UNIVERSIDADE FERNANDO PESSOA

OSTEOPOROSE EM MULHERES PÓS-MENOPAÚSICAS BRASILEIRAS E SUA ASSOCIAÇÃO COM A EXPOSIÇÃO AMBIENTAL AO CÁDMIO

[Osteoporosis in Brazilian postmenopausal women and its association with environmental exposure to cadmium]

Tese de Doutoramento

3º Ciclo de Estudos em Ecologia e Saúde Ambiental

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PUBLICAÇÕES

Os artigos e comunicações originais abaixo listados foram elaborados no âmbito da presente tese. Carlos T. Kunioka declara ter contribuído de forma significativa para a concepção, desenho e execução técnica dos trabalhos, bem como para a aquisição de dados, a análise e interpretação dos resultados, e a redação dos manuscritos que integram esta tese.

Artigos em revistas científicas internacionais:

1. Kunioka, C. T., Manso, M. C., & Carvalho, M. (2022). Association between Environmental Cadmium Exposure and Osteoporosis Risk in Postmenopausal Women: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, *20*(1), 485. https://doi.org/10.3390/ijerph20010485
2. Kunioka, C.T., Cruz, J. C., de Oliveira Souza, V. C., Rocha, B. A., Barbosa Jr, F., Belo, L., Manso, M. C., & Carvalho, M. (2025). Low-Level Environmental Cadmium Exposure and Its Effects on Renal and Bone Health in Brazilian Postmenopausal Women: A Cross-Sectional Study. *Exposure and Health*. *In press* (publicado *online* a 13 de junho de 2025). https://doi.org/10.1007/s12403-025-00715-2
3. Kunioka, C. T., de Oliveira Souza, V. C., Rocha, B. A., Júnior, F. B., Belo, L., Manso, M. C., & Carvalho, M. (2025). Association of Urinary Cadmium and Antimony with Osteoporosis Risk in Postmenopausal Brazilian Women: Insights from a 20 Metal(loid) Biomonitoring Study. *Toxics*, *13*(6), 489. https://doi.org/10.3390/toxics13060489

Resumos em revistas científicas internacionais:

1. Kunioka, C. T., Manso, M. C., & Carvalho, M. (2022). Environmental cadmium exposure is associated with higher risk of osteoporosis in postmenopausal women: a systematic review and meta-analysis. *RevSALUS*, 4, S160. https://doi.org/10.51126/revsalus.v4iSup.392
2. Kunioka, C., Cruz, J., Souza, V., Rocha, B., Júnior, F. B., Mota, C., Manso, M.

C., & Carvalho, M. (2024). Bone and renal effects of low-level environmental exposure to cadmium in postmenopausal women: a cross-sectional study in Brazil. *Scientific Letters*, *1*(Sup 1). https://doi.org/10.48797/sl.2024.219

3. Kunioka, C., Souza, V., Rocha, B., Júnior, F., Belo, L., Manso, M., & Carvalho, M. (2025). Environmental exposure to metal(loid)s: an emerging risk factor for osteoporosis in postmenopausal women? *Scientific Letters*, *1*(Sup 1). https://doi.org/10.48797/sl.2025.364

4. Kunioka, C., Cruz, J., Souza, V., Rocha, B., Júnior, F., Belo, L., Manso, M., & Carvalho, M. (2025). Subclinical Renal Tubular Dysfunction in Postmenopausal Women Exposed to Low-Level Environmental Cadmium. *Nephrology Dialysis Transplantation (in press).*

Comunicações na forma de poster em conferências:

1. Kunioka, C. T., Manso, M.C., & Carvalho, M. Is environmental cadmium exposure a risk factor for osteoporosis in postmenopausal women? A systematic review. *III Jornadas Ibéricas de Toxicologia*. Universidade da Beira Interior, 4 e 5 de junho de 2021.

2. Kunioka, C. T., Manso, M. C., & Carvalho, M. Environmental cadmium exposure is associated with higher risk of osteoporosis in postmenopausal women: a systematic review and meta-analysis. Congresso Internacional da APCF-TOXRUN, Centro de Congressos da Alfândega do Porto, 7 e 8 de abril de 2022.

3. Kunioka, C., Cruz, J., Souza, V., Rocha, B., Júnior, F. B., Mota, C., Manso, M. C., & Carvalho, M. Bone and renal effects of low-level environmental exposure to cadmium in postmenopausal women: a cross-sectional study in Brazil. III 1H-TOXRUN International Congress, Porto, 2 e 3 maio de 2024.

4. Kunioka, C. T., Cruz, J., Souza, V., Rocha, B., Júnior, F. B., Kunioka, L. N., Manso, M. C., & Carvalho, M. Osteoporose em mulheres pós-menopáusicas moradoras de Cascavel-pr, região sul do Brasil, e sua associação com a exposição ambiental ao cádmio. 11º BRADOO - Congresso Brasileiro de Densitometria, Osteoporose e Osteometabolismo, Brasília, Brasil, 21 a 24 de agosto de 2024.

5. Kunioka, C., Souza, V., Rocha, B., Júnior, F., Belo, L., Manso, M., & Carvalho,

M. Environmental exposure to metal(loid)s: An emerging risk factor for osteoporosis in postmenopausal women? IV 1H-TOXRUN International Congress, Porto, 8 e 9 maio 2025.

6. Kunioka, C., Cruz, J., Souza, V., Rocha, B., Júnior, F., Belo, L., Manso, M., & Carvalho, M. Subclinical Renal Tubular Dysfunction in Postmenopausal Women Exposed to Low-Level Environmental Cadmium. 62nd ERA Congress Viena, Áustria, 4 a 7 de junho de 2025.

Dedico esta tese, em primeiro lugar, a DEUS Onipresente que nos momentos da minha vida, seja nas dificuldades ou nas vitórias, sempre esteve presente guiando e iluminando os meus passos e o meu horizonte.

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RESUMO

A osteoporose é uma doença osteometabólica multifatorial caracterizada pela diminuição da densidade mineral óssea (DMO) e pela deterioração da microarquitetura óssea, o que conduz a um aumento da fragilidade esquelética e do risco de fratura. Esta condição apresenta elevada prevalência global, afetando aproximadamente uma em cada três mulheres, especialmente após a menopausa, e um em cada cinco homens acima dos 50 anos, assumindo proporções crescentes face ao envelhecimento populacional. O impacto socioeconómico e clínico da osteoporose é significativo, traduzindo-se em elevados índices de morbilidade, mortalidade e perda de qualidade de vida. Evidências recentes têm apontado para o papel de fatores ambientais como contribuintes adicionais para o risco de osteoporose, nomeadamente a exposição crónica a metais tóxicos. O cádmio (Cd), metal pesado não essencial, bioacumulativo e persistente no ambiente, tem sido implicado na patogénese de doenças ósseas e renais, mesmo em níveis considerados baixos. Este trabalho de investigação teve como objetivo investigar os efeitos da exposição ambiental a múltiplos metais e metaloides, com enfoque no Cd, sobre a saúde óssea e a função renal em mulheres pós-menopáusicas residentes em Cascavel (Brasil), região agrícola com potencial risco de contaminação ambiental. A investigação compreendeu três estudos distintos. O primeiro trabalho consistiu numa revisão sistemática com meta-análise de estudos observacionais (2008–2021), focados na associação entre os níveis urinários de Cd (UCd) e o risco de osteoporose em mulheres com idade igual ou superior a 50 anos. A meta-análise revelou uma associação significativa entre UCd ≥ 0,5 μg/g de creatinina e osteoporose (OR = 1,95; IC95%: 1,39–2,73; $p < 0,001$), reforçada por uma associação semelhante em exposições mais elevadas (UCd ≥ 5 μg/g: OR = 1,99; IC95%: 1,04–3,82; $p = 0,040$), confirmando a consistência do risco. O segundo estudo, de base populacional regional e desenho transversal, incluiu a participação de 380 mulheres pós-menopáusicas brasileiras, residentes em Cascavel. Foram colhidos dados demográficos e clínicos (incluindo os valores da densitometria óssea em diferentes regiões anatómicas) e obtidas amostras de urina, nas quais os diferentes metais/metaloides foram quantificados por espetrometria de massa com plasma indutivo acoplado (ICP-MS). A mediana de UCd foi de 0,30 μg/g de creatinina e a prevalência global de osteoporose foi de 19,2%. Os participantes com níveis de UCd ≥ 1,1 μg/g (percentil 95 adotado pelas autoridades nacionais para mulheres brasileiras) apresentaram DMO significativamente reduzida na coluna lombar e no colo femoral, bem como prevalência superior de osteoporose. Embora os modelos ajustados não tenham identificado uma associação linear estatisticamente significativa entre UCd e DMO, observaram-se tendências limítrofes (osteopenia femoral: $p = 0,073$; osteoporose lombar: $p = 0,109$), e a regressão bayesiana com máquina de kernel (BKMR) identificou uma relação não linear entre UCd e DMO, sugerindo um possível limiar de toxicidade óssea. Paralelamente, o UCd revelou ser um preditor significativo do aumento da excreção urinária de β2-microglobulina ($p < 0,001$), marcador de lesão tubular renal. O terceiro estudo analisou a biomonitorização de 20 metais/metaloides na mesma amostra populacional de Cascavel. Mulheres com diagnóstico de osteoporose apresentaram níveis urinários significativamente mais elevados de Cd ($p = 0,017$) e antimónio (Sb; $p = 0,001$). Após a correção para potenciais fatores de confusão (idade, índice de massa corporal, tempo de menopausa, tabagismo, inatividade física), tanto o Cd (OR = 1,495; $p = 0,026$) como o Sb (OR = 2,059; $p = 0,030$) mantiveram associação independente com a presença de osteoporose. A prevalência da doença foi de 44,4% nas mulheres com níveis urinários simultaneamente elevados de Cd e Sb (≥ percentil 90), comparativamente a 18,0% nas restantes ($p = 0,011$), sugerindo um possível efeito sinérgico na exposição a estes dois

elementos. Importa salientar que, ao contrário do Cd, o Sb não tem sido tradicionalmente associado à desmineralização óssea. A sua identificação nesta investigação sugere que o Sb pode representar um potencial fator de risco emergente, cuja relevância toxicológica merece investigação aprofundada em trabalhos futuros. Em conjunto, os resultados reforçam a evidência de que exposições ambientais crónicas a metais tóxicos, mesmo em concentrações reduzidas, podem comprometer simultaneamente a função renal e a saúde óssea. Estes dados sustentam a necessidade urgente de monitorização ambiental e de implementação de políticas públicas para mitigar a exposição a metais tóxicos, especialmente em populações vulneráveis.

Palavras-chave: Metais; Densidade mineral óssea; Exposição ambiental; Mulheres pós-menopáusicas; Função renal; Brasil.

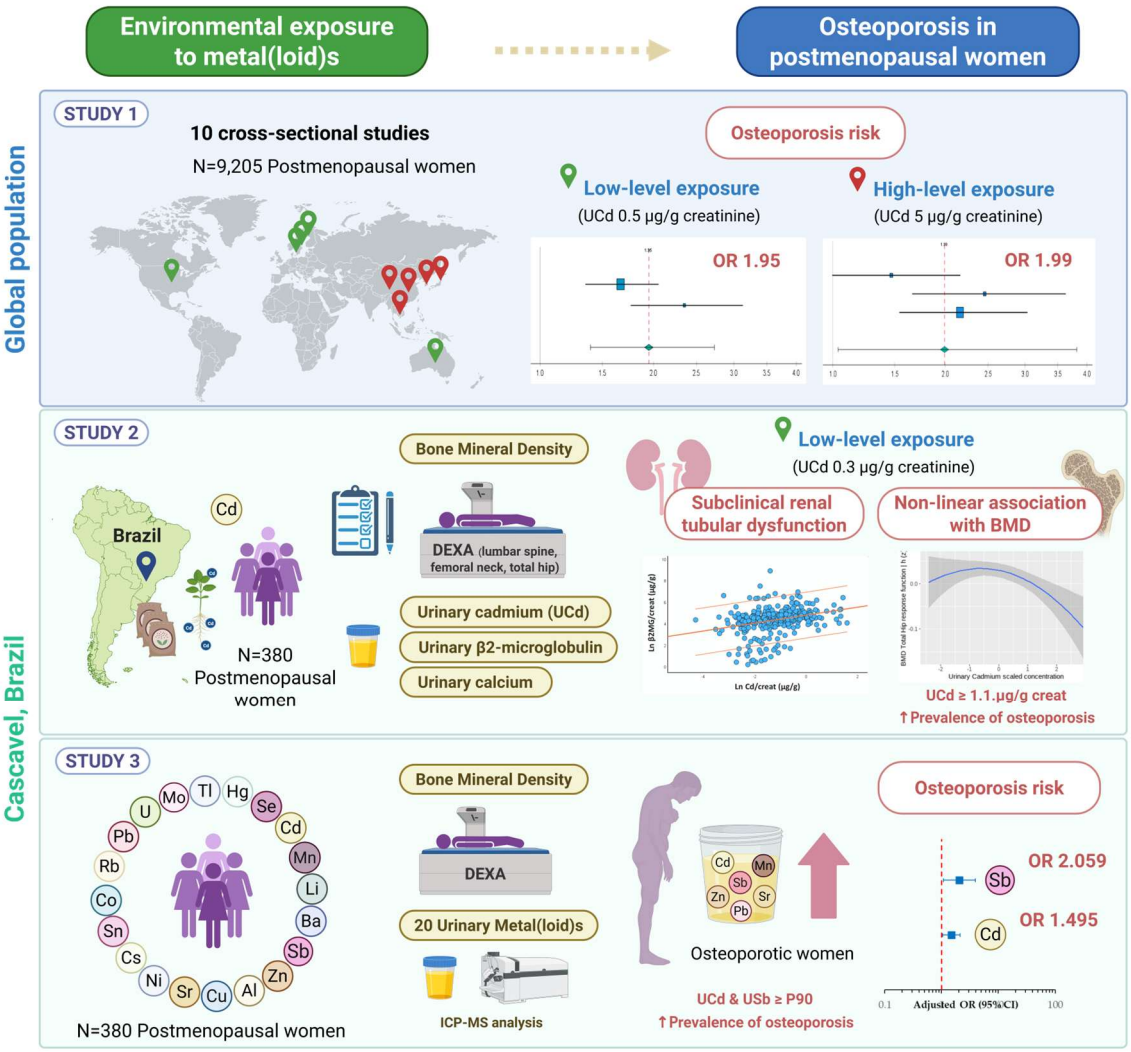
ABSTRACT

Osteoporosis is a multifactorial osteometabolic disease characterized by a decrease in bone mineral density (BMD) and deterioration of bone microarchitecture, which leads to increased skeletal fragility and risk of fracture. This condition has a high global prevalence, affecting approximately one in three women, especially after the menopause, and one in five men over the age of 50, taking on increasing proportions as the population ages. The socio-economic and clinical impact of osteoporosis is significant, resulting in high rates of morbidity, mortality and loss of quality of life. Recent evidence has pointed to the role of environmental factors as additional contributors to the risk of osteoporosis, namely chronic exposure to toxic metals. Cadmium (Cd), a non-essential heavy metal, bioaccumulative and persistent in the environment, has been implicated in the pathogenesis of bone and kidney diseases, even at levels considered low. This research project aimed to investigate the effects of environmental exposure to multiple metals and metalloids, with a focus on Cd, on bone health and kidney function in postmenopausal women living in Cascavel (Brazil), an agricultural region with a potential risk of environmental contamination. The research comprised three separate studies. The first study consisted of a systematic review with meta-analysis of observational studies (2008-2021) focused on the association between urinary Cd levels (UCd) and the risk of osteoporosis in women aged 50 and over. The meta-analysis revealed a significant association between UCd ≥ 0.5 µg/g creatinine and osteoporosis (OR = 1.95; 95%CI: 1.39-2.73; $p < 0.001$), reinforced by a similar association at higher exposures (UCd ≥ 5 µg/g: OR = 1.99; 95%CI: 1.04-3.82; $p = 0.040$), confirming the consistency of the risk. The second study, with a regional population base and cross-sectional design, included 380 Brazilian postmenopausal women living in Cascavel. Demographic and clinical data were collected (including bone densitometry values in different anatomical regions) and urine samples were obtained, in which the different metals/metalloids were quantified by inductively coupled plasma mass spectrometry (ICP-MS). The median UCd was 0.30 µg/g creatinine and the overall prevalence of osteoporosis was 19.2%. Participants with UCd levels ≥ 1.1 µg/g (95th percentile adopted by national authorities for Brazilian women) had significantly reduced BMD in the lumbar spine and femoral neck, as well as a higher prevalence of osteoporosis. Although the adjusted models did not identify a statistically significant linear association between UCd and BMD, borderline trends were observed (femoral osteopenia: $p = 0.073$; lumbar osteoporosis: $p = 0.109$), and Bayesian kernel machine regression (BKMR) identified a non-linear relationship between UCd and BMD, suggesting a possible bone toxicity threshold. At the same time, UCd proved to be a significant predictor of increased urinary excretion of β2-microglobulin ($p < 0.001$), a marker of renal tubular damage. The third study analyzed the biomonitoring of 20 metals/metalloids in the same population sample from Cascavel. Women diagnosed with osteoporosis had significantly higher urinary levels of Cd ($p = 0.017$) and antimony (Sb; $p = 0.001$). After correcting for potential confounding factors (age, body mass index, time since menopause, smoking, physical inactivity), both Cd (OR = 1.495; $p = 0.026$) and Sb (OR = 2.059; $p = 0.030$) maintained an independent association with the presence of osteoporosis. The prevalence of the disease was 44.4% in women with simultaneously high urinary levels of Cd and Sb (≥ 90th percentile), compared to 18.0% in the others ($p = 0.011$), suggesting a possible synergistic effect of exposure to these two elements. It should be noted that, unlike Cd, Sb has not traditionally been associated with bone demineralization. Its identification in this research suggests that Sb may represent a potential emerging risk factor, whose toxicological relevance merits in-depth investigation in future work. Taken together, the results reinforce the evidence that

chronic environmental exposures to toxic metals, even at low concentrations, can simultaneously compromise kidney function and bone health. These data support the urgent need for environmental monitoring and the implementation of public policies to mitigate exposure to toxic metals, especially in vulnerable populations.

Keywords: Metals; Osteoporosis; Bone mineral density; Environmental exposure; Postmenopausal women; Renal function; Brazil.

