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HIGHLIGHTS

- baPWV is negatively correlated with BMD.
- Pooled correlation coefficient is statistically significant in women, but not in men.
- Gender differences in baPWV and BMD association exist

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Is the association between Pulse Wave Velocity and Bone Mineral Density the same for men and women? - a systematic review and meta-analysis.

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Abstract: Background: Brachial aortic Pulse Wave Velocity (baPWV) and bone mineral density (BMD) are important indicators of cardiovascular health and bone strength, respectively. However, the gender-specific association between baPWV and BMD remains unclear. The aim of our study is to evaluate the relationship between baPWV and BMD in men and women populations **Methods:** A comprehensive search was conducted in electronic databases for relevant studies published between the 1st and 30rd of April 2023. Studies reporting the correlation between baPWV and BMD in both males and females were considered. A random-effects model was used to calculate pooled correlation coefficients (r). **Results:** Relevant data for both genders were found in six articles. In all publications included in the meta-analysis, the total number of studied individuals was 3800, with 2054 women and 1746 men. Pooled correlation coefficient was -0,24 (95% CI: -0.34; -0.15) in women population, and -0.12 (95%CI: -0.16, -0.06) in men. **Conclusions:** Based on the published data, we found that baPWV is negatively correlated with bone density in women. However, in men we do not find such a relationship. These findings suggest the importance of considering gender-specific factors when assessing the cardiovascular and bone health relationship.

Keywords: Bone mineral density, osteoporosis, brachial aortic Pulse Wave Velocity, arterial stiffness, gender differences.

1. Introduction

Osteoporosis is a systemic skeletal disorder characterized by low bone mass, leading to a deterioration of the microarchitecture of bone tissue, making bones brittle and prone to fractures, as well as a condition where the bones become fragile and brittle due to a decreased in bone density and mass, representing a bone-related disease characterized by the loss of bone mass and reduced bone density. [1,2]. The gold standard in the diagnosis of osteoporosis is the measurement of bone mineral density (BMD), which is assessed using a radiological (X-ray) measuring method called densitometry [3]. Decreased bone density, depending on the value, indicates osteoporosis or conditions predisposing to osteoporosis – osteopenia [4]. Osteoporotic fracture risk is higher in older women than in older men, and all postmenopausal women should be evaluated for signs of osteoporosis during routine physical examinations. [5]. For this reason, much attention is paid to updating the guidelines of the management of osteoporosis in postmenopausal women [6]. Arterial stiffness, which is an indicator of the severity of atherosclerosis, is a phenomenon of increased vascular stiffness, loss of elasticity, calcification of the vessel walls and restriction of blood flow that affects endothelium of large and medium-sized arteries [7]. The brachial ankle Pulse Wave Velocity (baPWV) is a measure of systemic arterial stiffness measured by brachial and tibial arterial wave analysis. BaPWV measurement is a non-invasive, effortless, repeatable and well standardized [8,9]. Early assessment of arterial stiffness is essential because its alteration can precede clinical manifestation of cardiovascular disease [10]. Arterial stiffness as well as osteoporosis share common risk factors and clinical manifestations [11-15]. Arterial stiffness as well as bone mineral density progressively increases with aging and are independent predictors of cardiovascular disease (CVD) risk [16]. In the aging process of the body, inflammatory processes play a significant role, which are an essential factor in the development of atherosclerosis [17]. This makes them more susceptible to fractures, even from minor injuries or falls. Inflammatory processes, on the other hand, are the body's natural defense mechanisms against injuries or infections. When tissues are damaged, the body triggers an inflammatory response to repair the damage and protect against further harm. There is a connection between osteoporosis and the inflammatory process. The inflammatory process is the body's response to tissue damage and can occur in various parts of the body. The connection between osteoporosis and inflammation lies in the fact that chronic inflammation, which persists over an extended period, can have a negative impact on bone health [18]. Inflammatory molecules and cells can interfere with the normal process of bone remodeling, which involves the continuous breakdown and rebuilding of bone tissue. When this balance is disrupted by ongoing inflammation, it can lead to increased bone resorption (breakdown) and decreased bone formation [19]. Over time, this imbalance can contribute to the development and progression of osteoporosis. Therefore, it's important to manage chronic inflammation effectively, not only for overall health but also to reduce the risk of

osteoporosis. Moreover, research suggests that chronic inflammation may play a role in the development of osteoporosis. Inflammatory processes can lead to increased bone resorption (the breakdown of bone tissue) and reduced synthesis of new bone tissue. Inflammatory reactions can influence the balance between bone formation and bone breakdown [20].

