BMI and the abdominal aorta diameter, mediated by different anatomical regions of the aorta. Through an approach of chain mediation (model 6 of PROCESS of Hayes), it was shown that BMI, particularly when within ranges of overweight and obesity, is significantly associated with an increase in the dimensions of certain proximal sections of the aorta, especially the aortic sinus of Valsalva and the sinotubular junction. This finding is coherent with the previous literature linking weight excess with vascular structural remodeling, even in absence of manifest cardiovascular disease.[12,13]

Although BMI did not show a significant direct association with the abdominal aortic diameter, the indirect effects through aortic mediators were statistically relevant. In particular, the trajectory that included the sequence aortic sinus of Valsalva → mid-descending aorta → aorta in the diaphragm → abdominal aorta presented the highest indirect coefficient (0.1807; 95% IC: 0.0878-0.2778), which emphasizes the role of the descending axis of the thoracic and diaphragmatic aorta as predominant path of transmission of the BMI effect on the abdominal aorta. This pattern suggests that the remodeling induced by BMI starts in proximal regions and advances toward distal segments, a phenomenon possibly mediated by cumulative hemodynamic and structural adaptations.

Furthermore, other significant paths like BMI → mid-ascending aorta → middle aortic arch → mid-descending aorta → abdominal aorta (coefficient = 0.0611; 95% CI: 0.0319-0.0981) and BMI → mid-descending aorta → abdominal aorta (coefficient = 0.0759; 95% CI: 0.0306-0.1343) reinforce the significance of the mid-descending aorta like a key node in mediation. This is consistent with studies that have reported that the diameters in the descending regions of the aorta are more closely related to metabolic factors and central adiposity.[13] The mid-descending aorta, when receiving the influence both from ascending regions and the aortic arch, acts as an anatomical and functional bridge in the propagation of the BMI effect toward the abdominal aorta.[14,15]

We should highlight that, although some sections like the mid-ascending aorta and the middle aortic arch did not show significant direct association with BMI, its participation in relevant mediator trajectories was identified from the analysis of indirect effects within the chain mediation model. This suggests that they could play a role in the transmission of the BMI effect toward the abdominal aorta, in spite of not having a significant direct link. This finding highlights that even anatomical segments with marginal contributions in the direct analysis may play relevant roles within chain models, where their effect strengthens when interacting with other structures.

Although the relationship between central obesity and aortic dilatation has been described previously, these results reinforce its clinical relevance. For example, in individuals with central obesity, the identification of dilatation in thoracic segments like the aortic sinus of Valsalva or the mid-descending aorta could be considered an anatomical indicator of progression toward dilatation in the abdominal aorta, even before becoming clinically significant. This suggests that the monitoring of these segments by imaging techniques (transthoracic echocardiography or CT) could improve the early detection of vascular structural changes. Similarly, these mediator paths could be useful in the risk stratification of abdominal aorta aneurysm, allowing earlier interventions in populations in high metabolic risk. Although an intensive control of the cardiovascular risk factors is a widely established recommendation in the presence of arterial disease, the findings in this study suggest that in patients with obesity and mid-descending aorta dilatation, even with abdominal aorta within normal parameters, could justify a closer surveillance and an anticipated therapeutic approach to prevent progression of the distal vascular damage.

This study has significant limitations. As its design is cross-sectional, it does not allow to establish causality between BMI and aortic changes. Furthermore, no possible confounding factors were considered, like blood pressure, physical activity or metabolic parameters. Measurements were static anatomical, not evaluating functions like aortic stiffness. Finally, the results cannot be extrapolated to other populations with different characteristics.

To conclude, the findings in this study suggest, in an exploratory manner, that BMI impact on the abdominal aorta diameter would not occur in isolation or linearly, but that could be mediated by a sequence of interconnected anatomical structures; however, these interpretations should be considered cautiously, given the limitations of the study, among them its cross-sectional design, the omission of relevant clinical variables (like blood pressure or physical activity), and the lack of functional evaluations of the aorta. In spite of these limitations, the proposed approach could work as a basis for the development of future research, and potentially, contribute to identifying clinical tools oriented toward an early detection of distal aortic dilatations in people with weight excess, from the analysis of proximal sections. This line of investigation may favor, in the long term, anatomical risk stratification and the orientation of more personalized therapeutic interventions in preventive contexts or in vascular surveillance.

Future longitudinal studies would allow to clarify whether these associations reflect reversible adaptive processes or if they represent early stages of progressive structural alterations in a context of weight excess. Furthermore, the incorporation of hemodynamic, inflammatory and genetic markers can contribute to clarify the specific mechanisms involved in the aortic remodeling induced by BMI.

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