GRAPHICAL ABSTRACT



ÍNDICE GERAL

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LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

ACR	Colégio Americano de Radiologia (*American College of Radiology*)
ADN	Ácido desoxirribonucleico
Al	Alumínio
ANDA	Associação Nacional para Difusão de Adubos
As	Arsénio
β2MG	β2-microglobulina
BKMR	Regressão bayesiana com máquina de kernel (*Bayesian kernel machine regression*)
BMP	Proteína morfogenética óssea (*Bone morphogenetic protein*)
Cd	Cádmio
CTX	Telopeptídeo C-terminal do colagénio tipo I (*C-terminal telopeptide of type I collagen*)
DEXA	Absorciometria de Raios-X de Dupla Energia (*Dual-energy X-ray absorptiometry*)
DMO	Densidade mineral óssea
FAO	Organização das Nações Unidas para a Alimentação e a Agricultura (*Food and Agriculture Organization of the United Nations*)
GH	Hormona do crescimento (*Growth hormone*)
Hg	Mercúrio
HPA	Eixo hipotálamo-hipófise-adrenocortical (*Hypothalamic-pituitary-adrenal axis*)
IMC	Índice de massa corporal
IOF	Fundação Internacional da Osteoporose (*International Osteoporosis Foundation*)
ISCD	Sociedade Internacional de Densitometria Clínica (*International Society for Clinical Densitometry*)
MAPKs	Proteínas cinases ativadas por mitogénios (*Mitogen-activated protein kinases*)
M-CSF	Fator estimulador de colónias de macrófagos (*Macrophage colony-stimulating factor*)
MSC	Células estaminais mesenquimatosas (*Mesenchymal stem cells*)
NFATc1	Fator nuclear de células T ativadas 1 (*Nuclear factor of activated T cells 1*)

NF-κB	Fator nuclear kappa-B (*Nuclear factor-κB*)
NTX	Telopeptídeo N-terminal do colagénio tipo I (*N-terminal telopeptide of type I collagen*)
OB	Osteoblastos
OC	Osteoclastos
OMS	Organização Mundial da Saúde
OPG	Osteoprotegerina
P1NP	Propeptídeo N-terminal do procolagénio do tipo I (*Procollagen type I N-terminal propeptide*)
Pb	Chumbo
PTH	Paratormona (*Parathyroid hormone*)
RANK	Recetor ativador do fator nuclear kappa-B (*Receptor activator of nuclear factor-κB*)
RANKL	Ligando do recetor ativador do fator nuclear kappa-B (*Receptor activator of nuclear factor-κB ligand*)
ROS	Espécies reativas de oxigénio (*Reactive oxygen species*)
Sb	Antimónio
SERMs	Moduladores seletivos dos recetores de estrogénio (*Selective estrogen receptor modulators*)
SOST	Esclerostina (*Sclerostin*)
TCQ	Tomografia computadorizada quantitativa
TNF	Fator de necrose tumoral (*Tumor necrosis factor*)
TRAP5b	Fosfatase ácida resistente ao tartarato 5b (*Tartrate-resistant acid phosphatase 5b*)

INTRODUÇÃO

A osteoporose representa, atualmente, um importante problema de saúde pública a nível mundial, cuja magnitude tem vindo a agravar-se com o envelhecimento progressivo das populações e o aumento significativo da longevidade em certos países. Esta condição, caracterizada pela diminuição da massa óssea e pela deterioração da microestrutura do tecido ósseo, conduz a um aumento significativo do risco de fraturas, especialmente em indivíduos idosos e do sexo feminino. As consequências clínicas da osteoporose traduzem-se numa perda acentuada de autonomia funcional, dor crónica, limitação da mobilidade, redução da qualidade de vida e aumento da mortalidade. Paralelamente, esta doença impõe uma carga substancial sobre os sistemas de saúde, quer pelos custos diretos associados ao tratamento das fraturas, quer pelos custos indiretos relacionados com a reabilitação prolongada e a necessidade de cuidados continuados. A dimensão e complexidade deste problema justificam a realização de mais estudos nesta área, com o objetivo de melhorar as estratégias de prevenção, diagnóstico e tratamento.

Para contextualizar a investigação efetuada no presente projeto, será feita uma revisão introdutória à problemática da osteoporose e a sua ligação à exposição ambiental a metais.

Definição e Classificação de Osteoporose

A osteoporose é uma patologia osteometabólica sistémica, caracterizada por uma redução da densidade mineral óssea (DMO) e deterioração da microarquitetura do tecido ósseo. Estas alterações comprometem a resistência óssea, aumentando a fragilidade do esqueleto e predispondo à ocorrência de fraturas, mesmo na ausência de traumatismos significativos (IOF, 2025; Xu et al., 2021). As fraturas por fragilidade representam, assim, um grave problema de saúde pública, estando associadas a níveis elevados de morbilidade e mortalidade, além de implicarem uma carga socioeconómica considerável e exigirem recursos substanciais dos sistemas de saúde (Marinho et al., 2014; Aziziyeh et al., 2019; Lorentzon et al., 2022; Shen et al., 2022; Singer et al., 2023).

Do ponto de vista etiológico, a osteoporose pode ser classificada como primária ou secundária. A forma primária inclui dois subtipos principais: a osteoporose pós-menopáusica (tipo I), que surge predominantemente em mulheres após a menopausa, e a osteoporose senil (tipo II), que ocorre em ambos os sexos como parte do processo de envelhecimento. Por sua vez, a osteoporose secundária resulta de condições clínicas ou

da utilização de fármacos que afetam adversamente o metabolismo ósseo, promovendo a perda de massa óssea e elevando o risco de fraturas (Amarnath et al., 2023).

As formas secundárias de osteoporose são relativamente frequentes em ambos os sexos, podendo ter diversas etiologias, como certas endocrinopatias, doenças gastrointestinais, distúrbios nutricionais ou de má-absorção, bem como a utilização de certos fármacos, entre outras (cf. Tabela 1) (Sobh et al., 2022). A identificação da etiologia subjacente é fundamental, uma vez que estas formas são, em muitos casos, potencialmente tratáveis. O diagnóstico correto permite orientar a terapêutica, prevenir fraturas e travar a progressão da doença.

Tabela 1.

Causas de osteoporose secundária

Grupo causal	**Exemplos**
Endocrinopatias	Hiperparatiroidismo primário Hipertiroidismo Hipogonadismo primário e secundário Diabetes *mellitus*
Distúrbios renais	Hiperparatiroidismo secundário a doença renal Acidose tubular renal Osteodistrofia renal
Distúrbios imunológicos	Lúpus eritematoso sistémico Esclerose múltipla Artrite reumatoide
Doenças hematológicas	Mieloma múltiplo Linfomas e leucemias Hemoglobinopatias
Infeções	VIH, VHB, VHC Tuberculose
Doenças pulmonares	Doença pulmonar obstrutiva crónica Asma
Má nutrição e síndromes má-absorção	Anorexia nervosa Consumo excessivo de álcool

Tabela 1 (continuação)

Grupo causal	Exemplos
	Baixo consumo de cálcio e vitaminas C e D
	Doença inflamatória intestinal
	Cirurgia bariátrica
Uso de fármacos	Glucocorticoides
	Inibidores da bomba de protões (uso crónico)
	Imunossupressores
	Quimioterápicos
	Anticonvulsivantes (ex. fenobarbital, carbamazepina)
Outras	Tabagismo
	Sedentarismo
	Causas genéticas

Nota. Abreviaturas: VHB, vírus da hepatite B; VHC, vírus da hepatite C; VIH, vírus da imunodeficiência humana. Fonte: Adaptado de "Secondary Osteoporosis and Metabolic Bone Diseases", de M. M. Sobh et al., 2022, Journal of Clinical Medicine, 11, p. 2382. (https://doi.org/10.3390/jcm11092382).

Epidemiologia da Osteoporose

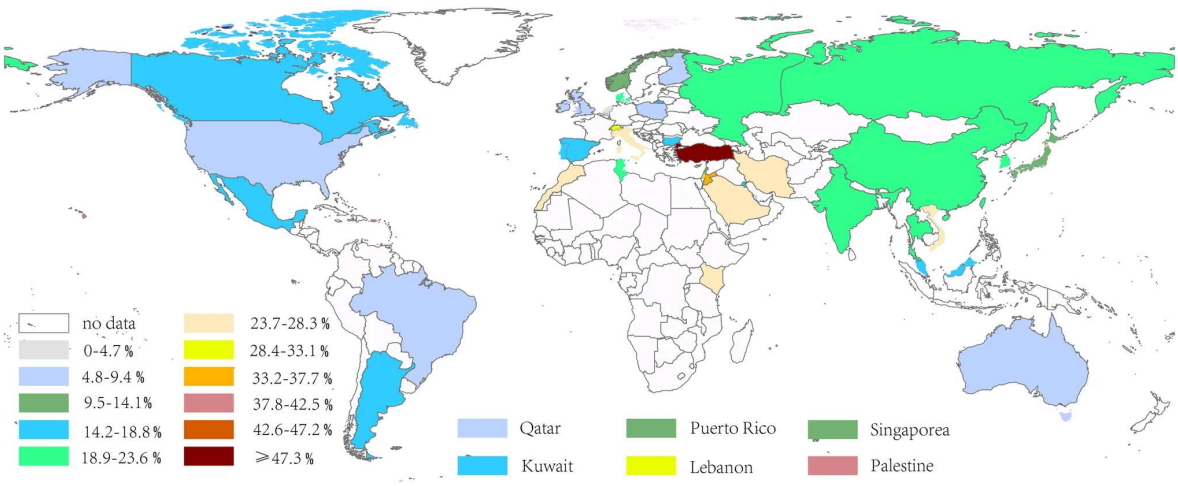
A compreensão da distribuição e dos determinantes da osteoporose a nível global é essencial para antecipar os desafios que esta doença representa para os sistemas de saúde, sobretudo em contextos de envelhecimento populacional. Estima-se que a osteoporose afete mais de 200 milhões de pessoas em todo o mundo. De acordo com os dados da Fundação Internacional da Osteoporose (IOF), cerca de uma em cada três mulheres e um em cada cinco homens com mais de 50 anos sofrerão, ao longo da vida, uma fratura osteoporótica (IOF, 2025; Salari et al., 2021).

A prevalência mundial estimada da osteoporose em mulheres é de 18,3% (IC 95%: 16,2–20,7) (IOF, 2025; Salari et al., 2021). Num estudo publicado em 2022, com base em 343.704 participantes de 37 países, a prevalência global de osteoporose foi de 19,7% (IC 95%, 18,0%–21,4%) (cf. Figura 1). A nível nacional, a prevalência mais elevada foi observada na Turquia, Palestina, Jordânia e Irão. Em contraste, a prevalência foi menor na Holanda, Qatar, Inglaterra, Finlândia e Brasil. A nível continental, a prevalência foi mais elevada na Ásia e África, e foi mais baixa na Europa, América do Norte, América do Sul e Oceânia (Xiao et al., 2022). A variação da distribuição da osteoporose entre

países é influenciada por fatores genéticos, ambientais, dietéticos e do acesso aos cuidados de saúde.

Figura 1.

Distribuição global da prevalência de osteoporose



Nota: Os países de difícil identificação no mapa estão listados separadamente. Adaptado de "Global, regional prevalence, and risk factors of osteoporosis according to the World Health Organization diagnostic criteria: a systematic review and meta-analysis", de P. L. Xiao et al., 2022, Osteoporosis International, 33, pp. 2137-2153 (https://doi.org/10.1007/s00198-022-06454-3).

No Brasil, país de dimensão continental e com acentuadas desigualdades regionais, a prevalência de osteoporose entre mulheres pós-menopáusicas apresenta valores igualmente significativos, variando entre 10,8% (Marinho et al., 2014) e 40% (Costa et al., 2016), com estudos mais recentes a apontarem para valores intermédios, entre 20% e 24% (Astolfo et al., 2024). De acordo com o Ministério da Saúde do Brasil (2022), a osteoporose representa uma das principais causas de morbilidade e mortalidade em indivíduos com mais de 50 anos (Ministério da Saúde, 2022).

O envelhecimento populacional constitui um dos principais fatores de agravamento do panorama atual da osteoporose, dada a relação positiva entre o avanço da idade e a prevalência da doença. Países com elevada longevidade já sentem os impactos socioeconómicos e clínicos desta realidade (Xiao et al., 2022). Por sua vez, países em desenvolvimento, como os da América Latina e de África, embora ainda com populações relativamente jovens, enfrentarão em breve um envelhecimento populacional acelerado. Tal processo, aliado à melhoria progressiva das condições sanitárias, nutricionais e

educacionais, resultará num aumento da sobrevida, particularmente entre as mulheres, implicando um aumento do fardo associado às fraturas osteoporóticas e aos custos para os sistemas de saúde (Odén et al., 2015; Zamani et al., 2018).

Fatores de Risco de Osteoporose

A osteoporose é uma doença multifatorial cuja etiologia envolve a interação entre fatores genéticos, hormonais, comportamentais, nutricionais e ambientais (Carey et al., 2022; Pouresmaeili et al., 2018). Estes fatores são habitualmente classificados como modificáveis e não modificáveis, de acordo com a possibilidade de intervenção preventiva ou terapêutica (cf. Figura 2).

Figura 2.

Fatores de risco modificáveis e não modificáveis para a osteoporose

Nota: Criada pelo autor em BioRender.com (2025).

Os fatores modificáveis são aqueles passíveis de controle através de mudanças no estilo de vida, nutrição ou ambiente. Destaca-se a ingestão nutricional inadequada,

nomeadamente de cálcio, vitamina D e proteínas, que compromete a formação e manutenção da DMO (Joy et al., 2024; Martiniakova et al., 2022). A inatividade física, o baixo peso corporal e a perda de massa muscular reduzem o estímulo mecânico necessário à manutenção óssea e aumentam o risco de fratura (Alghadir et al., 2025; Park et al., 2023).

O tabagismo e o consumo excessivo de álcool ou cafeína interferem negativamente no metabolismo ósseo por vias hormonais e celulares, embora alguns efeitos possam ser reversíveis com a cessação (Al-Bashaireh et al., 2018; Cusano, 2015; Zhu & Prince, 2015).

A exposição à poluição atmosférica, particularmente a partículas finas e metais pesados, tem sido associada a inflamação crónica e desregulação do metabolismo mineral (Allen et al., 2024; Prada et al., 2023).

Por fim, o stress psicológico crónico afeta negativamente o osso através da ativação do eixo hipotálamo-hipófise-adrenocortical (HPA) e da resposta inflamatória, além de influenciar comportamentos de risco como sedentarismo e má alimentação (Ng & Chin, 2021; Azuma et al., 2015).

Entre os fatores não modificáveis, incluem-se a idade avançada e o sexo feminino. O envelhecimento conduz a alterações estruturais e celulares no tecido ósseo, incluindo senescência celular e aumento da porosidade (Smit et al., 2024). A maior prevalência da doença nas mulheres deve-se essencialmente à menor massa óssea e à perda estrogénica após a menopausa (Gordon et al., 2017).

A etnia constitui igualmente um fator determinante no risco de osteoporose, dada a existência de variações significativas na DMO e na arquitetura esquelética entre diferentes populações (Wu & Dai, 2023; Durdin et al., 2020). Mulheres de origem caucasiana, asiática, hispânica e nativo-americana apresentam um risco mais elevado de desenvolver osteoporose quando comparadas a mulheres negras, o que é, em grande parte, atribuído a diferenças na DMO. Apesar das bases biológicas subjacentes a esta disparidade não estarem totalmente esclarecidas, é amplamente reconhecido que indivíduos afrodescendentes tendem a possuir uma DMO mais elevada e um menor risco de fraturas (Wu & Dai, 2023; Cauley & Nelson, 2021). Importa, contudo, salientar que estas diferenças étnicas na DMO são fortemente influenciadas pelo peso corporal.

Por último, a história familiar de osteoporose reforça a importância dos determinantes genéticos e epigenéticos na etiologia da doença, influenciando quer a DMO, quer a microarquitetura óssea (Visconti et al., 2021; Xu et al., 2021). A presença de antecedentes familiares de fraturas osteoporóticas constitui igualmente um fator de risco relevante para o desenvolvimento desta doença.

Risco de Fratura e Impacto Societal da Osteoporose

A osteoporose é uma condição esquelética geralmente silenciosa, frequentemente subdiagnosticada e subtratada, com milhões de pessoas em risco de fraturas por fragilidade sem conhecimento da sua situação clínica (Aggarwal et al., 2021; Cho et al., 2021). O impacto das fraturas osteoporóticas é profundo, tanto a nível individual como social, comprometendo a autonomia dos doentes e gerando elevados custos em saúde (Rashki-Kemmak et al., 2020).

Conforme já mencionado, estima-se que uma em cada três mulheres e um em cada cinco homens com mais de 50 anos sofram, ao longo da vida, uma fratura por fragilidade (IOF, 2025; Brown, 2017). As previsões globais apontam para um aumento substancial nos próximos anos. Prevê-se que até 2050 as fraturas do quadril poderão crescer 310% nos homens e 240% nas mulheres, face aos valores de 1990 (Shen et al., 2022). Globalmente, ocorrem mais de 8,9 milhões de fraturas por ano, ou seja, uma a cada três segundos (Johnston & Dagar, 2020).

O risco de fraturas osteoporóticas supera, em muitos casos, o de doenças como o cancro da mama, e acarreta mais dias de internamento hospitalar do que várias patologias crónicas comuns. Na Europa, o grau de incapacidade resultante da osteoporose é comparável ao provocado por doenças como cancro, artrite reumatoide ou insuficiência cardíaca (IOF, 2025).

As fraturas vertebrais causam dor, deformidade e perda de estatura. Após uma fratura do quadril, 40% dos doentes perdem a capacidade de caminhar sem ajuda, 60% requerem apoio prolongado e 20–24% morrem no primeiro ano (Shen et al., 2022; Hsieh et al., 2024; IOF, 2025). Alarmantemente, cerca de 80% dos casos não recebem diagnóstico ou tratamento para osteoporose. Além disso, apenas uma minoria recupera totalmente a função pré-fratura.

A lenta ou deficiente consolidação das fraturas pode contribuir significativamente para o

agravamento da comorbilidade. Exemplos disso incluem a ocorrência de trombose venosa profunda, frequentemente associada à imobilidade, e o sedentarismo. Acrescem ainda consequências como a perda de qualidade de vida e a diminuição da independência nas atividades da vida diária.

Mecanismos Fisiopatológicos da Osteoporose

A remodelação óssea é um processo dinâmico e contínuo que garante a renovação do tecido ósseo, a adaptação às cargas mecânicas e a manutenção da homeostase mineral, particularmente do cálcio e fósforo (Föger-Samwald et al., 2020). Este equilíbrio entre formação e reabsorção óssea é regulado por múltiplos fatores, incluindo genéticos, hormonais, mecânicos e ambientais, sendo fundamental para a integridade estrutural do esqueleto (cf Figura 3). A homeostasia óssea envolve quatro fases: ativação, reabsorção, inversão e formação (Ponzetti & Rucci, 2019). Cada uma destas fases é desempenhada por diferentes tipos celulares, nomeadamente osteoclastos, osteoblastos, osteócitos e células do revestimento ósseo, que atuam de forma coordenada no microambiente ósseo. A ativação inicia-se com o recrutamento de pré-osteoclastos para a superfície óssea, seguindo-se a reabsorção, onde os osteoclastos degradam a matriz mineralizada. A fase de inversão marca a transição para a formação, permitindo a preparação da superfície óssea para a ação dos osteoblastos, responsáveis pela síntese de nova matriz óssea.

Na osteoporose, ocorre um desequilíbrio entre estes processos, com predomínio da reabsorção, levando à perda de massa óssea e à fragilidade esquelética (Bonewald, 2011; Tsai et al., 2023). Os osteócitos desempenham papel central, regulando osteoblastos e osteoclastos por meio de moléculas como o fator estimulador de colónias de macrófagos (M-CSF) e o ligando do recetor ativador do fator nuclear kappa-B (RANKL), que promovem a osteoclastogénese (Jacome-Galarza et al., 2019; Nakashima et al., 2011). Os linfócitos T também contribuem para a produção de RANKL em contextos inflamatórios (Leibbrandt & Penninger, 2008).

Durante a reabsorção, os osteoclastos degradam a matriz óssea por secreção de ácidos e enzimas como a catepsina-K (Teitelbaum, 2000). A via RANK/RANKL/OPG é um ponto de controlo crítico, sendo que a osteoprotegerina (OPG), secretada por osteoblastos, atua como inibidor competitivo do RANKL, reduzindo a ativação osteoclástica (Ono et al.,

2020; Barnsley et al., 2021). Este sistema é modulado por hormonas como estrogénios, que aumentam a OPG, e glucocorticoides, que a inibem (Hofbauer & Schoppet, 2004).