Chronic inflammation, characterized by persistent and prolonged inflammation in the body, can have detrimental effects on various tissues and organs, including bones. When the body is in a state of chronic inflammation, it releases inflammatory molecules and immune cells that can affect bone health. One of the key mechanisms through which chronic inflammation contributes to osteoporosis is by promoting increased bone resorption. Inflammatory cytokines, which are signaling molecules involved in the immune response, can activate osteoclasts, specialized cells responsible for breaking down bone [21]. This leads to a higher rate of bone resorption, where bone tissue is broken down more rapidly than it is rebuilt. At the same time, chronic inflammation can interfere with the process of bone formation. It can suppress the activity of osteoblasts, the cells responsible for building new bone tissue. This dual effect—increased bone resorption and reduced bone formation—creates an imbalance in bone remodeling, ultimately resulting in the loss of bone density and increased fragility seen in osteoporosis. Therefore, it is crucial to manage chronic inflammation effectively, not only to prevent osteoporosis but also for overall health. Lifestyle modifications, such as adopting an anti-inflammatory diet, engaging in regular physical activity, and avoiding smoking, can help reduce inflammation. In some cases, healthcare providers may recommend medications to control chronic inflammation and protect bone health, especially for individuals at risk of osteoporosis due to inflammatory conditions or other factors [22,23].

In the context of conditions like rheumatoid arthritis, where chronic inflammation is a hallmark feature, the persistent presence of these proinflammatory cytokines can disrupt the delicate balance between bone resorption and bone formation [24]. This imbalance ultimately leads to bone loss and the increased risk of osteoporosis [25]. Therefore, individuals with chronic inflammatory conditions are at greater risk of developing osteoporosis, and it underscores the importance of managing both the underlying inflammation and bone health in these patients. Healthcare providers often work to control inflammation using medications and other strategies, and they may also consider interventions to prevent or treat osteoporosis in individuals with chronic inflammatory diseases [26,27].

The research on the association between Pulse Wave Velocity (baPWV) and Bone Mineral Density (BMD), as outlined in the systematic review and meta-analysis, holds significant implications for the field of gerontology and our understanding of the aging process [28].

As individuals age, they often face increased risks of cardiovascular issues and bone health deterioration, both of which can significantly impact their overall well-being and quality of life [29]. Evidence supports that there are sex differences in the time course of aging-related arterial stiffness and the associated CVD risk, which increases disproportionately in postmenopausal women [30]. Since there are many common risk factors for bone loss and the advancement of atherosclerosis, it may be assumed that increased arterial stiffness may be a diagnostic marker for the development of osteoporosis. In the context of aging, preventive measures become increasingly important to maintain the health and well-being of older individuals. One crucial aspect of preventive care is assessing bone mineral density (BMD) in

individuals, especially those who may have atherosclerosis. Atherosclerosis is a condition characterized by the buildup of plaque in the arteries, and it is associated with an increased risk of cardiovascular events such as heart attacks and strokes.

Given these connections, assessing BMD in individuals with atherosclerosis may be relevant in certain cases. It can help identify those at increased risk of osteoporosis and its complications, such as fractures resulting from falls [31]. If low bone density is detected, appropriate interventions can be implemented, including lifestyle modifications, dietary changes, and potentially medication to strengthen bones. Ultimately, this holistic approach to healthcare, considering the interconnectedness of various health conditions, is in line with the principles of gerontology, which aims to improve the overall well-being and quality of life of older individuals [32]. That is why we are looking for a non-invasive diagnostic marker that will help us identify groups of patients at high risk of osteoporosis - requiring in-depth diagnostics and implementation of targeted treatment.. The aim of our study is to evaluate the relationship between baPWV and BMD in male and female populations.

2. Materials and Methods

Between the 1st and 30th of April 2023, we searched the PubMed, Web of Science, Scopus and Cochrane with the following terms: (bone mineral density [Title/Abstract]) AND (arterial stiffness [Title/Abstract]); (bone mineral density [Title/ Abstract]) AND (pulse wave velocity [Title/Abstract]); (bone mineral density [Title/Abstract]) AND (brachial ankle pulse wave velocity[Title/Abstract]). We additionally searched the reference lists of the retrieved manuscripts and checked the manuscripts citing the retrieved papers. We especially searched through the reference lists of previous narrative reviews of the topic. Figure 1 presents the flow of the inclusion of studies in the present review.