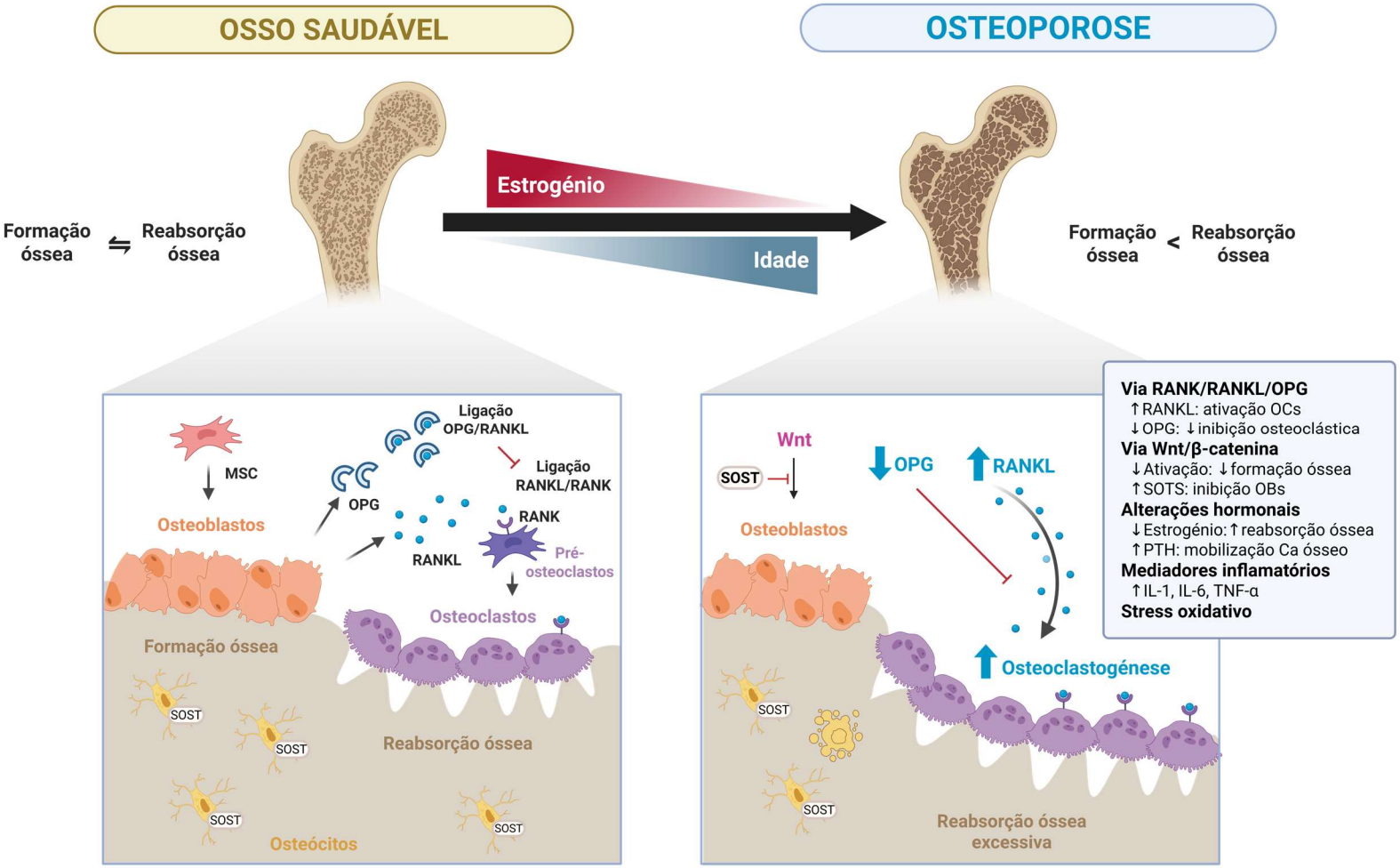
Na fase de formação, os osteoblastos depositam matriz osteóide, rica em colagénio tipo I, que é posteriormente mineralizada por cristais de hidroxiapatita (Gao et al., 2021). Uma parte destes osteoblastos diferencia-se em osteócitos, que, em estado de repouso, produzem esclerostina (SOST), um inibidor da via Wnt, suprimindo a atividade osteoblástica (Bonewald, 2011). A diferenciação osteoblástica depende de vias moleculares como Wnt, BMP e Notch, que ativam fatores de transcrição osteogénicos como Runx2 e Osterix (Ballhause et al., 2021; Ren et al., 2021).

Durante a menopausa, a queda nos níveis de estrogénios acentua a reabsorção óssea, promovendo a ativação dos osteoclastos e acelerando a perda de massa óssea (Perez & Weilbaecher, 2006; de Villiers, 2024). Fatores ambientais, como o sedentarismo, a baixa exposição solar, o consumo excessivo de álcool, o tabagismo, uma alimentação deficiente em cálcio e vitamina D, bem como a exposição a poluentes ambientais, nomeadamente metais pesados, disruptores endócrinos e partículas finas, podem agravar este processo, aumentando o risco de osteoporose e de fraturas associadas (Peng et al., 2025).

Em síntese, a osteoporose resulta de uma falha na regulação da remodelação óssea, envolvendo um complexo sistema de interações celulares e moleculares. A sua compreensão é essencial para o desenvolvimento de abordagens preventiva ou terapêuticas eficazes.

Figura 3.

Mecanismos fisiopatológicos da osteoporose



Nota. Os osteoblastos (OB) regulam de forma coordenada o processo de remodelação óssea, em resposta a sinais de ativação mediados por fatores sistémicos como a hormona do crescimento (GH), interleucinas (ex. IL-1 e IL-6), paratormona (PTH) e a diminuição dos níveis de estrogénios. Entre os principais fatores produzidos pelos OB que influenciam o recrutamento e a diferenciação dos osteoclastos (OC) destacam-se o fator estimulador de colónias de macrófagos (M-CSF) e o ligando do recetor ativador do fator nuclear kappa-B (RANKL). A osteoprotegerina (OPG), igualmente sintetizada pelos OB, atua como um recetor solúvel "isca", impedindo a ativação do RANK e, consequentemente, a formação e atividade dos OC. A inibição ou modulação negativa destes sinais osteoblasto-osteoclasto conduz a uma redução da reabsorção óssea. Adicionalmente, a esclerostina (SOST), um peptídeo secretado pelos osteócitos, limita a formação de novo osso ao antagonizar a via de sinalização Wnt. Abreviaturas: MSC, células estaminais mesenquimatosas; TNF-α, fator de necrose tumoral α. Fonte: Criada pelo autor em BioRender.com (2025).

Diagnóstico da Osteoporose

Segundo a Organização Mundial de Saúde (OMS), a absorciometria de raios X de dupla energia (DEXA) é o método de referência para o diagnóstico da osteoporose. Esta técnica permite a quantificação da DMO, expressa em g/cm², sendo particularmente aplicada às regiões do colo femoral e da coluna lombar (OMS, 1998).

De acordo com os critérios da OMS, o diagnóstico de osteoporose é estabelecido quando a medição da DMO, expressa em termos de T-score (desvio padrão em relação à média de adultos jovens saudáveis) é igual ou inferior a -2,5 (cf. Tabela 2). Valores entre -1,0 e -2,5 indicam osteopenia, um estado de baixa massa óssea que representa risco aumentado de progressão para osteoporose (Camacho et al., 2020; Yang et al., 2025). Valores acima de -1,0 são considerados normais (Aibar-Almazán et al., 2022; Ha et al., 2024).

Tabela 2.

Critérios diagnósticos para a osteoporose com base na densidade mineral óssea (DMO) definidos pela Organização Mundial de Saúde (OMS)

DMO T-score	Classificação
T-score ≥ -1	Normal
-2.5 < T-score < -1	Osteopenia
T-score ≤ -2.5	Osteoporose
T-score ≤ -2.5 + fratura por fragilidade	Osteoporose severa

A avaliação morfológica de fraturas vertebrais pode ser realizada concomitantemente com a DEXA, utilizando uma dose de radiação cerca de 200 vezes inferior à das

radiografias convencionais (Oliveira et al., 2022). Esta técnica permite a identificação precoce de fraturas vertebrais assintomáticas, muitas vezes negligenciadas clinicamente.

A tomografia computadorizada quantitativa (TCQ) constitui uma alternativa válida, permitindo a avaliação da DMO trabecular em mg/cm³, com sensibilidade superior na deteção de alterações estruturais precoces, particularmente na coluna lombar. Segundo a Sociedade Internacional de Densitometria Clínica (ISCD) e o Colégio Americano de Radiologia (ACR), a osteoporose é diagnosticada pela TCQ com valores ≤ 80 mg/cm³ e a osteopenia entre 80 e 120 mg/cm³ (Yu et al., 2022).

Importa sublinhar que a presença de uma fratura por fragilidade (resultante de trauma mínimo) é, por si só, suficiente para o diagnóstico clínico de osteoporose, independentemente do valor da DMO (Siris et al., 2014; Lin et al., 2015).

Outras técnicas de imagem, como a ultrassonografia quantitativa, a ressonância magnética ou a análise da microarquitetura óssea por microtomografia ou microressonância magnética, têm sido exploradas como ferramentas complementares, mas a sua aplicação clínica na predição de fraturas ainda carece de validação (Chang et al., 2017; Cortet et al., 2021; Idoko et al., 2024).

Além das técnicas imagiológicas, os biomarcadores do *turnover* ósseo têm vindo a emergir como auxiliares na avaliação diagnóstica e na monitorização terapêutica. Os principais marcadores de formação óssea incluem a fosfatase alcalina óssea, osteocalcina e o propeptídeo N-terminal do procolagénio do tipo I (P1NP). Já os marcadores de reabsorção óssea incluem o telopeptídeo C-terminal do colagénio tipo I (CTX), o telopeptídeo N-terminal do colagénio tipo I (NTX), piridinolina, desoxipiridinolina e a fosfatase ácida resistente ao tartarato 5b (TRAP5b) (Bhattoa et al., 2025; Kanis et al., 2019; Lorentzon et al., 2019).

Tratamento da Osteoporose

O principal objetivo do tratamento da osteoporose, bem como da intervenção em indivíduos com fatores de risco (como idade avançada ou historial de fraturas), é a prevenção de novas fraturas. A abordagem terapêutica é multimodal, combinando medidas não farmacológicas, estratégias de prevenção de quedas e terapêutica farmacológica ("Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society", 2021; Cosman et al.,

2024).

As medidas não farmacológicas para a prevenção e tratamento da osteoporose incluem a prática regular de atividade física com carga mecânica moderada, como a marcha ou o treino de resistência, uma alimentação equilibrada com ingestão adequada de cálcio, vitamina D e proteínas, a cessação do consumo de tabaco e a limitação da ingestão de bebidas alcoólicas. Adicionalmente, a adaptação do ambiente doméstico, como a remoção de tapetes soltos, melhoria da iluminação e uso de calçado adequado, é fundamental para a prevenção de quedas.

A terapêutica farmacológica tem como objetivo aumentar a DMO e a resistência estrutural do esqueleto, sendo várias as classes de fármacos aprovadas para este fim (Anam & Insogna, 2021; Brown, 2017). Os bifosfonatos, como o alendronato, o risedronato e o ácido zoledrónico, atuam inibindo a reabsorção óssea mediada pelos osteoclastos. Os moduladores seletivos dos recetores de estrogénio (SERMs), como o raloxifeno, exercem um efeito agonista no tecido ósseo e antagonista no tecido mamário. Os inibidores do RANKL, como o denosumab, reduzem a atividade osteoclástica, enquanto os análogos da paratormona (PTH), como a teriparatida e a abaloparatida, estimulam a formação óssea. Por fim, os inibidores da SOST, como o romosozumab, promovem a osteogénese e simultaneamente reduzem a reabsorção óssea ("Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society", 2021; Cosman et al., 2024).

A seleção do tratamento depende do perfil clínico do doente, da gravidade da osteoporose, da presença de fraturas prévias, da idade do doente e da resposta ao tratamento anterior. Terapias sequenciais podem ser mais eficazes em casos de alto risco. A monitorização periódica da DMO, da adesão terapêutica e da presença de efeitos adversos é essencial para avaliar a eficácia do tratamento, permitir ajustes terapêuticos atempados e garantir a continuidade e segurança da intervenção ao longo do tempo (Anam & Insogna, 2021).

Efeitos da Exposição a Metais na Saúde Óssea

A exposição a metais tóxicos representa um importante fator de risco para a saúde óssea, sendo o cádmio (Cd) um dos elementos mais estudados nesta área. A gravidade da toxicidade do Cd sobre o sistema esquelético tornou-se evidente com o surto da doença de "Itai-Itai" no Japão, associada a quadros severos de osteomalácia e a elevada

mortalidade (Genchi et al., 2020). O Cd, após absorção por via inalatória (considerada a mais eficiente) ou por via oral, acumula-se no organismo, sobretudo nos rins, fígado e tecido ósseo, com uma meia-vida biológica que pode ultrapassar três décadas. Esta persistência prolongada deve-se à sua forte ligação a proteínas como as metalotioneínas, que, embora desempenhem um papel protetor, não impedem a libertação progressiva do metal na sua forma livre, responsável pelos efeitos tóxicos intracelulares (Charkiewicz et al., 2023; Genchi et al., 2020).

No tecido ósseo, o Cd compromete a homeostase entre os processos de formação e reabsorção óssea, promovendo um desequilíbrio que favorece a perda progressiva de massa óssea. A via RANKL/RANK/OPG constitui um dos mecanismos moleculares mais amplamente estudados e melhor caracterizados neste contexto. A exposição ao Cd induz a sobre-expressão do ligando RANKL e, simultaneamente, reduz os níveis de OPG, promovendo a ativação de osteoclastos e intensificando a reabsorção óssea (Lv et al., 2019; Chen et al., 2009; Hofbauer & Schoppet, 2004).

A par desta via central, o Cd ativa vias intracelulares fundamentais para a osteoclastogénese, nomeadamente a via do fator nuclear kappa B (NF-κB), as proteínas cinases ativadas por mitogénios (MAPKs), com destaque para as subvias p38 e JNK, e a via do fator nuclear de células T ativadas 1 (NFATc1), intensificando a diferenciação e atividade osteoclástica (Luo et al., 2021).

Simultaneamente, o Cd inibe mecanismos envolvidos na osteoblastogénese. Especificamente, a via ERK1/2, essencial para a proliferação e sobrevivência dos osteoblastos, é suprimida, ao passo que a ativação da via p38 MAPK promove apoptose celular nestas células (Brama et al., 2012; Arbon et al., 2012; Hu et al., 2015). O Cd induz ainda um aumento significativo na produção de espécies reativas de oxigénio (ROS), gerando stress oxidativo que compromete a viabilidade celular e interfere negativamente na diferenciação de células estaminais mesenquimatosas (MSC) em osteoblastos (He & Zhang et al., 2025; Monteiro et al., 2018).

Este stress oxidativo é exacerbado pela disfunção mitocondrial induzida pelo Cd e pela depleção de enzimas antioxidantes, como a superóxido dismutase e a glutationa peroxidase, contribuindo de forma significativa para os danos celulares e consequente redução da DMO (Đukić-Ćosić et al., 2020; Fernández-Torres et al., 2022; Ou et al., 2021).

Para além dos mecanismos já descritos, estudos recentes demonstraram que o Cd interfere também na via de sinalização Wnt/β-catenina, essencial para a osteoblastogénese, inibindo a diferenciação osteoblástica de MSC, o que reforça ainda mais o efeito deletério deste metal na formação óssea (Wu et al., 2019).

Em conjunto, esses efeitos promovem um desequilíbrio profundo na dinâmica óssea, aumentando o risco de osteoporose associado à exposição ambiental ao Cd.

Além do Cd, outros metais apresentam efeitos deletérios bem estabelecidos sobre o tecido ósseo, destacando-se o chumbo (Pb), alumínio (Al), mercúrio (Hg) e arsénio (As). O Pb, por exemplo, acumula-se na matriz óssea ao longo da vida e interfere no metabolismo do cálcio e da vitamina D, diminuindo a absorção intestinal e renal destes minerais. Estes efeitos resultam numa redução da mineralização óssea e num maior risco de fraturas (Collin et al., 2022).

O Al, por sua vez, compete com o cálcio durante o processo de mineralização, substituindo-o nas regiões de formação óssea e conduzindo à osteomalácia. Este metal também inibe a secreção de PTH e interfere na ativação da vitamina D, perturbando a regulação do metabolismo fosfocálcico (Jackson & Rout, 2024; Klein, 2019; Mizuno et al., 2022).

O Hg, particularmente na sua forma orgânica, é reconhecido pelo seu impacto neurológico, mas estudos em modelos animais indicam que também pode prejudicar a remodelação óssea, afetando negativamente a densidade e a estrutura microarquitetónica do osso (Charkiewicz et al., 2023; Nunes et al., 2022; Jalili et al., 2020; Rodríguez & Mandalunis, 2018).

Finalmente, o As, amplamente presente no ambiente, tem demonstrado capacidade de se acumular no tecido ósseo e interferir com a formação da matriz mineral, ao competir com o grupo fosfato e formar compostos instáveis. A exposição crónica ao As reduz a expressão de genes osteogénicos e compromete a diferenciação e função dos osteoblastos, conduzindo à diminuição da densidade óssea e ao aumento da fragilidade esquelética (Hsueh et al., 2021; Hu et al., 2025; Ximenez et al., 2021; Xu et al., 2023).

Face à crescente evidência dos efeitos osteotóxicos destes metais, a exposição ambiental crónica, ainda que em concentrações relativamente baixas, constitui não só uma preocupação relevante de saúde pública, como também um domínio que justifica investigação científica aprofundada.

Justificação da Investigação

As estimativas do crescimento marcado da população mundial, bem como da longevidade, nas próximas décadas impõe a necessidade de aumentar proporcionalmente a produção global de alimentos, de forma a mitigar o risco de insegurança alimentar. Segundo estimativas da Organização das Nações Unidas para a Alimentação e Agricultura (FAO), será necessário incrementar a produção de alimentos em cerca de 50% até 2050 (UNDESA, 2022), sendo o uso de fertilizantes considerado uma componente estratégica essencial para alcançar esse objetivo (Khatun et al., 2022).

Neste contexto, o Brasil assume um papel de destaque como um dos maiores produtores de alimentos à escala mundial. A produção brasileira, que atualmente alimenta cerca de 1,6 mil milhões de pessoas, um excedente substancial face à sua população interna, aumentou mais de 500% desde a década de 1970, altura em que ainda dependia de ajuda alimentar externa (Santos, 2022). Este crescimento tem sido sustentado por uma intensificação progressiva da utilização de fertilizantes, posicionando o país como o quarto maior consumidor global, com uma quota de aproximadamente 8% do consumo mundial (Benício, 2022).

O estado do Paraná, responsável por uma parte significativa da produção agrícola nacional, é o segundo maior produtor de grãos e o quarto maior exportador do agronegócio brasileiro (DERAL, 2022). Em 2022, consumiu mais de quatro milhões de toneladas métricas de fertilizantes, dos quais mais de 650 mil toneladas corresponderam a fertilizantes fosfatados (ANDA, 2023). No município de Cascavel, localizado na região oeste do Paraná e com uma população estimada em 348.051 habitantes (IBGE, 2022), a agricultura intensiva constitui um dos pilares económicos. Este município destaca-se como o maior produtor estadual de soja e apresenta expressiva produção de milho e trigo, cujo sucesso está intrinsecamente associado ao uso intensivo de fertilizantes (Farias et al., 2021).

Nos últimos anos, a presença de Cd em fertilizantes fosfatados tem gerado uma crescente preocupação internacional. Estes fertilizantes podem conter concentrações elevadas de Cd, o qual, quando aplicado repetidamente em solos agrícolas, tende a acumular-se, aumentando os seus níveis em até 87%, especialmente em solos ácidos onde a sua solubilidade é maior (Kubier et al., 2019; Wei et al., 2020; Snoj-Tratnik et al., 2022). Esta acumulação contínua ao longo dos anos representa uma via de exposição ambiental relevante para a população humana, com implicações potencialmente graves, dado que o

Cd é um metal de elevada toxicidade, mesmo em concentrações reduzidas (Akesson et al., 2006; Nordberg et al., 2018; Peana et al., 2023).

Em resposta a esta evidência, a Comissão Europeia propôs, em 2016, a limitação dos teores de Cd permitidos em fertilizantes fosfatados, visando a proteção da saúde pública e dos solos agrícolas europeus (European Parliament, 2024). Contudo, subsiste ainda a incerteza quanto ao real impacto da exposição ao Cd, por via agrícola, na saúde óssea da população, sendo este um tema que carece de investigação populacional dirigida (Husejnović et al., 2021; Roberts, 2014).

Este problema reveste-se de particular relevância para mulheres pós-menopáusicas, grupo populacional especialmente vulnerável à perda de massa óssea, o que poderá exacerbar os efeitos deletérios da exposição ao Cd e a outros metais tóxicos (Wang et al., 2023). Assim, a presente investigação visa colmatar esta lacuna no conhecimento, através da avaliação da exposição a metais e metaloides, com especial enfoque no Cd, e da sua associação com a saúde óssea de mulheres pós-menopáusicas residentes numa região agrícola com uso intensivo e prolongado de fertilizantes, como a de Cascavel.

Este estudo reveste-se de grande importância para a saúde pública e para a segurança alimentar, já que decisões regulatórias inadequadas poderão comprometer tanto a sustentabilidade da produção de alimentos como a saúde das populações expostas. A investigação proposta poderá fornecer dados relevantes para a definição de estratégias de monitorização, mitigação e intervenção em contextos de exposição ambiental a metais tóxicos.

Objetivos da Investigação

O principal objetivo deste estudo foi o de avaliar a associação entre a exposição ambiental a metais e metaloides, com ênfase no Cd, e o risco de osteoporose em mulheres pós-menopáusicas, através de uma abordagem multidisciplinar integrando dados epidemiológicos, biomarcadores de exposição e avaliação da DMO.

Foram definidos como objetivos específicos deste estudo:

- Investigar a associação entre a exposição ambiental ao Cd e o risco de osteoporose em mulheres pós-menopáusicas, numa perspetiva global;

- Determinar a prevalência de osteoporose e identificar os principais fatores de risco numa população específica do município de Cascavel, estado do Paraná (Brasil), uma região caracterizada pelo uso intensivo de fertilizantes;
- Quantificar os níveis urinários de metais e metaloides como indicadores biológicos de exposição ambiental;
- Analisar a associação entre os níveis urinários destes elementos e potenciais alterações clínicas, com foco primário na saúde óssea e, secundariamente, na (dis)função renal.

CAPÍTULO I. ASSOCIAÇÃO ENTRE EXPOSIÇÃO AMBIENTAL AO CÁDMIO E O RISCO DE OSTEOPOROSE EM MULHERES PÓS-MENOPÁUSICAS: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

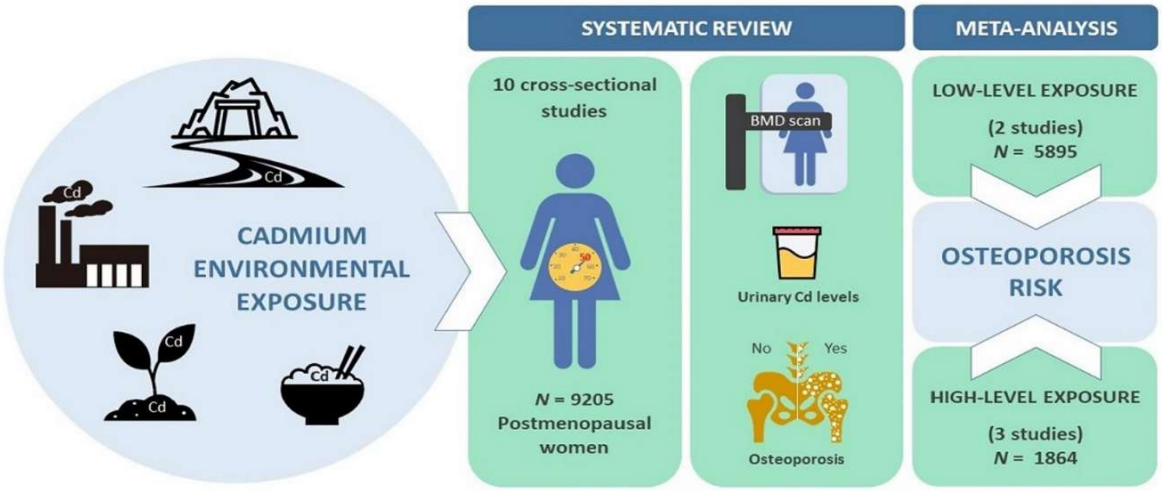
Este capítulo apresenta uma revisão sistemática com meta-análise, com o objetivo de sintetizar a evidência existente sobre a associação entre a exposição ambiental ao Cd e a DMO, bem como o risco osteoporose em mulheres pós-menopáusicas.

O conteúdo deste capítulo corresponde, na íntegra, ao artigo científico que se apresenta abaixo, na sua forma final publicada em revista.

Kunioka, C. T., Manso, M. C., & Carvalho, M. (2022). Association between Environmental Cadmium Exposure and Osteoporosis Risk in Postmenopausal Women: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, *20*(1), 485. https://doi.org/10.3390/ijerph20010485

Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

Graphical Abstract



Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

International Journal of *Environmental Research and Public Health*

MDPI

Review

Association between Environmental Cadmium Exposure and Osteoporosis Risk in Postmenopausal Women: A Systematic Review and Meta-Analysis

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Abstract: Osteoporosis is a common and serious health issue among postmenopausal women. We conducted a systematic review and meta-analysis study to determine whether environmental exposure to cadmium (Cd) is a risk factor for postmenopausal osteoporosis. A PROSPERO-registered review of the literature was performed on studies evaluating the relationship between urinary Cd (UCd) concentration, an indicator of long-term Cd exposure, and bone mineral density or osteoporosis in women aged 50 years and older. PubMed, Embase, Science Direct, Web of Science, and B-on databases were searched for articles published between 2008 and 2021. The association between UCd levels and osteoporosis risk was assessed by pooled odds ratio (OR) and 95% confidence interval (CI) using random-effect models. Ten cross-sectional studies were included in the qualitative analysis, of which five were used for meta-analysis. We separately assessed the risk of osteoporosis in women exposed to Cd at low environmental levels (n = 5895; UCd $\geq$ 0.5 μg/g creatinine versus UCd < 0.5 μg/g creatinine) and high environmental levels (n = 1864; UCd $\geq$ 5 μg/g creatinine versus UCd < 5 μg/g creatinine). The pooled OR for postmenopausal osteoporosis was 1.95 (95% CI: 1.39–2.73, $p < 0.001$) in the low exposure level group and 1.99 (95% CI: 1.04–3.82, $p = 0.040$) in the high exposure level group. This study indicates that environmental Cd exposure, even at low levels, may be a risk factor for osteoporosis in postmenopausal women. Further research based on prospective studies is needed to validate these findings.

Keywords: environmental cadmium; bone density; osteoporosis; risk factor; menopause; women; meta-analysis

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1. Introduction

Osteoporosis is a global disease that has an important impact on the health and economy of countries [1,2]. It is estimated that more than 500 million people worldwide suffer from osteoporosis [3], and the disease's incidence is rising as the population ages and lifestyle habits change [4,5]. This bone disorder is characterized by a decreased bone mineral density (BMD) and deterioration of skeletal microarchitecture, predisposing to low-impact, fragility fractures [6]. Osteoporotic fractures have a significant negative impact on patient's quality of life, as well as increased morbidity, mortality, and disability [1,7], resulting in enormous healthcare costs [8,9]. Certain risk factors associated with the development of osteoporosis and associated fractures have been identified, including non-modifiable ones such as advanced age, female gender, menopause, genetics, and modifiable ones such as

Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

excessive alcohol intake, smoking, low physical activity, underweight, and chronic use of glucocorticoids [10–12]. Human exposure to heavy metals, such as cadmium (Cd), has also been shown to affect bone metabolism, predisposing to an increased prevalence of osteoporosis [13,14]. As the global burden of osteoporosis grows, it is critical to identify risk factors linked to the loss of bone mass, particularly those that can be avoided, such as Cd exposure, thus helping to control the incidence of this complex condition.

Cd is a naturally occurring heavy metal, but human exposure to it is increased by anthropogenic activity [15]. One of the primary sources of Cd pollution is industrial activity. Cd can be found in landfills from smelters, iron and steel plants, electroplating, and battery manufacturing industries, whereas mining is a common source of Cd in water [16]. Additionally, the use of Cd-containing fertilizers is of particular concern due to metal uptake from soil and bioaccumulation by crops [17]. Excessive amounts of Cd have been shown to enter the food chain system and the general population is primarily exposed to Cd through contaminated food (mostly cereals and leafy vegetables) and water [18]. Additionally, Cd can enter the human body via other sources, including tobacco smoking (because tobacco plants absorb Cd from the soil and concentrate it in the leaves) and occupational exposure to Cd fumes or dust in the workplace [19].

Several adverse health effects of Cd exposure have been reported including renal dysfunction, lung and cardiovascular diseases, bone disorders, and cancers [19–21]. Kidneys and bones are the primary target organs of Cd toxicity in chronic, low-level Cd exposure patterns that are more common in the general population. Cd accumulates in the kidneys, mainly in the proximal tubular epithelial cells, and high levels cause renal injury [19,22]. Because of its low clearance rate, Cd has an exceptionally long half-life of 10–30 years. The toxic effect of high-level Cd exposure on bone became evident with the outbreak of Itai-Itai disease in Japan in the 1950s [19]. Several subsequent population-based studies have shown that Cd exposure, even at low environmental levels, may result in decreased bone mass and an increased risk of osteoporosis and bone fractures [14,23,24], though some studies reported no or a weak association between low-level Cd exposure and bone disorders [25–27].

To date, previous meta-analysis studies have only investigated the relationship between Cd exposure and bone disorders (osteopenia, osteoporosis [28,29], and any fracture [30]) in the general population. However, women are more likely than men to suffer from osteoporosis and associated fractures [2], which worsens with the onset of menopause [12]. As a result, postmenopausal women are a more relevant population to study this association. Herein, we performed a systematic review and meta-analysis study to (1) summarize the evidence on the relationship between environmental exposure to Cd and BMD or osteoporosis in the postmenopausal women population, and (2) determine whether environmental Cd exposure is a risk factor for postmenopausal osteoporosis.

2. Methods

2.1. Literature Search

This literature review was registered in PROSPERO (CRD42021241377) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]. Databases of PubMed, Embase, Science Direct, Web of Science and B-on were systematically searched for relevant studies published between January 2008 and December 2021 using the search terms: (cadmium AND women AND bone density AND environmental exposure). Grey literature was searched using Google Scholar and the OpenGrey online database. To find additional relevant studies, a manual search of all references of the included studies was also performed. A detailed PubMed search strategy is provided in Supplementary Table S1.

2.2. Study Selection and Data Extraction

Duplicates were found and removed from the initial search results. Two authors (C.T.K. and M.C.) independently reviewed the titles and abstracts of all studies to screen

for eligibility. The inclusion criteria were as follows: (1) observational studies; (2) studies including women aged 50 years and older; (3) studies that provided information on the relationship between UCd levels and BMD and/or osteoporosis risk; (4) papers published in the English language. The exclusion criteria were as follows: (1) review articles, brief communications, or case reports; (2) studies based on data from populations occupationally exposed to Cd; (3) articles that only reported findings on men or did not allow to separate results in men and women; and (4) in vitro or laboratory studies. Any disagreement about the inclusion and exclusion of studies was resolved by a third author (M.C.M.). For the meta-analysis, retrieved eligible studies that reported UCd levels and prevalence of osteoporosis in women aged $\geq$ 50 years were included. Urinary levels of Cd were used as a measure of cumulative long-term exposure to this metal [32] and osteoporosis was defined based on the WHO criteria of a T score of -2.5 or lower [33].

All authors independently reviewed the full text of the articles for the final study collection based on the inclusion criteria. If more than one paper based on the same dataset was published, the most recent paper or the one with the best outcome assessment was included. When required, the authors of the original studies were contacted to obtain additional data.

The data extracted from each study included first author's last name, publication year, country and design of the study, sample size, age, smoking status, UCd measurement method, urine sample type, UCd levels, BMD measurement technique and body region examined, BMD levels, osteoporosis prevalence, adjusted variables, and relevant study findings.

2.3. Assessment of Methodological Quality

Two reviewers (C.T.K. and M.C.) independently assessed the quality of the included studies using the Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies [34], which assesses study quality based on eight criteria, including bias, confounding, the validity of exposure and outcome measurement, and the validity of methods of analyses. Each item was labeled as "yes", "no" or "unclear". A third reviewer resolved any disagreements (M.C.M.). The final score of each article was calculated based on the percentage of positive answers ('yes'), with scores greater than 70% indicating a 'low' risk of bias, scores ranging from 50% to 69% indicating a 'moderate' risk of bias, and scores less than 49% indicating a 'high' risk of bias.

2.4. Statistical Analysis

A random-effects model was used for the meta-analysis. Odds ratio (OR) with a 95% confidence interval (CI) was estimated for each study and used to assess the strength of the association between UCd levels and osteoporosis risk. The significance of the pooled OR was determined by the Chi-square test. Heterogeneity between the studies was assessed by a Chi-square-based Q-test and I^2 statistics and was considered significant if the p-value for the Q-test was <0.10 or $I^2 > 50\%$ [35]. Heterogeneity can be quantified as "low", "moderate", and "high", with upper limits of 25%, 50% and 75% for I^2, respectively. The Begg's funnel plot and the Egger's test were used to evaluate publication bias. Forest plot was used to show the effect measures of each included study and the pooled effect measures. All statistical analyses were performed using IBM® SPSS© Statistics vs.28.0 (IBM Corp. released 2021, Armonk, NY, USA). Unless indicated otherwise, all statistical tests were considered significant at $p < 0.05$.

3. Results

3.1. Study Selection

Figure 1 depicts the PRISMA flowchart used for the selection process. The initial database search retrieved 192 articles, with 122 remaining after duplicates were removed. Studies were then eliminated based on their title and/or abstract. The full texts of the remaining 58 publications were carefully reviewed and selected according to the inclusion

and exclusion criteria. Finally, ten articles that fulfilled the eligibility criteria were included in the present work for qualitative analysis and five for meta-analysis (Figure 1).

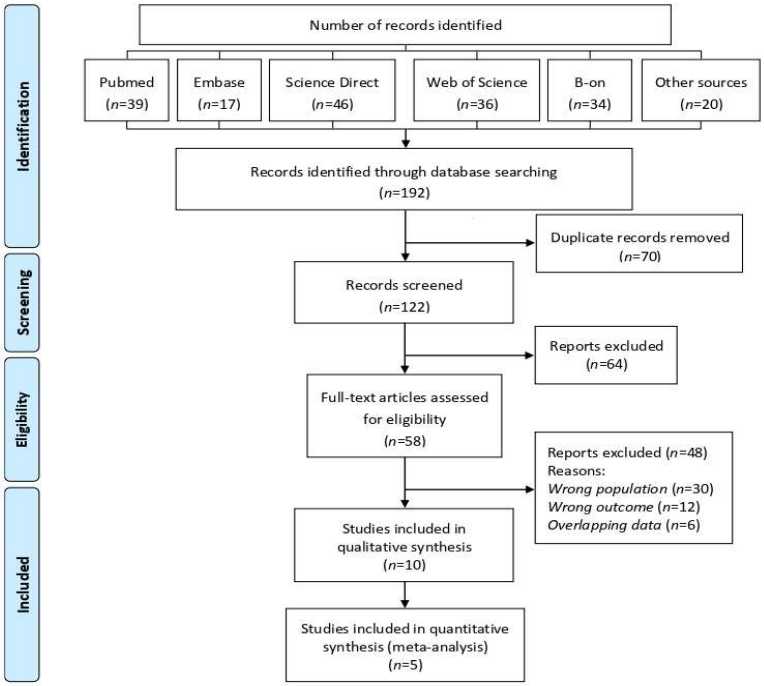

Figure 1. PRISMA flow diagram for the systematic review on the association between environmental exposure to cadmium and risk of osteoporosis in postmenopausal women.

3.2. Study Characteristics

General characteristics of the included studies are described in Table 1 and are summarized below. Additional data inspection and conversion were performed to unify the database. Due to data overlap in serial articles by Chen et al. [36–40], only the one most relevant to this study was included [39]. The authors of three original studies [18,23,39] kindly provided additional unpublished data.

Ten studies published from 2008 to 2021 and a total of 9205 women were included in the systematic review. Three studies were conducted in Sweden [41–43], two in China [23,39], one in Japan [25], one in South Korea [26], one in the USA [44], one in Australia [14], and one in Thailand [18]. All studies had a cross-sectional design. The women's ages ranged from 50 to 90 years and non-smokers outnumbered smokers in all studies. Cd concentrations in urine samples were determined using atomic absorption spectrometry (AAS) in five studies [18,25,26,39,44] or inductively coupled plasma mass spectrometry (ICP-MS) in the other five [14,23,41–43]. UCd values were adjusted to the urine creatinine concentrations and ranged from less than 0.065 up to 16.17 μg/g creatinine. Dual-energy X-ray absorptiometry (DXA) is the gold standard for measuring BMD [12] and was used in all studies except one, which used ultrasound bone densitometry (USBD) [26]. The skeletal sites for BMD measurements differed between studies and included the forearm in three [23,25,39]; the wrist in two [42,43]; the calcaneus in two [18,26]; the hip in three [14,41,44]; and the proximal femur and lumbar spine in two [14,41].

Table 1. Characteristics of studies included in the systematic review and meta-analysis evaluating the effects of environmental cadmium exposure on bone mineral density or osteoporosis in women aged 50 and older from 2008 to 2021.