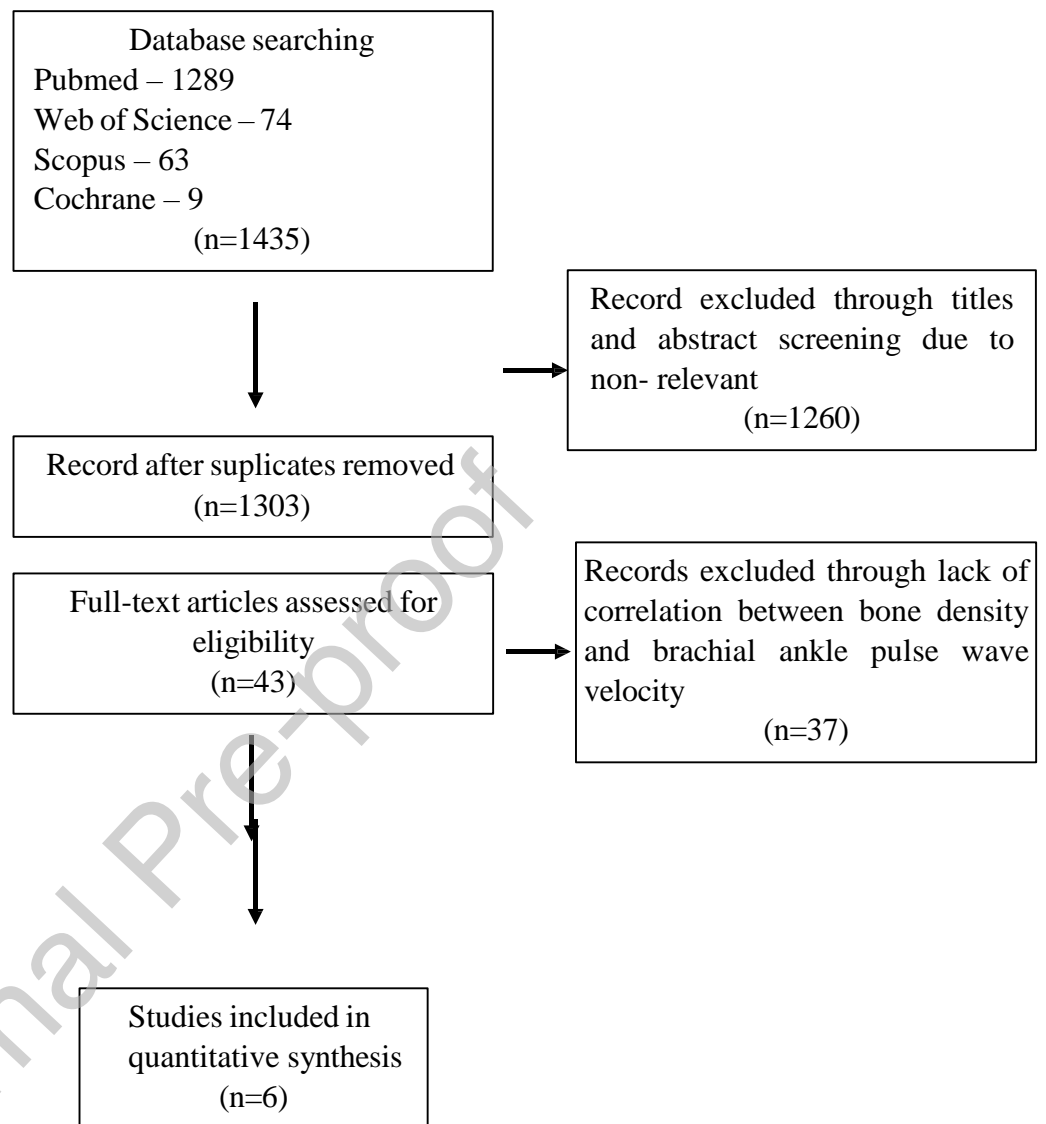


Figure 1. The PRISM diagram for the review and the meta-analysis).

The review was performed according to the systematic reviews and meta-analysis (PRISMA) guidelines [33,34]. The literature search and manuscript selection were performed by two independent researchers (IJ, JB). The data extraction was performed by IJ and RO with the help of MM and JB. The quality of the included studies was rated using Newcastle - Ottawa Quality Assessment Scale [35]. The values on this scale pertain to data selection and study groups (A-D). The comparability of primary and secondary factors among groups is also assessed (E). The methods used to collect information from patients are examined as well (F-H). We limited our search to the English language reports of human studies.

2.1 Inclusion and exclusion criteria

Studies were included if they measured correlation coefficient between BMD and baPWV. To increase the homogeneity of the included studies, we decided to include articles that measure BMD at the lumbar spine and exclude articles that measure BMD at other locations. For data from one research study that was published in several articles, the article with the most comprehensive data was included. The following information from the articles was extracted: journal name, first author name, publication year, research type, research population, age, sample size, research area, Pearson correlation coefficients between BMD measurement in lumbar spine and baPWV. The second aspect pertains to the exceptional quality of the publications as measured by the Newcastle - Ottawa Quality Assessment Scale, which scores between 7–8 points. Only one article achieved a score below 7 on the aforementioned scale. Moreover, it should be noted that four out of the six studies included were prospective studies. The last advantage is that the studies involved quite large groups of patients. Only one study included in the meta-analysis had fewer than 100 participants..

2.2 Heterogeneity and sensitivity

The heterogeneity of the articles was assessed using the Cochran Q test and I^2 inconsistency index (0%-100%). The higher the I^2 , the greater the heterogeneity. The values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively. The sensitivity testing was conducted by removing individual studies from the overall result.