Study	Country/Study Design	Sample Size	Age (Years)/ Menopausal Status	Smoking Status	UCd Measurement Method/Sample Type	UCd (μg/g Creatinine)	BMD Measurement Technique/ Location	BMD (g/cm²)	Prevalence of Osteoporosis (%)	Adjusted Variables	Relevant Findings
Gallagher et al., 2008 [a] [44]	USA/Cross-sectional	n = 3207 (UCd < 0.5, n = 870; UCd 0.5–1.0, n = 1201; UCd > 1.0, n = 1136)	67 (50–90)/ Not specified	Never: 61%, Ever: 39%	AAS/ Spot urine	0.96 (0.007–16.17)	DXA/Hip	Not specified	UCd < 0.5: 14.6%; UCd 0.5–1.0: 21.4%; UCd > 1.0: 24.0%	Age, race, income, underweight, and smoking status	UCd was significantly associated with a greater risk for osteoporosis at levels ≤1.0 μg/g creatinine.
Engstrom et al., 2009 [42]	Sweden/Cross-sectional	n = 85 (Low UCd, n = 45); High UCd, n = 40)	58 (54–63)/ Post-menopausal: 100%	Low UCd: Never: 76%, Ever: 24% High UCd: Never: 30%, Ever: 70%	ICP-MS/ Not specified	Low UCd: 0.36 (0.18–0.73); High UCd: 1.1 (0.69–1.7)	DXA/Wrist	Low UCd: 0.45 (0.35–0.53); High UCd: 0.43 (0.31–0.54)	Not determined	No	BMD was significantly lower in the high-level Cd exposure group.
Horiguchi et al., 2010 [25]	Japan/Cross-sectional	n = 252 (Control area, n = 123; Polluted area, n = 129)	Control area, 54.8 ± 7.9 Polluted area, 56.6 ± 8.1/ Perimenopausal: 30.5%; Post-menopausal 49.6%	Never: 100%	Flameless AAS/ Spot urine	Control area: 3.36 ± 1.86; Polluted area: 6.30 ± 1.98	DXA/Forearm	Control area: 0.431 ± 0.078; Polluted area: 0.423 ± 0.090	Not determined	No	BMD was not statistically different between control and Cd-polluted areas.
Suwazono et al., 2010 [43]	Sweden/Cross-sectional	n = 794	58 (54–63)/ Postmenopausal: 46%	Never: 55%, Former: 23%, Current: 22%	ICP-MS/Morning urine	0.67 (0.31–1.57)	DXA/Wrist	0.44 (0.33–0.54)	7.7%	Age, weight, menopausal status or HRT use, and sampling season	UCd was significantly and inversely associated with T-score.

Table 1. *Cont.*

Study	Country/Study Design	Sample Size	Age (Years)/ Menopausal Status	Smoking Status	UCd Measurement Method/Sample Type	UCd (μg/g Creatinine)	BMD Measurement Technique/ Location	BMD (g/cm²)	Prevalence of Osteoporosis (%)	Adjusted Variables	Relevant Findings
Chen et al., 2011 # [39]	China/Cross-sectional	*n* = 238 (Control area, *n* = 61; Moderate polluted area, *n* = 80; Heavy polluted area, *n* = 97)	Control area: 50–86, Moderate polluted area: 50–83, Heavy polluted area: 50–82/ Not specified	Non-smoker: 100%	GF-AAS/ Not specified	Control area: 3.1 ± 2.3; Moderate polluted area: 5.2 ± 3.5; Heavy polluted area: 11.7 ± 7.7	DXA/Forearm	Control area: 0.68 ± 0.01; Moderate polluted area: 0.64 ± 0.008; Heavy polluted area: 0.60 ± 0.007	Control area: 42.6%; Moderate polluted area: 31.2%; Heavy polluted area: 64.9%	Age	BMD was significantly lower in the moderate and high Cd-exposure groups.
Engstrom et al., 2011 [a] [41]	Sweden/Cross-sectional	*n* = 2688 (UCd < 0.50, *n* = 2067; UCd 0.50–0.75, *n* = 449; UCd ≥ 0.75, *n* = 172)	56–69, UCd < 0.50, 63 (60–69); UCd 0.50–0.75, 64 (60–69); UCd ≥ 0.75, 63 (60–69)/ Post-menopausal: 100%	UCd < 0.50, Non-smoker: 47%; UCd 0.50–0.75, Non-smoker: 74%; UCd ≥ 0.75, Non-smoker: 81%	ICP-MS/ Morning urine	UCd < 0.50: 0.30 (0.14–0.47); UCd 0.50–0.75: 0.59 (0.51–0.72); UCd ≥ 0.75: 0.87 (0.76–1.5)	DXA/ Femoral neck; Total hip and Lumbar spine (data not shown)	UCd < 0.5 μg/g: 0.89 (0.73–1.1) UCd 0.50–0.75 μg/g: 0.88 (0.69–1.1) UCd ≥ 0.75 μg/g: 0.85 (0.67–1.1)	UCd < 0.50 μg/g: 6.5%; UCd 0.5–0.75 μg/g: 13%; UCd ≥ 0.75 μg/g: 17%	Age, education, height, total fat mass, lean body mass, parity, HRT, corticosteroids use, physical activity, smoking status, alcohol intake, inflammatory joint diseases, kidney diseases, liver diseases, and malabsorption	UCd was inversely associated with BMD at the femoral neck and total hip. There was a statistically significant dose-dependent increase in osteoporosis risk across UCd groups. These associations were independent of tobacco smoking.
Kim et al., 2014 [a] [26]	Korea/Cross-sectional	*n* = 630 (UCd < 5, *n* = 501; UCd > 5, *n* = 129)	65.2 ± 10.9/ Postmenopausal: 88%	Non-smoker: 94%, Smoker: 6%	Flameless AAS/ Morning urine	2.9 ± 1.9	Ultrasound bone densitometer/ Calcaneus	Not specified	UCd < 5: 45%; UCd > 5: 54%	Age, smoking status, alcohol intake, BMI, diabetes, hypertension, and menopause	A high Cd body burden did not significantly increase the risk of osteoporosis.

Table 1. *Cont.*

Study	Country/Study Design	Sample Size	Age (Years)/ Menopausal Status	Smoking Status	UCd Measurement Method/Sample Type	UCd (µg/g Creatinine)	BMD Measurement Technique/ Location	BMD (g/cm^2)	Prevalence of Osteoporosis (%)	Adjusted Variables	Relevant Findings
Callan et al., 2015 [14]	Australia/Cross-sectional	$n = 77$	59.6 ± 7.0 (50–83)/ Amenorrhea: 97%, Postmenopausal: 86%	Never: 65%, Former: 35%, Current: 0%, Smokers at household within last 6 months: 15%	ICP-MS/ Morning urine	0.26 (<0.065–1.03)	DXA/ Total hip; Femoral neck; Lumbar spine; Whole body	Total hip: 0.89 ± 0.14; Femoral neck: 0.76 ± 0.13; Lumbar spine: 0.99 ± 0.15; Whole body: 0.91 ± 0.10	Not determined	Age, years since last menstrual cycle, and BMI	An inverse relationship between UCd and BMD was discovered in all body regions studied. These associations were independent of tobacco smoking.
Lv et al., 2017 [a,#] [23]	China/Cross-sectional	$n = 444$ (Control area, $n = 118$; Polluted area, $n = 326$)	Control area: 60.5 ± 6.1; Polluted area: 59.2 ± 6.8/ Post-menopausal: 100%	Non-smoker: 98.7%, Smoker: 1.3%	ICP-MS/ Morning urine	Control area: 1.92 (1.37–2.73); Polluted area: 7.20 (3.79–14.78)	DXA/ Forearm	Control area: 0.355 ± 0.078; Polluted area: 0.339 ± 0.083	UCd 0–2: 17.5%; UCd 2–5: 35.0%; UCd 5–10: 42.9%; UCd 10–20: 51.9%; UCd 20–40: 55.9%; UCd > 40: 75.0%	Age, BMI, serum albumin, smoking status, and urinary levels of calcium, NAG, α1-microglobulin, β2-microglobulin, and albumin	The prevalence of osteoporosis increased as UCd concentrations increased.
La-Up et al. 2021 [a,#] [18]	Thailand/Cross-sectional	$n = 790$ (UCd < 2, $n = 230$; UCd 2–4.9, $n = 338$; UCd 5–9.9, $n = 184$; UCd ≥ 10, $n = 38$)	59.9 ± 7.1/ Postmenopausal: 91%	Never: 75.8%, Former: 10.6%, Current: 9.6%	AAS/ Morning urine	3.98 ± 3.15	DXA/ Calcaneus	UCd < 2: 0.40 ± 0.07; UCd 2–4.9: 0.37 ± 0.07; UCd 5–9.9: 0.36 ± 0.08; UCd ≥ 10: 0.35 ± 0.09	UCd < 2: 13.0%; UCd 2–4.9: 26.9%; UCd 5–9.9: 34.8%; UCd ≥ 10: 47.4%	Age, BMI, and smoking status	There was a negative relationship between UCd and BMD and a positive association between UCd ≥ 10 µg/g creatinine and the prevalence of osteoporosis.

Notes: Data is presented as mean ± standard deviation or median (5th–95th percentile); [a] study included in meta-analysis; [#] data provided by authors considering only women aged 50 and older; Abbreviations: AAS, atomic absorption spectrometry; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; GF-AAS, graphite-furnace atomic absorption spectrometry; HRT, hormone replacement therapy; ICP-MS, inductively coupled plasma mass spectrometry; NAG, N-acetyl-β-D-glucosaminidase; OR, odds ratio; UCd, urinary cadmium.

Six studies provided data on the relationship between UCd levels and osteoporosis prevalence [18,23,26,39,41,44], but only five with a total of 7759 women provided UCd stratified data that allowed for comparisons between studies and thus were included in the meta-analysis. There were clear differences in UCd concentrations between studies, with North America [44] and Europe [41] presenting lower UCd concentrations than Asian countries, including China [23,39], South Korea [26], and Thailand [18]. As a result, these studies were divided into two groups for further statistical analysis based on reported UCd levels: the low-level Cd exposure group (with a cut-off value of 0.5 μg/g creatinine) comprising the studies conducted in the USA and Europe with a total of 5895 women; and the high-level Cd exposure group (with a cut-off-value of 5 μg/g creatinine) comprising three studies conducted in Asian countries with a total of 1864 women. Because everyone in the population is exposed to Cd through food, a reference group with no exposure cannot be defined; thus, two exposure categories were used for the low-level (UCd $\geq$ 0.5 μg/g creatinine versus UCd < 0.5 μg/g creatinine) and high-level (UCd $\geq$ 5 μg/g creatinine versus UCd < 5 μg/g creatinine) groups.

3.3. Study Quality Assessment

The quality assessment of the ten included articles was assessed through the JBI critical appraisal tool and showed that all studies were of high quality (Supplementary Table S2).

3.4. The Association between UCd Levels and BMD

Six of the ten studies included in the systematic review found an association between UCd concentrations and BMD. Among these, UCd levels were significantly inversely correlated with BMD in 5 studies [14,18,39,41,42], while no association between UCd and BMD was found in one [25] (Table 1).

3.5. The Association between UCd Level and Osteoporosis

Four of the five studies included in the meta-analysis found a statistically significant positive association between UCd levels and osteoporosis outcome [18,23,41,44], while one failed to find an association [26]. However, it must be noted that in our meta-analysis the latter study was borderline significant ($p = 0.05$). Because of the above-mentioned heterogeneity in UCd concentrations across studies, the meta-analysis separately assessed the risk of osteoporosis in low- and high-level exposure groups, and the corresponding forest plots are shown in Figure 2A,B, respectively. The OR for osteoporosis in postmenopausal women whose UCd level was higher than 0.5 μg/g creatinine was 1.95 (95% CI: 1.39–2.73, $p < 0.001$) when compared to those with a UCd level less than 0.5 μg/g creatinine. The OR for osteoporosis in postmenopausal women with a UCd level higher than 5 μg/g creatinine was 1.99 (95% CI: 1.04–3.82, $p = 0.040$) when compared to those with a urinary Cd level less than 5 μg/g creatinine. The heterogeneity between studies was high in the high-level exposure group ($I^2 = 72\%$, $p = 0.06$) but moderate in the low-level exposure group ($I^2 = 45\%$, $p = 0.16$).

3.6. Publication Bias

There was no evidence of publication bias for the studies included in meta-analysis as illustrated by the symmetrical distribution of funnel plot tests (Figure 3A,B, respectively). In addition, the Egger's test also shows no publication bias ($p = 0.17$) for the studies included in the high-level exposure group (Supplementary Table S3). Because only two studies were included in the low-level exposure group, Egger's test could not be performed.

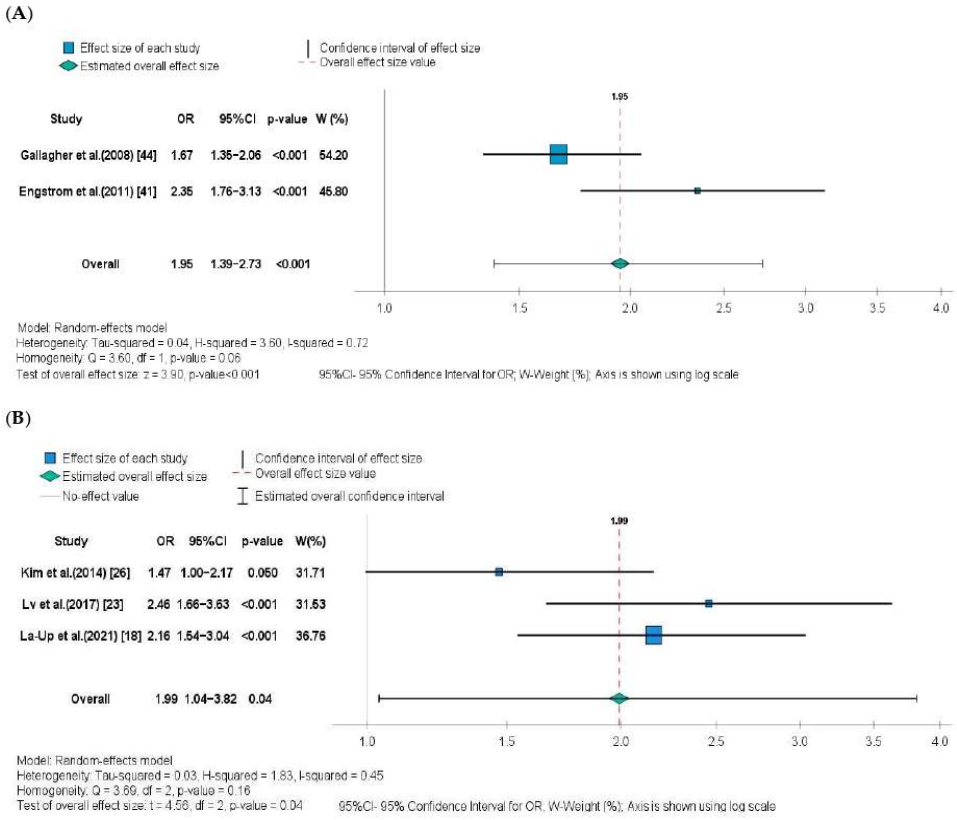

Figure 2. Forest plot and pooled effect estimates of the association between UCd levels and risk of osteoporosis in the (**A**) low-level Cd exposure group [41,44], and (**B**) high-level Cd exposure group [18,23,26].

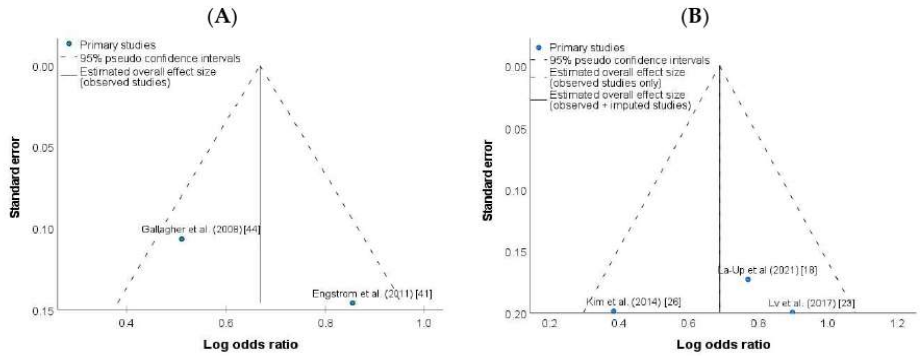

Figure 3. Funnel plot of studies investigating the association between UCd levels and risk of osteoporosis in the (**A**) low-level Cd exposure group [41,44], and (**B**) high-level Cd exposure group [18,23,26].

4. Discussion

The present study retrieved worldwide studies reporting the relationship between UCd concentrations and BMD or osteoporosis in postmenopausal women and conducted a meta-analysis of the original data to explore the association between environmental Cd exposure and risk of osteoporosis. To the best of our knowledge, this is the first global systematic study investigating whether environmental exposure to Cd is a risk factor for postmenopausal osteoporosis. Women in our study were at least 50 years old, which is the median age of natural menopause onset [45,46], and more than 90% of those included in the meta-analysis had confirmed postmenopausal status (Table 1). Women also had no known history of occupational Cd exposure, ensuring that the environment was the only source of Cd exposure. Furthermore, because tobacco use increases the body's burden to Cd and is also a risk factor for osteoporosis [47], postmenopausal women were largely non-smokers (61 to 99%) to preclude any smoking-related impact of Cd exposure. In this regard, it is worth noting that smoking has been shown to have no effect on the relationship between UCd and BMD or osteoporosis [14,43,44].

Based on the inclusion criteria, ten studies with a total of 9205 women were included in this systematic review. Study quality was not considered to be a potential source of heterogeneity, as all studies were of high quality. The studies were conducted in different geographical regions, including East Asian countries such as China [23,39], Japan [25], South Korea [26], Western Europe, primarily Sweden [41–43], and North America [44]. According to the reported data, the studies reflected two distinct exposure scenarios. Postmenopausal women in Asian countries had approximately ten times higher UCd values than women in Europe or the United States, indicating that they were exposed to higher environmental levels of Cd. This is consistent with the fact that many areas in East Asian countries, such as China, are heavily polluted by Cd. Indeed, the Chinese agricultural soil and water resources are contaminated by Cd from industrial activities, mining, smelting, intensive use of Cd-containing fertilizers, and a high geological background of Cd [48,49], which is taken up by crops and vegetables and enters the human body through the food chain. Therefore, the observed disparity in UCd levels can be attributed to differences in dietary Cd exposure, as ingestion of contaminated food is the main source of Cd exposure in the non-smoking population. In line with this, food analysis revealed that Asian food products (primarily rice) contain higher levels of Cd than European or North American food [50,51].

Our systematic review supports the notion that higher UCd levels are associated with lower bone density in postmenopausal women, since only one study [26] failed to show an association (Table 1). Furthermore, the results of the meta-analysis showed that increased urinary levels of Cd were associated with increased risk of postmenopausal osteoporosis. Indeed, postmenopausal women with a low-level environmental exposure to Cd had a 95% increased risk of osteoporosis, whereas those with a high-level environmental exposure had a 99% increased risk, when compared with the respective reference groups with lower UCd levels. These results show that the risk of osteoporosis in the high-level exposure group was comparable to that in the low-level exposure group, though previous research using UCd stratified levels has found a dose-dependent increase in osteoporosis risk [23,41]. This discrepancy is likely related to the diverse populations (Caucasian versus Asian) included in our study that may have been influenced by genetic factors. In any case, a major finding in this study was that Cd exposure affects bone mass and increases the risk of osteoporosis even at low environmental levels.