3. Results

3.1. The Characteristics of the Included Studies

A total 6 full-text studies were included in the quantitative analysis. Relevant data for both genders were found in six articles, data for women only were in three articles. In all publications included in the meta-analysis, the total number of studied individuals was 3800, with 2054 women and 1746 men. The mean age of patients was less than 60 years in the most included articles. BMD at the lumbar spine (LS) was measured by dual-energy X-ray absorptiometry at all included studies. PWV was assessed using the brachial-ankle cuff, where the waveforms from the arm and calf are obtained with plethysmographic method. Details are presented in table 1.

Table 1. Study characteristics.

Author, publication year, country	Population	Study design	Measured BMD with	Measured PWV with
Kim NL, et al., 2014, Korea	Men – 111 Women - 128	Retrospective study, MC	DXA (Lunar Prodigy Advance, GE Lunar, Medison, WI, USA)	Automatic waveform analyzer (VP-1000; Nippon Colin Ltd., Komaki, Japan)
Liang DK, et al., 2014, China	Men – 168 Women - 222	Cross-sectional study, SC	DXA (Osteocore 2; Medilink Inc).	Automatic waveform analyzer (form PWV/ABI; Colin Co
Wang YQ, et al., 2015, China	Men – 1467 Women - 1020	Prospective study, MC	DXA (Discovery A, Hologic, USA)	Automatic waveform analyser (Colin Co., Komaki, Japan)
Mikumo M, et al., 2019, Japan	Women - 143	Prospective study, SC	DXA (QDR4500, Hologic Inc., USA)	Automated device (form PWV/ABI; Colin Co. Ltd., Komaki, Japan)
Jaalkhorol M, et al., 2019, Japan	Women - 446	Prospective study, MC	DXA (QDR4500 A, Hologic, Bedford, MA, US)	Volume plethysmographic apparatus (Form PWV/ABI; Fukuda Colin Co., Ltd. Tokyo, Japan)
Sumino H, et al., 2006, Japan	Women - 95	Prospective study, SC	DXA (QDR-1000W, Hologic, Waltham, MA, USA)	Automatic waveform analyser (Colin Co., Komaki, Japan)

3.2. BMD and baPWV relationship

We decided to provide metaanalysis calculations separately for both genders.

Pooled correlation coefficient was -0,24 (95% CI: -0.34; -0.15) in women population (fig.2).

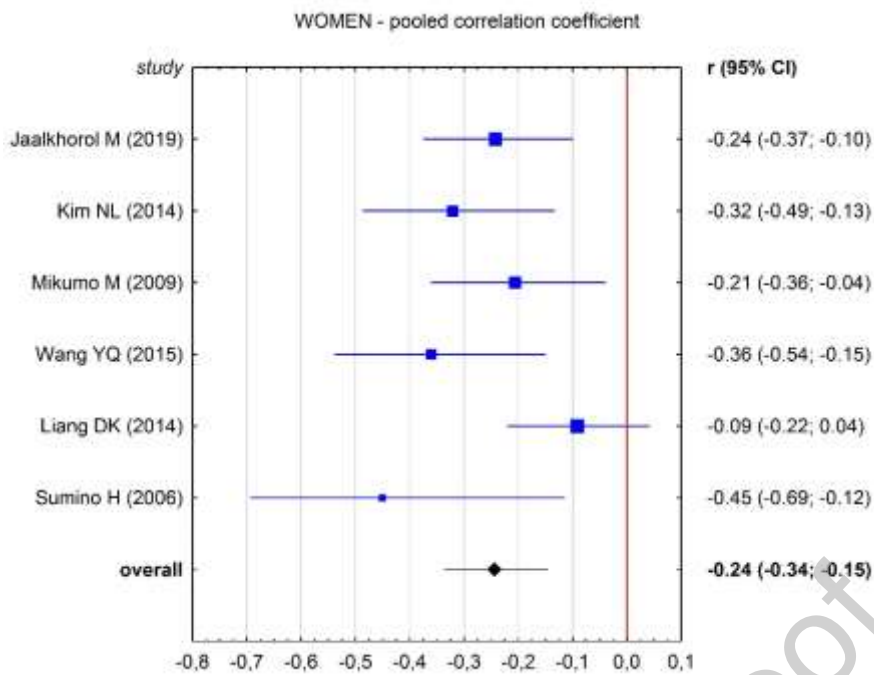


Figure 2. Forest plot, women.

There was moderate heterogeneity among the included studies: $Q = 8.2$; $p = 0.117$ and inconsistency index $I^2 = 43\%$ (95% CI; 0% - 77%).

Sensitivity analysis showed that exclusion of individual studies did not significantly change the results. Correlation coefficient values ranged from -0.22 (95% CI, -0.32 to -0.13) to -0.28 (95% CI, -0.36 to -0.20).

Table 2. Sensitivity analysis, women.