The biological mechanisms by which Cd exerts its toxic effect on bone structure are complex and have not been fully elucidated yet. Osteoporosis caused by Cd may be associated with Cd-induced kidney damage by decreasing renal tubular reabsorption and increasing the urinary excretion of elements such as calcium and phosphorus, which are critical for maintaining bone metabolism and health [52]. Cd also decreases vitamin D [1,25(OH)2D] synthesis in kidneys, reducing the uptake of calcium in the gastrointestinal tract [53]. In addition, current evidence supports that Cd has a direct osteotoxic effect that

can occur independently of renal dysfunction [54]. Bone tissue homeostasis is maintained by a balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. An imbalance in bone remodeling leads to bone loss and osteoporosis [55]. Cd has been shown to directly disrupt the differentiation and metabolism of osteoblasts and their precursors, stimulate osteoclasts formation and activity, interfere with the production of bone collagen, and accelerate bone remodeling [13,52,56–60]. The mechanisms underlying the detrimental effects of Cd on bone metabolism are not completely understood, but they are likely to include cellular senescence, oxidative stress, DNA damage, mitochondrial dysfunction, apoptosis, and autophagy [61–66]. At the molecular level, Wu et al. [60] demonstrated that Cd suppresses osteogenic differentiation of bone marrow mesenchymal stem cells by inhibiting the canonical Wingless-related integration site (Wnt)/β-catenin pathway, which is known to play a crucial role in bone development and homeostasis, specially by modulating progenitor cells proliferation and differentiation [55]. Another master signaling pathway that regulates bone tissue metabolism is the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [66]. Activation of the PI3K/Akt pathway has been shown to stimulate osteoblast proliferation and differentiation while also influencing osteoclast formation. Importantly, recent research by Ma et al. [56,65] has highlighted the role of the PI3K/Akt pathway in Cd-induced osteoporosis. The authors demonstrated in animal models and in vitro that Cd causes osteoporosis by suppressing PI3K/Akt-mediated osteoblast and osteoclast differentiation. Other signaling pathways, however, may be involved in Cd-induced osteoporosis, which requires further investigation.

Women are at greater risk of developing Cd toxicity than men [26,40], especially after menopause. Because Cd absorption in the intestine is primarily mediated by the ferrous iron transporter [67], uptake of this metal is increased prior to menopause due to the low iron stores commonly observed in women of childbearing age. As women's iron requirements decrease during menopause, so will their absorption of dietary Cd. However, because this coincides with the peak of renal Cd, health effects from exposure may occur at this time [68]. Estrogen depletion caused by menopause might be an important factor influencing the bone effects of Cd in women. Moreover, the presence of Cd may accelerate bone loss and cause osteoporosis together with other cofactors. Therefore, Cd exposure may be a major risk factor for this population group. In this regard, some studies were already conducted to provide a reference for risk assessment of Cd exposure in the female population. Suwazono et al. (2010) estimated benchmark dose of UCd for osteoporosis in a Swedish female population aged 53–64 years to be 1.8 and 2.9 μg/g creatinine, with their 95% lower confidence limits (BMDL) of 1.0 and 1.6 μg/g creatinine, for benchmark responses of 5% and 10%, respectively [43]. A similar study performed by Chen et al. (2013) based on a Chinese female population aged 40–86 years showed that the benchmark dose of UCd concentration related to osteoporosis was 5.30 and 9.06 μg/g creatinine and BMDL of 3.78 and 6.36 μg/g creatinine, respectively, for the same benchmark responses [69], which was much higher than those reported in the Swedish population. However, in a more recent study by Lv et al. (2017) [23], also conducted in a Chinese postmenopausal female population, the calculated benchmark dose of 0.64 and 1.77 μg/g creatinine and BMDL of 0.17 and 0.76 μg/g creatinine were much lower than those in both previous studies. Importantly, the benchmark dose for a 5% additional risk of osteoporosis was 0.64 μg/g creatinine which is consistent with the UCd cut-off value of 0.5 μg/g creatinine used in the present study for the low-level exposure group. Nonetheless, because of the significant differences in benchmark doses among the populations studied, more research in this area is mandatory.

Overall, the present study provides novel insights into the association between environmental Cd exposure and osteoporosis risk in postmenopausal women; however, it has significant limitations that must be recognized. First, there were a small number of studies that met our meta-analysis inclusion criteria, which could imply that the observed significant relationship between Cd exposure and osteoporosis is not sufficiently robust. Second, the cross-sectional design of the included studies precludes any inference of causal-

ity. However, it should be noted at this point that UCd is a biomarker of long-term Cd exposure, indicating accumulation in the body over years prior to BMD assessment. Third, the studies included in this systematic review may be affected by heterogeneity among methodologies and detection sites of BMD measurements, population genetic characteristics, among other factors. Finally, the heterogeneity of confounder adjustment strategies of the included studies may lead to additional bias for pooled effect size in meta-analyses. Therefore, our findings should be interpreted with caution, and further confirmation using large, high-quality prospective studies are required. In this regard, a prospective study published this year (after the end of our data collection period) in a cohort of Swedish postmenopausal women found that long-term exposure to very low levels of environmental Cd (median UCd concentrations of 0.33 μg/g creatinine) increased the risk of fractures, supporting our findings that environmental Cd exposure is a risk factor for bone damage even at low levels.

Finally, it must be noted that Cd accumulates gradually in the human body and, therefore, preventive strategies to reduce the environmental exposure to Cd and the associated burden of disease must be implemented early in life. In line with this, Chen [36] and Horiguchi [25] revealed that UCd levels remained high in residents of formerly polluted areas even after exposure was discontinued for more than ten years, implying that adverse effects continue even after exposure has stopped. Hence, Cd pollution control measures must be immediately strengthened if this risk factor is to be reduced for future generations.

5. Conclusions

The present study adds support to the evidence that environmental Cd exposure, even at low levels, is a risk factor for osteoporosis in postmenopausal women. However, further research with well-designed prospective studies is needed to validate this conclusion. Because this is a preventable risk factor, global environmental policy programs aimed specifically at reducing dietary Cd exposure have the potential to reduce the burden of postmenopausal osteoporosis in future generations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph20010485/s1. Table S1. PubMed search strategy; Table S2. Individual quality assessment of studies included in the systematic review using the Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies; Table S3. Egger's test of studies investigating the association between UCd levels and risk of osteoporosis in the high-level Cd exposure group.

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Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

Supplementary Materials

Association between environmental cadmium exposure and osteoporosis risk in postmenopausal women: a systematic review and meta-analysis

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Table S1. PubMed search strategy.

Database	Search strategy	Search results
PubMed	((("cadmium"[MeSH Terms] OR "cadmium"[All Fields]) AND ("womans"[All Fields] OR "women"[MeSH Terms] OR "women"[All Fields] OR "woman"[All Fields] OR "women s"[All Fields] OR "womens"[All Fields] OR ("womans"[All Fields] OR "women"[MeSH Terms] OR "women"[All Fields] OR "woman"[All Fields] OR "women s"[All Fields] OR "womens"[All Fields]) OR ("femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "females"[All Fields])) AND ("bone density"[MeSH Terms] OR ("bone"[All Fields] AND "density"[All Fields]) OR "bone density"[All Fields]) AND ("environmental exposure"[All Fields] OR ("environ"[All Fields] OR "environment"[MeSH Terms] OR "environment"[All Fields] OR "environments"[All Fields] OR "environment s"[All Fields] OR "environs"[All Fields])) AND 2008/01/01:2021/12/31[Date - Publication]) NOT (("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) AND ("animals"[MeSH Terms:noexp] OR "animal"[All Fields]))	44

Table S2. Individual quality assessment of studies included in the systematic review using the Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	%	Risk
Gallagher *et al.* 2008	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Engstrom *et al.* 2009	✓	✓	✓	✓	X	X	✓	✓	75	Low
Horiguchi *et al.* 2010	✓	✓	✓	✓	X	X	✓	✓	75	Low
Suwazono *et al.* 2010	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Chen *et al*. 2011	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Engstrom *et al.* 2011	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Kim *et al.* 2014	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Callan *et al.* 2015	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
Lv *et al.* 2017	✓	✓	✓	✓	✓	✓	✓	✓	100	Low
La-Up *et al.* 2021	✓	✓	✓	✓	✓	✓	✓	✓	100	Low

Q1. Were the criteria for inclusion in the sample clearly defined?; Q2. Were the study subjects and the setting described in detail?; Q3. Was the exposure measured in a valid and reliable way?; Q4. Were objective, standard criteria used for measurement of the condition?; Q5. Were confounding factors identified?; Q6. Were strategies to deal with confounding factors stated?; Q7. Were the outcomes measured in a valid and reliable way?; Q8. Was appropriate statistical analysis used?

'✓' indicates yes, and '✕' indicates no

Table S3. Egger´s test of studies investigating the association between UCd levels and risk of osteoporosis in the high-level Cd exposure group.

Egger's Regression-Based Test[a]

					95% Confidence Interval	
Parameter	Coefficient	Std. Error	t	Sig. (2-tailed)	Lower	Upper
SE[b]	-4.430	16.3412	-0.271	0.831	-212.065	203.204
Bias	0.001	0.0015	0.692	0.166	-0.019	0.020

[a] Random-effects meta-regression
[b] Standard error of effect size

CAPÍTULO II. EXPOSIÇÃO AMBIENTAL A NÍVEIS BAIXOS DE CÁDMIO E SEUS EFEITOS NA SAÚDE RENAL E ÓSSEA EM MULHERES BRASILEIRAS PÓS-MENOPÁUSICAS: UM ESTUDO TRANSVERSAL

Este capítulo apresenta um estudo transversal realizado com o objetivo de investigar os efeitos da exposição ambiental a baixos níveis de Cd na saúde renal e óssea de mulheres brasileiras pós-menopáusicas residentes numa região agrícola.

O conteúdo deste capítulo corresponde, na íntegra, ao artigo científico que se apresenta abaixo, na sua forma final publicada em revista.

Kunioka, C.T., Cruz, J. C., de Oliveira Souza, V. C., Rocha, B. A., Barbosa Jr, F., Belo, L., Manso, M. C., & Carvalho, M. (2025). Low-Level Environmental Cadmium Exposure and Its Effects on Renal and Bone Health in Brazilian Postmenopausal Women: A Cross-Sectional Study. *Exposure and Health*. https://doi.org/10.1007/s12403-025-00715-2

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ORIGINAL PAPER

Low-Level Environmental Cadmium Exposure and Its Effects on Renal and Bone Health in Brazilian Postmenopausal Women: A Cross-Sectional Study

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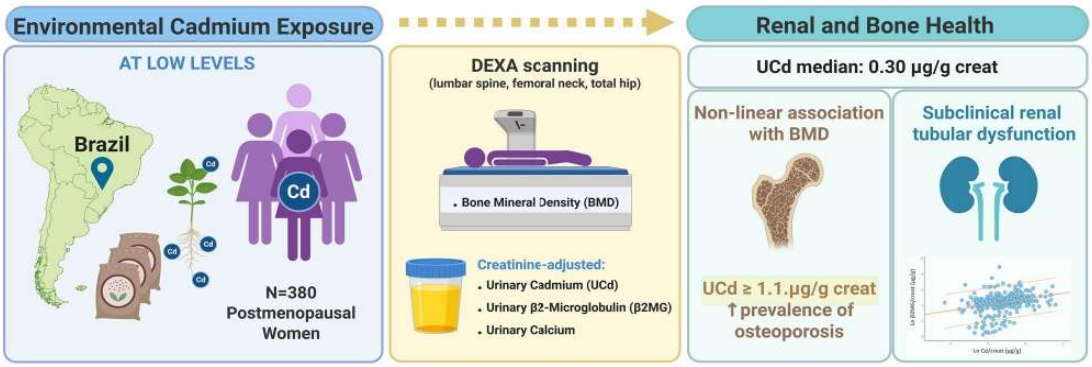
Abstract

This study aimed to investigate the long-term effects of low-level, chronic exposure to cadmium (Cd) on renal and bone health. A cross-sectional study was conducted on postmenopausal women ($n = 380$) from Cascavel, Brazil, an agricultural region where the use of Cd-containing fertilizers may exacerbate environmental contamination. Demographic and clinical data were collected, and cumulative Cd exposure was assessed through urinary Cd (UCd) concentrations using inductively coupled plasma mass spectrometry (ICP-MS). Renal tubular function was evaluated by measuring urinary β2-microglobulin, and bone mineral density (BMD) at the lumbar spine, femoral neck, and total hip was assessed using dual-energy X-ray absorptiometry. Median UCd concentrations confirmed low exposure (0.30 µg/g creatinine; interquartile range: 0.15–0.55). Univariate analysis revealed a borderline association between higher UCd concentrations and lower BMD at the femoral neck across normal, osteopenic, and osteoporotic groups ($p = 0.067$). Multiple linear regression analysis showed that UCd was not independently associated with reduced BMD but was a significant predictor of renal tubular damage ($p < 0.001$). These findings underscore a pressing environmental and public health issue: even low levels of Cd exposure correlate with subclinical renal tubular dysfunction. Enhanced monitoring and stricter environmental regulations are critical to prevent long-term kidney damage and related health risks, especially in vulnerable populations.

Graphical Abstract



Keywords Cadmium · Environmental exposure · Bone mineral density · β2-microglobulin · Postmenopausal women

Extended author information available on the last page of the article

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Introduction

Cadmium (Cd), a hazardous heavy metal and pervasive environmental pollutant, represents a growing threat to public health worldwide. While naturally present in the earth's crust, its environmental dissemination is predominantly driven by industrial emissions, improper waste disposal, and phosphate fertilizer use. These activities result in the contamination of soil, water, and agricultural products, ultimately leading to bioaccumulation in plants and grains (Clemens and Ma 2016). For non-smokers, the primary route of Cd exposure is through dietary intake of contaminated food (Schaefer et al. 2020). This issue is becoming increasingly critical as global food production intensifies to meet the demands of a growing population. The reliance on phosphate fertilizers, which often contain Cd, has risen significantly. Brazil, one of the world's leading agricultural producers, illustrates this trend with its substantial consumption of phosphate fertilizers to sustain high crop yields (Benício 2022). Alarmingly, the application of these fertilizers can elevate soil Cd concentrations by up to 87%, particularly in acidic soils, where the metal's bioavailability is enhanced, increasing its uptake into the food chain (Shen et al. 2020). Therefore, it is critical to investigate the health effects of chronic, low-level dietary Cd exposure to deepen our understanding of its potential long-term impacts on human health.

The systemic toxicity of Cd has been recognized since the early twentieth century, particularly following the outbreak of Itai-Itai disease in Japan, a landmark event that drew widespread attention to its harmful effects on human health (Aoshima 2016). Since then, a growing body of evidence has established strong links between chronic Cd exposure and a range of adverse health outcomes, including carcinogenesis (Peana et al. 2022), cardiovascular diseases (Verzelloni et al. 2024), type 2 diabetes (Filippini et al. 2022), and irreversible damage to multiple organ systems, most notably the skeletal system (Kunioka et al. 2022; Ma et al. 2021) and the kidneys (Bautista et al. 2024; Doccioli et al. 2024).

The kidney is particularly vulnerable to Cd toxicity, with epidemiological studies consistently highlighting its susceptibility to tubular and glomerular damage (Satarug et al. 2020, 2010; Shen et al. 2020). However, the clinical implications of Cd-induced renal effects remain a subject of ongoing debate and have not been fully elucidated. Even low-level environmental exposure to Cd has become a significant public health concern due to its potential role in chronic kidney disease (CKD) development (Doccioli et al. 2024), a growing global health issue characterized by high morbidity and mortality (Levey et al. 2007). Cd primarily accumulates in renal proximal tubular cells through transport mechanisms involving DMT1, ZIP8, and metallothionein-mediated uptake, resulting in intracellular Cd overload (Fujishiro and Himeno 2019; Genchi et al. 2020). This accumulation induces oxidative stress by generating reactive oxygen species (ROS), impairing mitochondrial function, and promoting lipid peroxidation. ROS activate signaling pathways, including NF-κB and MAPKs, promoting inflammation, apoptosis, and autophagy dysregulation (Bautista et al. 2024; Prozialeck and Edwards 2012). Epigenetic modifications, including DNA methylation and histone acetylation changes, have also been linked to Cd's nephrotoxic effects, suggesting a role in long-term gene expression changes and disease progression (Qu and Zheng 2024).

Exposure to Cd has also been associated to bone-related disorders such as osteoporosis and osteomalacia (Ciosek et al. 2023; Kunioka et al. 2022). Osteoporosis is a common osteometabolic disorder characterized by decreased bone mass and deteriorated microarchitecture, leading to increased bone fragility and fracture susceptibility. These fractures result in significant morbidity, mortality, and socioeconomic burdens, which are expected to escalate with global population aging (Amin et al. 2023). Postmenopausal women face heightened vulnerability to osteoporotic fractures due to the combined impact of hormonal decline and age-related skeletal deterioration (Feng et al. 2024). Estrogen plays a pivotal role in bone homeostasis by suppressing osteoclast-mediated bone resorption and promoting osteoblast activity. Its abrupt decline during menopause disrupts this regulatory balance, leading to accelerated bone loss (Cheng et al. 2022; Emmanuelle et al. 2021). Simultaneously, aging contributes to diminished osteoblast function, reduced calcium absorption, and progressive microarchitectural degradation, compounding the risk of osteoporosis (Mi et al. 2024; Zhang et al. 2023). In addition to established risk factors such as advanced age, female sex, hormonal changes, smoking, low body mass index, nutritional deficiencies, chronic illnesses, and specific medications, emerging evidence highlights environmental exposure to Cd, even at low levels, as a potential exacerbating factor for bone demineralization, particularly in susceptible populations like postmenopausal women (Kunioka et al. 2022).

Cd has been shown to impair bone remodeling by directly inhibiting osteoblast differentiation and promoting osteoclast-mediated bone resorption. Molecular studies revealed that Cd disrupts Wnt/β-catenin signaling, critical for osteoblast activity, while upregulating RANKL expression, enhancing osteoclastogenesis (Elahmer et al. 2024; Luo et al. 2021; Wu et al. 2019). Cd-induced oxidative stress and inflammation further exacerbate bone resorption through activation of NF-κB and increased expression of inflammatory cytokines such as IL-6 and TNF-α (Luo et al. 2021). Additionally, Cd interferes with the vitamin D receptor

pathway, reducing the renal synthesis of 1,25-dihydroxy-vitamin D and impairing calcium absorption (Engström et al. 2009). Advances in proteomics and metabolomics have highlighted changes in bone matrix proteins and mineralization processes, further explaining Cd's detrimental effects on skeletal integrity (Chen et al. 2022). Epidemiological studies have linked chronic Cd exposure to reduced bone mineral density (BMD), increased risk of fractures, and elevated urinary excretion of bone resorption markers such as deoxypyridinoline (Callan et al. 2015; Sughis et al. 2011). These effects are particularly pronounced in populations with high environmental or occupational exposure to Cd, where bone-related symptoms often appear alongside renal dysfunction.

This study investigates the association between environmental Cd exposure and bone and renal health in postmenopausal women, using urinary Cd (UCd) as a biomarker for long-term exposure. Focusing on this population is particularly relevant due to their increased risk for age-related declines in bone and renal function, which may be further exacerbated by the hormonal changes associated with menopause. Notably, the participants reside in a highly agricultural region of Brazil, where Cd exposure may be heightened due to the use of Cd-containing fertilizers in agricultural practices.

Materials and Methods

Study Design and Study Population

This study used an observational, cross-sectional design. Data were collected from March 2022 to February 2024. Ethical approval was obtained from the Research Ethics Committee of Fernando Pessoa University (Porto, Portugal), Western Paraná State University (Cascavel, Brazil), and Plataforma Brasil (approval number: 2.636.746). All participants provided written informed consent.

Participants were recruited through advertisements on social networks, universities, medical offices, health centers, hospitals, and regional and local health departments. Eligibility criteria included women aged 50–70 years, postmenopausal status (defined retrospectively as 12 consecutive months of amenorrhea), and residency in the region for at least 10 years. Exclusion criteria encompassed the presence of severe active diseases such as liver or kidney failure and cancer, a confirmed diagnosis of secondary osteoporosis (e.g., hyperparathyroidism, neoplasia, or chronic corticosteroid use), and prior employment in industries associated with Cd exposure, such as battery manufacturing, plating, pigments, plastics, or fertilizer handling.

After providing informed consent, participants completed a questionnaire designed to assess risk factors for osteoporosis, dietary or occupational exposure to Cd, and other relevant data. Following the questionnaire, participants'weight and height were measured. Body mass index (BMI) was subsequently calculated using the formula: body weight (kg) divided by squared height (m^2). A member of the research team then coordinated and scheduled the participants for urine collection and bone density testing. Of the 431 volunteers who completed the questionnaire, underwent bone densitometry, and were referred for urinary tests, 380 successfully completed all the proposed examinations and requirements.

Biochemical parameters and urinary Cd concentrations quantification

Morning spot urine samples (first-morning void) were collected in metal-free tubes and frozen at − 20 °C until Cd quantification was performed to assess long-term exposure to the metal. Additionally, urinary calcium, β2-microglobulin (β2MG), and creatinine concentrations were analyzed to assess renal dysfunction. UCd analyses were performed by using an Inductively Coupled Plasma Mass Spectrometry (ICP-MS) equipped with Quadrupole Ion Deflector (NexION® 2000, PerkinElmer, Shelton, CT, USA), as described by (Barbosa et al. 2023). In order to verify the accuracy of the data, reference urine samples obtained from the Institut National de Sante'Publique (INSP) du Quebec (Quebec, Canada) were used as part of the external quality assessment schemes (EQAS), being also analyzed. Results were always in good agreement with target values (*t* test, 95%). Creatinine was measured using the Alkaline Picrate method (Atellica® CH-Siemens); calcium, by the automated colorimetric method (Atellica® CH, Siemens) and β2 microglobulin by chemiluminescence (Atellica® IM-1600, Siemens).

Bone Mineral Density Measurement

Participants were subjected to bone densitometry by dual-energy X-ray emission (DEXA) in the same radiological service, same HOLOGIC device (Horizon-A model) in the classic sites of the lumbar spine, femoral neck, total hip (defined as the combined area of neck, greater trochanter, and intertrochanteric area); in cases of imaging interference such as the presence of prostheses, degenerative or metabolic diseases in these bone sites, the 33% radius was used for the diagnosis of osteoporosis or osteopenia. T-scores were used to diagnose postmenopausal osteoporosis to comply with established clinical guidelines (Camacho et al. 2020). According to World Health Organization (WHO) criteria, osteopenia is defined as a T-score between −1.0 and

−2.5, while a T-score of −2.5 or lower at any skeletal site is diagnostic of osteoporosis.

Statistical Analysis

Data analysis was performed using R software, version 4.2.2. Whenever statistical tests have been applied, the considered level of significance was $\alpha = 0.05$, and all p values refer to two-sided hypotheses.

Categorical variables were described using absolute and relative frequencies (n, %) and compared using the Chi-square test or Fisher's exact test, as appropriate. For quantitative variables, the data were summarized as medians with interquartile ranges (IQRs, expressed as Q1 and Q3) and compared using the Mann–Whitney (for two groups) or the Kruskal–Wallis test (for more than two groups).

To investigate the independent associations between creatinine-adjusted urinary Cd concentrations (UCd/creat) and either creatinine-adjusted urinary calcium concentrations (UCa/creat) or β2-microglobulin concentrations (β2MG/creat), a multiple regression analysis was performed. Additional multiple linear regression was conducted to assess the relationship between UCd concentrations and bone health outcomes, including BMD and T-scores at the spine, femoral neck, and total hip.

To explore potential non-linear effects, Bayesian Kernel Machine Regression (BKMR) was used. This approach allowed for estimation of the univariate exposure–response function for cadmium on the outcomes, while holding the other impacting variables constant at their 50th percentile values.

Finally, ordinal logistic regression was applied to evaluate the association between UCd and the risk of low bone density (defined as osteopenia or osteoporosis) at each skeletal site.

Due to the skewed distributions of urinary Cd concentrations and the outcomes UCa/creat and β2MG/creat, these variables were log-transformed to approximate a normal distribution. Covariates considered for inclusion in the models were age and BMI. In addition, prolonged bed rest (28 days or longer), insufficient physical activity (less than 30 min of exercise per day), history of prior fractures, and arthritis were also included to account for potential changes in Cd bioavailability and distribution related to bone and mineral metabolism.

Results

Characteristics of the Study Population

The sociodemographic characteristics and healthy habits of the postmenopausal women included in this study are summarized in Table 1. The table also presents a comparison of these variables between two groups based on UCd concentrations, categorized according to whether they were above or below the 95th percentile (P95) threshold of 1.1 µg/g creatinine, as per the reference values for Brazilian women (Barbosa et al. 2023).

All participants were postmenopausal, with a median age of 60 years and no prior history of occupational exposure to Cd, ensuring that the environment was the only source of Cd exposure. The study population included 73.7% never-smokers ($n = 280$), 20.0% former smokers, and 17.4% current smokers ($n = 24$). Notably, 94% of participants were not current smokers, thereby reducing the potential confounding effect of tobacco-related Cd exposure. This is important given that smoking is a known source of elevated Cd levels and a recognized risk factor for both osteoporosis (Li et al. 2020a, b) and CKD (Hallan and Orth 2011).

The prevalence of osteoporosis was 19.2%, consistent with the documented range for the female Brazilian population (Marinho et al. 2014). Arthritis was reported by 19% of the participants. More than half (56%) were taking medication on a regular basis. The median BMI was 27 kg/m^2, with 75% of the population presenting a BMI above the normal cutoff of 25 kg/m^2. The median UCd level was 0.30 µg/g creat (interquartile range: 0.15–0.55).

The groups with UCd concentrations above and below P95 (1.1 µg/g creat) were similar in terms of age, BMI, exercise activity, smoking status, and bone-specific medication use (Table 1). Notably, corticosteroid use was twice as prevalent in women with UCd concentrations below P95 compared to those with concentrations above P95 (24% vs. 11%, respectively), although the difference was of borderline statistical significance ($p = 0.079$). However, a history of prior fractures was more prevalent among women with UCd concentrations below P95 (31% vs. 8.3%, $p < 0.001$). Women with UCd concentrations above P95 showed significantly higher UCa/creat and β2MG/creat concentrations compared to those below P95 (0.18 vs. 0.13, $p = 0.036$; 111 vs. 87 units, $p = 0.002$, respectively). Additionally, spine T-scores were significantly lower in women with UCd concentrations above P95 (− 1.3 vs. − 1.0, $p = 0.035$), and osteoporosis prevalence at the spine was substantially higher in this group (33% vs. 14%, $p = 0.012$). Similar trends were observed at the femoral neck and total hip, with significant differences in BMD ($p < 0.001$), T-scores ($p < 0.001$), and osteoporosis prevalence at the femoral neck ($p = 0.024$). However, no significant difference was found in osteoporosis prevalence at the total hip ($p = 0.200$).

Table 1 Sociodemographic characteristics and health habits of the study population, presented overall and categorized by cadmium concentrations relative to the Brazilian women's reference levels (P_{95} = 1.1 µg/g creat) (Barbosa et al. 2023)

Variables	Overall, n = 380[a]	UCd level ≥ 1.1 µg/g creat, n = 36[a]	UCd level < 1.1 µg/g creat, n = 344[a]	p-value[b]
Age (years)	60.0 (56.0; 65.8)	63.0 (58.8; 66.0)	60.0 (56.0; 65.0)	0.079
BMI (kg/m^2)	27.0 (24.4; 30.2)	25.9 (23.1; 29.7)	27.1 (24.8; 30.2)	0.120
Prior fracture (yes)	109 (29%)	3 (8.3%)	106 (31%)	**0.005**
Arthritis (yes)	72 (19%)	10 (28%)	62 (18%)	0.200
Vitamin D intake (yes)	183 (48%)	16 (44%)	167 (49%)	0.600
Corticosteroids (yes)	88 (23%)	4 (11%)	84 (24%)	0.072
Prolonged bed rest (yes)	28 (7.4%)	1 (2.8%)	27 (7.8%)	0.500
No Exercise	135 (36%)	10 (28%)	125 (36%)	0.300
Calcium intake	100 (26%)	7 (19%)	93 (27%)	0.300
Alcohol intake	1 (0.3%)	1 (2.8%)	0 (0%)	0.095
Smoking	24 (6.3%)	2 (5.6%)	22 (6.4%)	> 0.9
Antiresorptive medications				0.500
Bisphosphonates	10 (2.6%)	1 (2.8%)	9 (2.6%)	
Bisphosphonates & HRT	1 (0.3%)	0 (0%)	1 (0.3%)	
HRT	45 (12%)	2 (5.6%)	43 (13%)	
No	324 (85%)	33 (92%)	291 (85%)	
UCa/creat	0.13 (0.08; 0.22)	0.18 (0.10; 0.25)	0.13 (0.07; 0.22)	**0.036**
β2MG/creat (µg/g creat)	90 (56; 124)	111 (86; 177)	87 (54; 121)	**0.002**
BMD lumbar spine (g/cm^2)	0.92 (0.82; 1.06)	0.91 (0.73; 1.00)	0.93 (0.83; 1.06)	0.057
T-score lumbar spine	− 1.10 (− 2.00; 0.10)	− 1.30 (− 2.85; − 0.38)	− 1.00 (− 1.90; 0.13)	**0.035**
Diagnosis lumbar spine				**0.012**
Normal	181 (48%)	14 (39%)	167 (49%)	
Osteopenia	138 (36%)	10 (28%)	128 (37%)	
Osteoporosis	61 (16%)	12 (33%)	49 (14%)	
BMD femoral neck (g/cm^2)	0.73 (0.65; 0.82)	0.66 (0.60; 0.74)	0.74 (0.66; 0.83)	**< 0.001**
T-score femoral neck	− 1.10 (− 1.73; − 0.20)	− 1.70 (− 2.23; − 0.98)	− 1.00 (− 1.70; − 0.10)	**< 0.001**
Diagnosis femoral neck				**0.024**
Normal	170 (45%)	9 (25%)	161 (47%)	
Osteopenia	185 (49%)	23 (64%)	162 (47%)	
Osteoporosis	25 (6.6%)	4 (11%)	21 (6.1%)	
BMD total hip (g/cm^2)	0.87 (0.78; 0.96)	0.83 (0.71; 0.86)	0.88 (0.79; 0.97)	**0.001**
T-score total hip	− 0.60 (− 1.30; 0.10)	− 0.90 (− 1.83; − 0.50)	− 0.50 (− 1.20; 0.20)	**0.004**
Diagnosis total hip				0.200
Normal	249 (66%)	19 (53%)	230 (67%)	
Osteopenia	121 (32%)	16 (44%)	105 (31%)	
Osteoporosis	10 (2.6%)	1 (2.8%)	9 (2.6%)	
UCd (µg/g creat)	0.30 (0.15; 0.55)	1.47 (1.18; 2.39)	0.27 (0.14; 0.43)	**< 0.001**

[a]Median (Q1; Q3); n (%)

[b]Mann–Whitney test; Pearson's Chi-squared test; Fisher's exact test. Abbreviations: BMD—Bone mineral density; β2MG—β2-microglobulin; BMI—Body mass index; HRT—Hormone replacement therapy; UCa—Urinary calcium; UCd—Urinary cadmium

Statistically significant p-values are shown in bold

Characteristics of the Study Population by Bone Condition

Table 2 presents a univariate analysis comparing sociodemographic factors and health habits based on osteoporosis diagnosis. Age showed a significant positive association with both osteopenia and osteoporosis at all three bone sites: lumbar spine, femoral neck, and total hip. In contrast, BMI demonstrated a significant negative association, with higher values observed in women with normal BMD and lower values in those with osteoporosis. The use of calcium supplementation, bisphosphonate use,

Table 2 Sociodemographic and healthy lifestyle habits of the study population summarized by bone condition

Variables	Lumbar Spine				Femoral Neck				Total Hip			
	Normal	Osteopenia	Osteoporosis	p-value[b]	Normal	Osteopenia	Osteoporosis	p-value[b]	Normal	Osteopenia	Osteoporosis	p-value[b]
	n = 181[a]	n = 138[a]	n = 61[a]		n = 170[a]	n = 185[a]	n = 25[a]		n = 249[a]	n = 121[a]	n = 10[a]	
Age (years)	59.0 (55.0; 65.0)	62.0 (57.3; 66.0)	62.0 (59.0; 65.0)	**< 0.001**	58.0 (55.0; 63.0)	62.0 (58.0; 66.0)	64.0 (61.0; 67.0)	**< 0.001**	59.0 (55.0; 64.0)	63.0 (59.0; 66.0)	65.0 (63.3; 67.0)	**< 0.001**
BMI (kg/m^2)	28.0 (25.3; 32.5)	26.6 (24.2; 28.9)	26.1 (23.4; 28.0)	**< 0.001**	28.9 (25.8; 32.8)	26.2 (23.8; 28.6)	25.1 (22.9; 26.8)	**< 0.001**	27.9 (25.6; 32.0)	25.5 (23.4; 28.1)	24.2 (20.8; 28.2)	**< 0.001**
Prolonged bed rest	6 (3.3%)	15 (11%)	7 (11%)	**0.011**	9 (5.3%)	18 (9.7%)	1 (4.0%)	0.300	17 (6.8%)	11 (9.1%)	0 (0%)	0.700
Antiresorptive medication				**0.005**				**0.003**				**0.012**
BP	1 (0.6%)	3 (2.2%)	6 (9.8%)		0 (0%)	8 (4.3%)	2 (8.0%)		3 (1.2%)	5 (4.1%)	2 (20%)	
BP & HRT	0 (0%)	0 (0%)	1 (1.6%)		0 (0%)	1 (0.5%)	0 (0%)		0 (0%)	1 (0.8%)	0 (0%)	
HRT	20 (11%)	17 (12%)	8 (13%)		22 (13%)	17 (9.2%)	6 (24%)		28 (11%)	15 (12%)	2 (20%)	
No	160 (88%)	118 (86%)	46 (75%)		148 (87%)	159 (86%)	17 (68%)		218 (88%)	100 (83%)	6 (60%)	
β2MG (μg/g creat)	83 (53; 116)	95 (64; 129)	94 (62; 131)	0.200	83 (53; 115)	93 (60; 136)	104 (76; 159)	**0.018**	87 (54; 119)	92 (58; 138)	104 (75; 157)	0.300
BMD lumbar spine (g/cm^2)	1.06 (1.00; 1.16)	0.87 (0.82; 0.90)	0.73 (0.70; 0.76)	**< 0.001**	1.05 (0.94; 1.15)	0.88 (0.79; 0.96)	0.76 (0.72; 0.85)	**< 0.001**	1.00 (0.90; 1.11)	0.83 (0.76; 0.91)	0.71 (0.63; 0.76)	**< 0.001**
BMD femoral neck (g/cm^2)	0.81 (0.74; 0.90)	0.68 (0.62; 0.73)	0.65 (0.59; 0.71)	**< 0.001**	0.85 (0.78; 0.92)	0.67 (0.63; 0.72)	0.55 (0.54; 0.56)	**< 0.001**	0.78 (0.72; 0.88)	0.64 (0.60; 0.68)	0.54 (0.49; 0.55)	**< 0.001**
BMD total hip (g/cm^2)	0.95 (0.88; 1.05)	0.81 (0.74; 0.88)	0.76 (0.70; 0.85)	**< 0.001**	0.97 (0.91; 1.05)	0.81 (0.75; 0.86)	0.70 (0.64; 0.72)	**< 0.001**	0.93 (0.87; 1.00)	0.75 (0.71; 0.79)	0.62 (0.58; 0.63)	**< 0.001**
UCd (μg/g creat)	0.30 (0.15; 0.49)	0.29 (0.14; 0.51)	0.38 (0.19; 0.74)	0.110	0.28 (0.14; 0.42)	0.33 (0.15; 0.61)	0.42 (0.19; 0.69)	0.067	0.30 (0.14; 0.53)	0.30 (0.16; 0.57)	0.32 (0.23; 0.65)	0.600
UCd concentrations				**0.012**				**0.024**				0.200
≥ 1.1 μg/g creat	14 (7.7%)	10 (7.2%)	12 (20%)		9 (5.3%)	23 (12%)	4 (16%)		19 (7.6%)	16 (13%)	1 (10%)	
< 1.1 μg/g creat	167 (92%)	128 (93%)	49 (80%)		161 (95%)	162 (88%)	21 (84%)		230 (92%)	105 (87%)	9 (90%)	

[a]Median (Q1; Q3); *n* (%)

[b]Kruskal—Wallis rank sum test; Pearson's Chi—squared test. Abbreviations: BMD—Bone uniformity; β2MG—β2-Microglobulin; BMI—Body mass index; BP—Bisphosphonates; HRT—Hormone replacement therapy; UCd—Urinary cadmium

Statistically significant p-values are shown in bold

and hormone replacement therapy (HRT) increased significantly from the normal group to the osteopenia and osteoporosis groups. Creatinine-adjusted urinary β2MG concentrations progressively rose with osteoporosis prevalence, reaching statistical significance at the femoral neck ($p = 0.018$).

Osteoporosis at one bone site was strongly associated with diagnoses of osteopenia and/or osteoporosis at other sites (Supplementary Fig. S1). Among the 73 women diagnosed with osteoporosis, 56 had osteoporosis at one bone site, 11 at two bone sites, and six at all three bone sites.

The prevalence of UCd concentrations above P95 increased progressively from the normal group to the osteopenia and osteoporosis groups at both the femoral neck ($p = 0.024$) and lumbar spine ($p = 0.012$) (Table 2).

Association of UCd and Other Study Variables with BMD and Renal Outcomes

To further investigate the influence of potential confounders on the relationship between UCd/creat and BMD outcomes, multiple linear regression analyses were performed (Table 3). In fully adjusted models, age and prior fracture history were both significantly associated with lower BMD and T-scores across all three bone sites (lumbar spine, femoral neck, and total hip). Age showed a strong inverse effect on BMD ($p < 0.001$) and *T*-scores ($p < 0.001$), while prior fractures had a smaller but significant negative effect on these outcomes (BMD: $p = 0.033$ to $p = 0.005$; *T*-score: $p = 0.031$ to $p = 0.016$). Conversely, BMI was positively associated with both BMD and T-scores at all sites ($p < 0.001$).

Prolonged bed rest was associated with significantly lower *T*-scores at the lumbar spine ($p = 0.042$) and showed a borderline effect on BMD at the same site ($p = 0.059$). No significant effects of bed rest were observed for the femoral neck or total hip. In contrast, physical inactivity was significantly associated with higher BMD ($p = 0.030$) and *T*-scores ($p = 0.035$) at the lumbar spine, with no significant effects at other bone sites.

In multiple linear regression analysis, UCd/creat was not independently associated with BMD outcomes ($p \geq 0.2$), although it showed an inverse trend with both BMD and *T*-scores. Similarly, arthritis, medication use (HRT, bisphosphonates, corticosteroids), alcohol consumption, and smoking did not significantly affect BMD outcomes in these models.

We also used a BKMR model to investigate potential non-linear effects of Cd on the study outcomes. Figure 1 presents the univariate exposure–response functions for Cd, with other covariates held at their median values. For BMD outcomes, Cd demonstrated a non-linear relationship, where increasing urinary Cd concentrations initially produced minimal impact, but at higher levels, a more pronounced decline in BMD was observed. In contrast, for renal function outcomes, rising UCd concentrations were associated with a progressive increase in tubular proteinuria and urinary calcium excretion.