Excluded study	r	95% CI	p value	weight [%]
Jaalkhorol M (2019)	-0.25	-0.37; -0.13	<0.001	78%
Kim NL (2014)	-0.23	-0.34; -0.12	<0.001	84%
Mikumo M (2009)	-0.26	-0.37; -0.14	<0.001	81%
Wang YQ (2015)	-0.22	-0.32; -0.12	<0.001	87%
Liang DK (2014)	-0.28	-0.36; -0.20	<0.001	76%
Sumino (2006)	-0.23	-0.32; -0.13	<0.001	94%
<i>All studies included</i>	<i>-0.24</i>	<i>-0.34; -0.15</i>	<i><0.001</i>	<i>100%</i>

Pooled correlation coefficient for men population was -0.12 (95% CI: -0.18 ; -0.06). Forest plot is presented in figure 3.

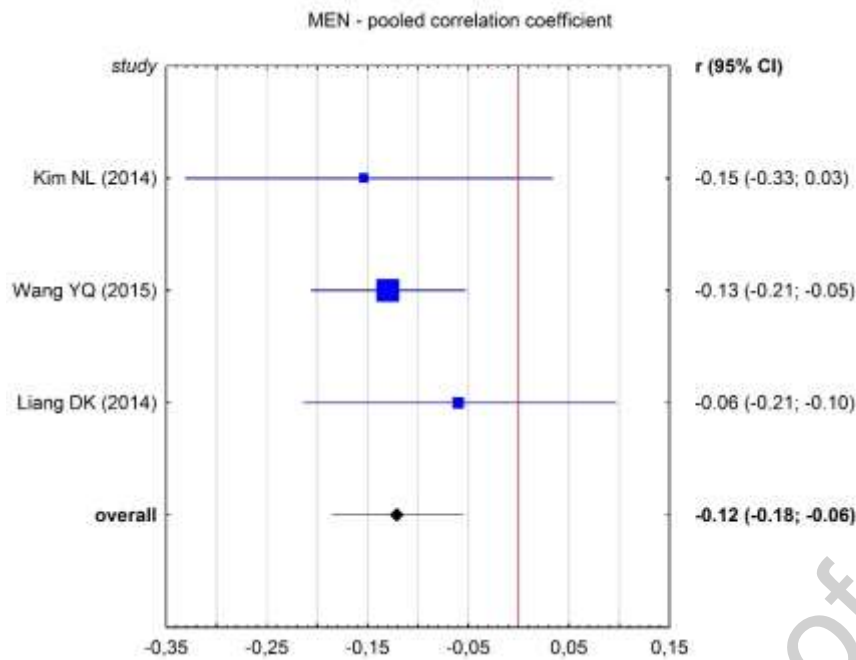


Figure 3. Forest plot, men

Studies analyzing men population demonstrated low heterogeneity: $Q = 0,7$; $p = 0.682$ and inconsistency index $I^2 = 0\%$ (95% CI; 0% - 91%).

Sensitivity analysis showed a small impact of individual studies on the overall result. Correlation coefficient values ranged from -0.10 (95% CI, -0.22 to 0.02) to -0.13 (95% CI, -0.20 to -0.06).

Table 3. Sensitivity analysis, men.

Excluded study	r	95% CI	p value	weight [%]
Kim NL (2014)	-0.12	-0.18; -0.05	0.001	88%
Wang YQ (2015)	-0.10	-0.22; 0.02	0.108	29%
Liang DK (2014)	-0.13	-0.20; -0.06	<0.001	76%
<i>All studies included</i>	<i>-0.12</i>	<i>-0.18; -0.06</i>	<i><0.001</i>	<i>100%</i>

3.3. Quality assessment

Using the Newcastle - Ottawa Quality Assessment Scale, it appears that the publications included in the meta-analysis show high quality, with the exception of the study by Kim NL, et al. Their study exhibited several methodological flaws and limitations. The retrospective nature of the study restricted the analysis to medical documentation from the participants. Furthermore, this paper does not distinguish between a study and a control group. Therefore, using the Newcastle - Ottawa Quality Assessment Scale, the publication by Kim NL, et al. collected the fewest points.

(table 4).

Table 4

Author	Year	Selections				Comparability	Outcome			Score
		A	B	C	D		E	F	G	
Kim NL, <i>et al</i>	2014	1	1	1	1	1				5
Liang DK, <i>et al</i>	2014	1	1	1	1	1	1	1		7
Wang YQ, <i>et al.</i> ,	2015	1	1	1	1	1	1	1		7
Jaalkhorol M, <i>et al</i>	2019	1	1	1	1	2	1	1		8
Mikumo M, <i>et al</i>	2019	1	1	1	1	1	1	1		7
Sumino H, <i>et al</i>	2006	1	1	1	1	1	1	1		7

4. Discussion

Based on the published data, it has been determined that the presence of bone density in women is negatively correlated with baPWV. The pooled correlation coefficient is -0.24 (95% confidence interval: -0.34; -0.15).. The correlation coefficient in the men population is -0.12 (95% CI: -0.18; -0.06).. We can interpret both of these values as a weak negative correlation. Especially the correlation coefficient in men is very weak. Some rules of interpretation would consider it as a lack of correlation, as a negligible correlation [36]. To the best of our knowledge, this is the first meta-analysis to demonstrate differences in correlation between PWV and BMD between genders.

Osteoporosis and atherosclerosis share common pathophysiological mechanisms. In osteoporosis, there is a decrease in the amount of calcium present in the bones, which, upon entering the bloodstream, is deposited in the arteries, resulting in an increase in arterial stiffness. Both diseases get worse with age [37]. Furthermore, the inflammatory basis of both osteoporosis and atherosclerosis is taken into account. Osteoporosis is more prevalent in women, whereas atherosclerosis is statistically more advanced in men, which can be attributed to a higher frequency of smoking and more advanced dyslipidemia [38].. In our analysis, it is important to clarify the observed gender-based differences in the impact of the correlation between elevated arterial stiffness (a predictor of atherosclerosis) and decreased bone density (a predictor of osteoporosis). It appears that this partial difference could be explained by the characteristics of the group of people included in the research. Women are more likely to suffer from osteoporosis, even though its severity increases after menopause. In the interim, the presented meta-analysis revealed that the average age in both gender groups fluctuated around 50, indicating a relatively youthful age for men and not indicating menopause in women. It is noteworthy that we did not conduct a correlation analysis between osteoporosis and atherosclerosis, but rather examined the correlations among the factors that predispose to these diseases, specifically lower bone mineral density and elevated peripheral vascular resistance.

Findings from our meta-analysis may impact the decision to diagnose women earlier and with greater attention for both atherosclerosis and osteoporosis. This in mind, we should take the time to actively look for the signs of osteoporosis in people with a history of cardiovascular disease, as well as assessing the cardiovascular risk more thoroughly in women with the condition.

In two articles included in the meta-analysis, BMD was a dependent variable and baPWV was an independent variable, and in four of them it was the opposite: baPWV was a dependent variable and BMD was an independent variable. However, we included in our meta-analysis

the values of Pearson's correlation coefficients between BMD and baPWV, which were a preliminary part of the analyzes conducted in these articles. We can therefore treat both variables as independent variables, without indicating which variable is the dependent and which is the independent variable.

In total, 54.1% of participants in these studies were female. In study Ya-Qin Wang et al. [39] population consisted of 2,487 subjects (1,467 men, 1,020 women) and were selected to be free of major diseases which might affect atherosclerosis and bone metabolism. The average age of men was 45.72 years, and the average age of women was 44.71 years. The baPWV was significantly associated with BMD in both male and female after adjusting for age only. The other variables of subclinical atherosclerosis (ABI, CIMT, eGFR or microalbuminuria) failed to reach statistical significance with the BMD. They detected that baPWV was an independent factor significantly correlated with BMD. Pearson's correlation was used to identify the BMD associated with the change in baPWV. baPWV was statistically significantly correlated with BMD in both genders. The correlation was stronger in females than in males; in females, the correlation was stronger in post-menopause than pre-menopause. In healthy Han Chinese population [40] consequently, 222 women and 163 men, aged 37– 87 years, with normal BMD, osteopenia, and osteoporosis were included in the analysis. In both genders, the differences of ABI, PWV, and CIMT among the three groups (BMD-dependent) were not found after adjustment for age. The study by NL Kim al. [41] participated 239 healthy people (women: 128, men: 111), mean age was 53 years old. History of hypertension, diabetes, dyslipidemia, thyroid disease, parathyroid disease, rheumatoid arthritis, history of taking steroids, diagnosed with cancer within the past 5 years, gonad dysfunction, patient taking hormonal agents – were excluded from the study. The other studies in our meta-analysis looked only at women. M. Mikumo et al. [42] an investigation carried out on the association between arterial stiffness, lumbar BMD and bone metabolic markers in Japanese 143 postmenopausal women (mean age 57.9 ± 8.3), where there was a significant negative correlation between baPWV and BMD ($r = -0.21$; $P = 0.0135$). An additional analysis included the remaining 75 subjects, but excluded subjects with hypertension and obesity. Here, a more negative correlation between baPWV and BMD ($r = -0.315$; $P = 0.006$), and a positive correlation between baPWV and BAP ($r = 0.248$; $P = 0.032$) were also significant. In earlier Japanese study [43] of 95 Japanese postmenopausal women (mean age: 55.4 ± 6.3 years) exclusion of a person with diabetes, hypertension, severe dyslipidemia, cardiovascular disease, or liver disorder, a history of osteoporotic fracture. Individuals were assigned to one of three groups according to their BMD in the lumbar spine: normal BMD (38 women), osteopenia (a BMD value 1–2.5 S.D. below the mean value for young adults, 32 women), and osteoporosis (a BMD value more than 2.5 S.D). After adjusting for age and years since menopause, women with osteoporosis had a significantly higher baPWV than those with normal BMD (1500 ± 220 cm/s versus 1340 ± 215 cm/s; $P < 0.05$), but no significant differences in baPWV were seen between the osteoporotic and osteopenic groups or between the osteopenic and normal BMD groups. In M. Jaalkhorol et. al [44] study they analyzed data from the 446 women with baPWV lower than 1800 cm/s, mean age 62.6 ± 7.9 . In this study, there were also people with current and past history of diseases including hypertension (36,6%), dyslipidemia (23,5%), and diabetes mellitus (3,5%). Age and BMDs were significantly correlated with baPWV at follow-up. A strong positive correlation was found between baPWV at baseline and at follow-up.

The negative correlation between baPWV and BMD observed in women suggests that as women age, their cardiovascular health may be intricately linked to their bone strength. This finding underscores the importance of comprehensive healthcare strategies tailored to the unique needs of aging individuals, particularly women, to mitigate the risks associated with cardiovascular diseases and osteoporosis. Moreover, higher absolute value of the correlation coefficient between baPWV and BMD in the group of women than in the group of men implies that gender-specific factors play a pivotal role in how cardiovascular health and bone density interact in aging populations. This underscores the importance of considering gender-specific variables in gerontological research and healthcare practices. In summary, this research bridges the gap between cardiovascular health and bone strength, providing crucial insights into how these factors are interconnected in the context of aging. Such knowledge is essential for gerontologists and healthcare providers alike, as it informs more effective strategies for promoting healthy aging and addressing age-related health challenges in a gender-specific manner.

In a study by Avramovski P et al 2018, it came out that the significance of age as a factor influencing PWV is evident. By integrating carotid-femoral Doppler PWV measurement into the standard diagnostic toolkit for assessing arterial stiffness, we can identify individuals at risk not only among the elderly population but also among younger patients with heightened cardiovascular risk. This enables earlier identification and prompts recommendations for preventive measures such as managing arterial stiffness, addressing hypertension, or initiating diabetes treatment when necessary [45].

In a study conducted by Zhang M et al. 2019, involving a cohort of 580 patients with an average age of 64.82 ± 11.4 years, the researchers reported a noteworthy finding. Specifically, they observed a statistically significant correlation between bone mineral density (BMD) in the thoracic spine (referred to as TH BMD) and Cardio-Ankle Vascular Index (CAVI) values among middle-aged and elderly Chinese inpatients. This finding suggests a potential link between the health of the thoracic spine and cardiovascular health, highlighting the importance of further investigation into the relationship between these two variables, especially in aging populations [46].

4.1. Lowering BMD as a prelude to osteoporosis especially in women.

With the ageing population osteoporosis is continually increasing, and it has become an important health problem globally. A study involving US adults aged 50 years reported that the prevalence of osteoporosis was 11%, whereas the prevalence of low bone mass ranged from 28% to 45% in 2013 [47]. Gender differences in the prevalence of the disease are also significant. A meta-analysis of 33 articles revealed that the prevalence of osteoporosis in Chinese people aged >60 years was 36%; comprising 23% men and 49% women [48]. Therefore, special studies on the diagnosis and management of osteoporosis in women have been developed [49]. The studies included in our meta-analysis show the correlations of increased arterial stiffness with bone density - at every stage - from normal BMD to osteopenia to osteoporosis.

4.2 Pulse wave velocity as still an important indicator of multimorbidity and mortality.

In a meta-analysis by Tomiyama et al. [8] demonstrated that the brachial-ankle PWV is an independent predictor of future cardiovascular events. Furthermore, the treatment of

cardiovascular risk factors and lifestyle modifications have been shown to improve the brachial-ankle PWV [50]. Pulse Wave Velocity is also considered marker that may predict cardiovascular and all-cause mortality of hemodialysis patients [51]; and together with Blood Pressure Variability they constitute prognostic indicators in elderly patients [52]. In the Sun study [53], increased baPWV was shown to be more strongly associated with sarcopenia and arteriosclerosis, which are known to be associated with osteoporosis and cause high mortality among patients.

4.3 Gender differences in Arterial Stiffness

In the literature, during the analysis of age groups, differences associated with gender in the mean values of the structural and functional parameters of the artery were absent in the age group 4–8 years, but at ~15 years, they began to appear [54]. Interestingly, for the different age groups, no gender-related difference was observed for arterial stiffness in the upper extremity, whereas, in males, cfPWV was found to be higher [55]. These results show that starting at ~15 years, for elastic arteries such as the aorta, gender-related differences can be found [56]. The research emphasized the role of different hormonal balance, including the protective effect of estrogens in premenopausal women compared to young men. However, the initially protective role of female sex hormones in combination with the subsequent acceleration of increased cardiovascular risk remains unclear [57-62].

4.4. Concatenation Arterial Stiffness and Osteoporosis

A very interesting explanation of the pathophysiological mechanisms of the combination of atherosclerosis and bone loss leading to osteoporosis was described by Szekanecz et al. [63]. The “Bermuda triangle” of atherosclerosis, osteoporosis, and inflammation. Under non-inflammatory states, common conventional risk factors and “low-grade” inflammation may link atherogenesis with bone loss. Cardiovascular disease and osteoporosis are crucial health problems [64]. They may occur simultaneously in the general population [65]. Furthermore, both have also been associated with inflammatory rheumatic musculoskeletal diseases, such as rheumatoid arthritis and ankylosing spondylitis [66]. Paper Pusztai et al. [67] describes common pathogenic pathways in inflammatory atherosclerosis and bone loss. In the Zhang et al. [68] study, it was shown that increased arterial stiffness, as measured by baPWV, was associated with the risk of functional disability, which can cause falls in people with osteoporosis.

4.5. The Impact of Methodology of PWV Assessment and Bone Mineral Density on the Meta-Analysis Results

We should also mention the literature on the subject, which, for reasons not meeting the criteria adopted by us, we did not include in the calculations. In the study Jiang et al. [69], divided patients into groups depending on baPWV - categorized into a normal (baPWV <1,400 cm/s) or high (baPWV ≥1,400 cm/s) - without giving an average overall correlation. After full adjustment for the relevant covariates, a boundary significant association was found between low BMD in the femoral neck and baPWV in postmenopausal women (odds ratio = 1.77, p = 0.049). After full adjustment, neither BMD nor low BMD were significantly associated with subclinical atherosclerosis in men or postmenopausal women. There are isolated reports of gender differences in this topic. In study Ranatunga et al. [70] demonstrated that markers of arterial stiffness (as aortic means cfPWV, carotid intima media

thickness -CMT) are associated with poorer bone health (whole body BMD) in Indian women, but not in men. In some studies, instead of measuring BMD using densitometry, appropriate questionnaires that could predict osteoporosis were used [71]. In the study by Huan Y et al. the authors investigated the correlation between arterial stiffness (baPWV), including a cutoff value, and the risk of osteoporosis as assessed by the Osteoporosis Self-Assessment Tool for Asia (OSTA). They showed a significant correlation between the OSTA index and baPWV, suggesting a potential predictive value of baPWV in elderly patients at high risk of osteoporosis. [72].

4.5. Limitations

Our meta-analysis has limitations. First, we chose articles with only baPWV and only lumbar BMD. Articles with cfPWV and other BMD measurement sites were not included in the analyses. We wanted the articles to be more homogeneous to limit heterogeneity. Secondly, all articles in the meta-analysis came from one continent (Asia), so the conclusion as it does not apply into the population. applies to the entire population. The meta-analysis contained a few articles. The aim was to reduce heterogeneity by aiming for homogeneity of articles. Moreover, there were significantly fewer publications that contained data pertaining to men in comparison to those pertaining to women. Our metaanalysis also possesses strengths. The first strength is the high degree of homogeneity observed in the included studies during the analysis. Our metaanalysis also possesses strengths. The first strength is the high degree of homogeneity observed in the included studies during the analysis.. The last advantage is that the studies involved quite large groups of patients. Only one study included in the meta-analysis had fewer than 100 participants.

5. Conclusion

In conclusion, this systematic review and meta-analysis provide evidence of a moderate negative correlation between baPWV and BMD in the female population, while the correlation in the male appears to be weaker. This study, by investigating the gender-specific relationship between baPWV and BMD, provides valuable insights into the factors that contribute to the age-related health concerns. The findings suggest that gender differences exist in the association between cardiovascular health (baPWV) and bone strength (BMD). These results underscore the importance of considering gender-specific factors when evaluating the connection between cardiovascular and bone health. However, further research is needed to explore the underlying mechanisms driving these gender differences and to elucidate their clinical implications:

1. Age as a Key Factor: Age is a critical factor in both atherosclerosis and osteoporosis, as both conditions tend to worsen with advancing age. It would be beneficial to discuss how age might interact with the observed correlations between baPWV and BMD in men and women. For instance, do these correlations change with age, and if so, in what way?
2. Age-Stratified Analysis: Consider conducting an age-stratified analysis to assess whether the strength of the correlation between baPWV and BMD varies across different age groups within the study population. This can help identify potential age-specific trends.
3. Menopause and Its Influence: Since menopause is a significant event in a woman's life associated with hormonal changes and increased risk of osteoporosis, explore whether

the strength of the correlation differs between pre-menopausal and post-menopausal women. Are there age-related trends in post-menopausal women that could explain the observed differences?

4. **Gender-Specific Trends:** Discuss any gender-specific trends that emerged from the analysis. For instance, if women in the study tended to be younger on average than men, consider whether this age difference may have contributed to the stronger correlation observed in women.
5. **Potential Mechanisms:** Explore potential mechanisms underlying the observed age and gender differences. Are there biological or physiological explanations for why baPWV and BMD might correlate differently in men and women of different ages?
6. **Clinical Implications:** Consider the clinical implications of age-specific variations in the correlation between baPWV and BMD. How might these findings impact the diagnosis and management of atherosclerosis and osteoporosis in different age and gender groups?

Future Research Directions: Suggest areas for future research, such as conducting longitudinal studies to track changes in baPWV and BMD over time in individuals of different ages and genders. This could help elucidate the dynamic nature of these relationships

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