Further multiple linear regression analyses were performed to identify factors associated with UCa/creat and β2MG/creat concentrations (Table 4). In fully adjusted models, log-transformed UCd/creat emerged as a significant predictor for both UCa/creat and β2MG/creat concentrations ($p < 0.001$ for both). A graphical illustration of the correlation between creatinine-adjusted urinary β2MG and UCd is shown in Supplementary Fig. S2. Additionally, the absence of physical exercise was positively associated with elevated β2MG/creat concentrations ($p = 0.007$).

Estimation of Risk Factors for Osteopenia and Osteoporosis

To assess the risk of osteopenia and osteoporosis at the lumbar spine, femoral neck, and total hip in relation to Cd exposure, multinomial logistic regression analyses were performed using continuous UCd/creat concentrations (Table 5).

Age was a significant risk factor for both conditions across all bone sites. Each additional year of age increased the risk of developing osteopenia by approximately 10.6% at the lumbar spine (OR = 1.106, 95% CI: 1.056–1.158), 12.4% at the femoral neck (OR = 1.124, 95% CI: 1.074–1.176), and 14.9% at the total hip (OR = 1.149, 95% CI: 1.093–1.207). Similarly, age significantly elevated the risk of osteoporosis, with increases of 9.9% at the lumbar spine (OR = 1.099, 95% CI: 1.035–1.167), 25.5% at the femoral neck (OR = 1.255, 95% CI: 1.136–1.385), and 28.1% at the total hip (OR = 1.281, 95% CI: 1.092–1.504).

BMI was significantly associated with a reduced risk of osteopenia and osteoporosis across all bone sites. Each unit increase in BMI reduced the risk of osteopenia by 11.4% at the lumbar spine (OR = 0.886, 95% CI: 0.838–0.936), 12.1% at the femoral neck (OR = 0.879, 95% CI: 0.834–0.926), and 19.5% at the total hip (OR = 0.805, 95% CI: 0.750–0.863). Similarly, each unit increase in BMI was associated with a 13.6% reduction in osteoporosis risk at the lumbar spine (OR = 0.864, 95% CI: 0.801–0.933), 19.4% at the femoral neck (OR = 0.806, 95% CI: 0.716–0.907), and 27.2% at the total hip (OR = 0.728, 95% CI: 0.594–0.891).

Prolonged bed rest significantly increased the risk of osteopenia by 231.2% (OR = 3.312, 95% CI: 1.190–9.216) and osteoporosis by 250.5% (OR = 3.505, 95% CI: 1.044–11.766) at the lumbar spine, but not at other bone sites. In contrast, lack of physical exercise reduced the risk of osteopenia at the lumbar spine by 43.7% (OR = 0.563,

Table 3 Multiple linear regression coefficients of the associations between studied variables and bone outcomes in the study population

Variables	BMD (g/cm^2)		T-score	
	Beta (95% CI)	p value	Beta (95% CI)	p value
Lumbar spine				
Age (years)	− 0.007 (−0.010; − 0.004)	**< 0.001**	− 0.062 (−0.090; − 0.035)	**< 0.001**
BMI (kg/m^2)	0.011 (0.007; 0.014)	**< 0.001**	0.097 (0.067; 0.127)	**< 0.001**
Prior fracture	− 0.039 (− 0.074; − 0.003)	**0.033**	− 0.360 (− 0.686; − 0.033)	**0.031**
Arthritis	0.024 (− 0.016; 0.065)	0.240	0.255 (− 0.120; 0.630)	0.180
Prolonged bed rest	− 0.059 (− 0.120; 0.002)	0.059	− 0.583 (− 1.146; − 0.020)	**0.042**
No exercise	0.037 (0.004; 0.071)	**0.030**	0.336 (0.024; 0.647)	**0.035**
UCd log[a]	− 0.006 (−0.023; 0.010)	0.460	− 0.063 (− 0.217; 0.090)	0.420
Femoral neck				
Age (years)	− 0.008 (− 0.010; − 0.006)	**< 0.001**	− 0.077 (− 0.097; − 0.058)	**< 0.001**
BMI (kg/m^2)	0.010 (0.007; 0.012)	**< 0.001**	0.087 (0.066; 0.109)	**< 0.001**
Prior fracture	− 0.031 (− 0.058; − 0.004)	**0.027**	− 0.328 (− 0.563; − 0.092)	**0.006**
Arthritis	0.016 (− 0.016; 0.047)	0.320	0.135 (− 0.134; 0.405)	0.320
Prolonged bed rest	0.000 (− 0.048; 0.047)	0.990	− 0.041 (− 0.446; 0.364)	0.840
No exercise	0.016 (− 0.010; 0.042)	0.220	0.189 (− 0.035; 0.413)	0.100
UCd/creat log[a]	− 0.004 (− 0.016; 0.009)	0.590	− 0.061 (− 0.171; 0.050)	0.280
Total hip				
Age (years)	− 0.008 (− 0.010; − 0.006)	**< 0.001**	− 0.061 (− 0.080; − 0.042)	**< 0.001**
BMI (kg/m^2)	0.013 (0.011; 0.016)	**< 0.001**	0.109 (0.088; 0.130)	**< 0.001**
Prior fracture	− 0.037 (− 0.063; − 0.011)	**0.005**	− 0.282 (− 0.512; − 0.053)	**0.016**
Arthritis	0.003 (− 0.026;0.033)	0.820	0.011 (− 0.253; 0.275)	0.940
Prolonged bed rest	− 0.007 (− 0.051; 0.038)	0.770	− 0.111 (− 0.507; 0.285)	0.580
No exercise	0.009 (− 0.015; 0.034)	0.460	0.12 (− 0.099; 0.338)	0.280
UCd/creat log[a]	− 0.007 (− 0.019; 0.005)	0.280	− 0.047 (− 0.155; 0.061)	0.390

[a]Cadmium coefficients are interpreted as the nominal increase in urinary concentrations of the outcomes for every 1% increase in the creatinine-adjusted Cd concentration (µg/g) [formula: nominal change = beta/100*log(1 + x%)]

Abbreviations: BMD Bone mineral density; BMI Body mass index; Significant associations are shown in bold

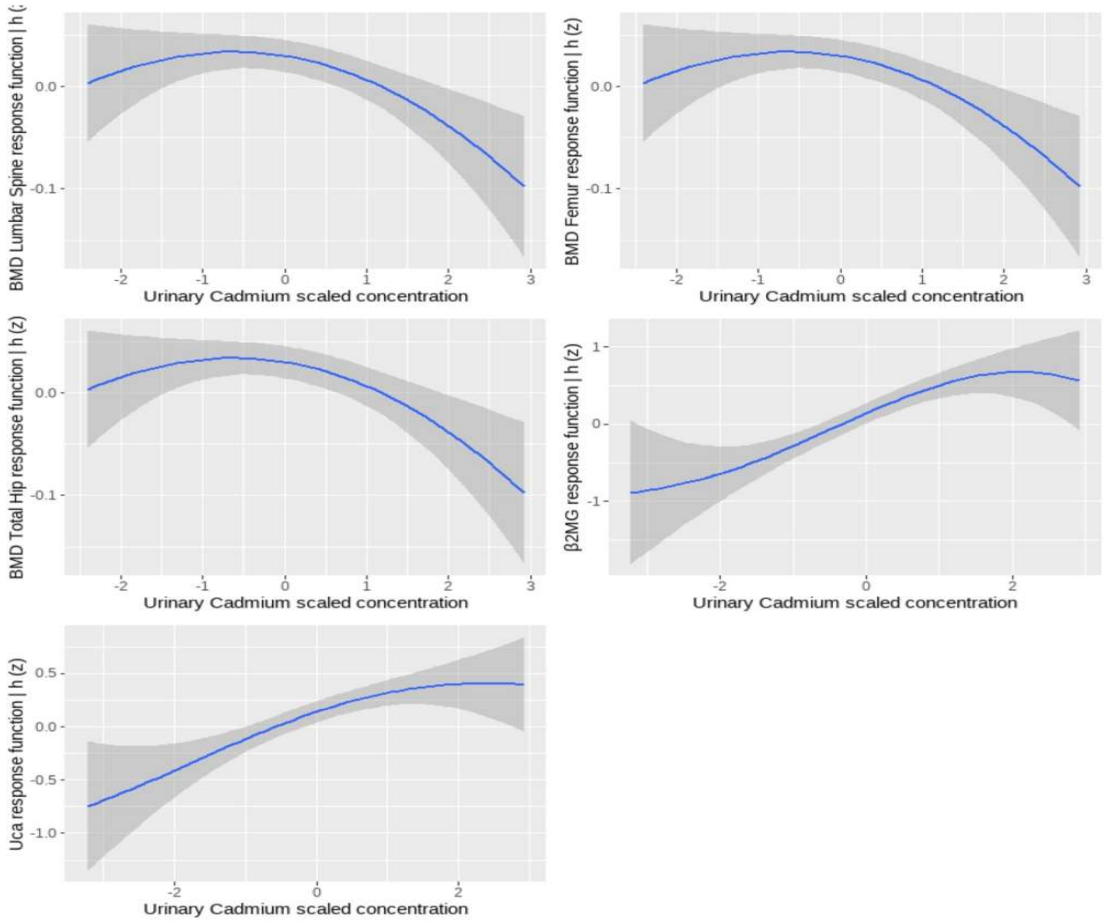

Fig. 1 Univariate exposure–response functions (blue lines) and 95% confidence intervals (gray shaded areas) for the association between urinary cadmium concentrations and selected bone and renal outcomes, estimated using Bayesian Kernel Machine Regression (BKMR). Outcomes include bone mineral density (BMD) at the lumbar spine, femoral neck and total hip, as well as β2-microglobulin (β2MG) and urinary calcium (UCa)

95% CI: 0.337–0.943), but also not observed at other bone sites.

A borderline positive association was observed between UCd and osteopenia at the femoral neck ($p = 0.073$), as well as between UCd and osteoporosis at the lumbar spine ($p =$ 0.109), while no significant association was found at the total hip.

Table 4 Multiple linear regression coefficients of the associations between investigated variables and biochemical parameters in the study population

	UCa/creat		β2MG (µg/g creat)	
Variables	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value
Age (years)	0.995 (0.979–1.010)	0.520	1.001 (0.981–1.021)	0.930
BMI (kg/m^2)	0.983 (0.967–1.000)	0.054	0.978 (0.957–1.001)	0.057
Prior fracture	1.044 (0.867–1.259)	0.650	0.900 (0.705–1.150)	0.400
Arthritis	1.044 (0.843–1.292)	0.690	0.906 (0.684–1.201)	0.490
Prolonged bed rest	0.880 (0.638–1.213)	0.430	1.097 (0.720–1.675)	0.660
No Exercise	0.868 (0.728–1.037)	0.120	0.726 (0.575–0.918)	**0.007**
UCd/creat log[a]	1.229 (1.125–1.340)	**< 0.001**	1.399 (1.247–1.571)	**< 0.001**

[a]Urinary cadmium coefficients are interpreted as the percent increase in urinary concentrations of the outcomes for every 1% increase in the creatinine-adjusted Cd concentration (µg/g creat) [formula: percent change = 1 + (x%/100) ^(beta-1)*100], where x is the percentage increase in the independent variable and beta is the regression coefficient. Covariates were log back transformed and are presented as multiplicative factor for every one-unit increase in the independent variable

Abbreviations: β2MG—β2-microglobulin; BMI—Body mass index; UCa—Urinary calcium; UCd—Urinary cadmium

Statistically significant p-values are shown in bold

Table 5 Multinomial logistic regression coefficients for the examined variables associated with osteopenia or osteoporosis in the study population

	Lumbar spine		Femoral neck		Total hip	
Variables	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Osteopenia						
Age (years)	1.106 (1.056–1.158)	**< 0.001**	1.124 (1.074–1.176)	**< 0.001**	1.149 (1.093–1.207)	**< 0.001**
BMI (kg/m^2)	0.886 (0.838–0.936)	**< 0.001**	0.879 (0.834–0.926)	**< 0.001**	0.805 (0.750–0.863)	**< 0.001**
Prior fracture	1.540 (0.898–2.642)	0.117	2.047 (1.209–3.465)	**0.008**	1.587 (0.919–2.741)	0.097
Arthritis	1.017 (0.555–1.864)	0.957	0.836 (0.464–1.507)	0.551	1.247 (0.660–2.358)	0.496
Prolonged bed rest	3.312 (1.190–9.216)	**0.022**	1.440 (0.578–3.584)	0.433	1.055 (0.419–2.659)	0.909
No exercise	0.563 (0.337–0.943)	**0.029**	0.890 (0.546–1.451)	0.640	0.749 (0.444–1.264)	0.280
UCd/creat log	0.900 (0.699–1.158)	0.414	1.251 (0.980–1.597)	0.073	1.012 (0.782–1.310)	0.927
Osteoporosis						
Age (years)	1.099 (1.035–1.167)	**0.002**	1.255 (1.136–1.385)	**< 0.001**	1.281 (1.092–1.504)	**0.002**
BMI (kg/m^2)	0.864 (0.801–0.933)	**< 0.001**	0.806 (0.716–0.907)	**< 0.001**	0.728 (0.594–0.891)	**0.002**
Prior fracture	1.925 (0.970–3.817)	0.061	1.898 (0.683–5.277)	0.219	1.861 (0.433–8.004)	0.404
Arthritis	0.908 (0.399–2.066)	0.817	0.727 (0.217–2.435)	0.605	0.536 (0.062–4.674)	0.573
Prolonged bed rest	3.505 (1.044–11.766)	**0.042**	0.563 (0.062–5.144)	0.611	n.a.*	n.a.*
No exercise	0.523 (0.264–1.036)	0.063	0.557 (0.209–1.488)	0.243	0.740 (0.184–2.981)	0.280
UCd/creat log	1.309 (0.942–1.819)	0.109	1.208 (0.762–1.913)	0.421	1.115 (0.560–2.219)	0.757

*n.a.—Not applicable, not considered in the logistic regression because of perfect separation events (when the events manifest in a single outcome)

Statistically significant p-values are shown in bold

Abbreviations: BMI—Body mass index; UCd—Urinary cadmium; OR (95% CI): Odds ratio and corresponding 95% confidence intervals

Discussion

To the best of our knowledge, this is the first cross-sectional study conducted in Brazil to investigate the effects of environmental exposure to Cd on renal and bone health. The study included 380 postmenopausal women, with a median age of 60 years.

Cd primarily accumulates in the kidneys and has a biological half-life in the human body ranging from 10 to 35 years (Genchi et al. 2020). For this reason, urine was selected as the biological matrix for assessing Cd exposure, as it reliably reflects long-term cumulative exposure and provides a comprehensive measure of overall body burden in the study population (Adams and Newcomb 2014). This approach is especially suitable for postmenopausal women, as the slow

excretion of Cd leads to higher body burdens with age. The UCd concentrations observed in our study population were relatively low (median of 0.30 µg/g creat), reflecting chronic environmental exposure rather than occupational or accidental sources. These concentrations are comparable to those reported for postmenopausal women in countries such as Sweden (0.4–0.6 µg/g creat) (Engström et al. 2009; Suwazono et al. 2010) and Western Australia (median of 0.26 µg/g creat) (Callan et al. 2015), but are substantially lower than those observed in highly Cd-polluted areas in East Asian countries, where UCd concentrations can be 10–15 times higher (Chen et al. 2011; Kim et al. 2014; La-Up et al. 2021). This indicates that the postmenopausal women in our study are exposed to Cd at relatively low environmental levels. Notably, despite living in a region characterized by intensive agricultural activity, their UCd concentrations were below the median reference value for the general female population in Brazil (0.44 µg/g creat) (Barbosa et al. 2023). This finding suggests that the extensive use of phosphate fertilizers in this region may not be a major contributor to the Cd burden in this group. Nevertheless, further research measuring Cd concentrations in local soil and food sources is required to more accurately evaluate the potential impact of agricultural practices and their implications for the health of local residents.

Aging is accompanied by physiological changes in the kidneys and bones, increasing susceptibility to conditions such as osteoporosis and CKD, particularly in the presence of environmental pollutants like Cd. As anticipated, age showed a significant negative correlation with BMD across all measured bone sites. In contrast, UCd concentrations demonstrated a non-significant negative trend with BMD, except in women with UCd concentrations at or above the 95th percentile of the Brazilian female reference value (≥ 1.1 µg/g creatinine). In this subgroup, a pronounced reduction in BMD and a higher prevalence of osteoporosis were observed, particularly at the lumbar spine and femoral neck. These results suggest that Cd's impact on bone health may be threshold-dependent, becoming clinically relevant only at elevated exposure levels. In accordance, the BKMR analysis demonstrated a non-linear relationship between urinary Cd and BMD outcomes. Further supporting this hypothesis, a prospective study of 4,024 Swedish postmenopausal women exposed to similar levels of environmental Cd as in our study (median UCd concentration of 0.33 µg/g creat versus 0.30 µg/g creat in our participants) showed a dose-dependent relationship between UCd concentrations and fracture risk (Tägt et al. 2022). Women in the highest UCd tertile (median: 0.54 µg/g creatinine) had a significantly higher risk of fracture compared to those in the lowest tertile (median: 0.20 µg/g creatinine). Given the rising prevalence of osteoporosis in Brazil (Aziziyeh et al. 2019) and the relatively low Cd exposure levels in our study population, the observed effects, though modest, should be interpreted as early warning indicators of potentially more serious health consequences.

It is worth noting that in our study, UCd concentrations were slightly higher in women with osteoporosis, particularly when assessed at the lumbar spine and, more notably, at the femoral neck, where a borderline statistically significant association was observed ($p = 0.067$; Table 2). In contrast, no relationship was found at the total hip. This lack of association may indicate the limited usefulness of total hip measurements in assessing Cd-related bone effects. Consistent with this, Engström et al. (2011) reported stronger associations between Cd exposure and bone outcomes at the femoral neck than at the lumbar spine or total hip (Engström et al. 2011).

Renal tubular function may be evaluated though different ways, namely by accessing its capacity of concentrating and acidifying the urine, and its ability to reabsorb glucose, ions, and proteins. β2MG is a small protein that is filtered by the glomerulus and reabsorbed by the proximal tubule. Elevated urinary β2MG concentrations are indicative of impaired tubular reabsorption, a hallmark of Cd-induced nephrotoxicity (Li et al. 2020a, b). The present study identified a significant positive correlation between UCd and β2MG concentrations (Table 4). These results are consistent with the nephrotoxicity effect of Cd at the tubular level, suggesting that this deleterious effect may be observed even at low environmental levels. Of note, urinary β2MG concentrations exceeding 300 µg/g creat are clinically recognized as a marker of ongoing renal tubular damage (Otaki et al. 2013). At these levels, Cd accumulation in the kidneys has typically reached critical thresholds, increasing the risk of progressive renal impairment and associated health consequences. Consequently, regulatory actions should ensure Cd exposure remains far below concentrations that could cause an increase in β2MG.

In addition to β2MG, our multiple linear regression analysis demonstrated that UCd was an independent predictor of urinary calcium. This supports the hypothesis that Cd-induced renal dysfunction disrupts calcium homeostasis, potentially contributing to bone loss. The downregulation of calcium tubular transport by Cd (Leffler et al. 2000) may explain the observed hypercalciuria in individuals with higher UCd concentrations, further linking Cd nephrotoxicity to bone health deterioration. These results underscore the need for further research to clarify the thresholds of Cd exposure that significantly impact bone health and to investigate the interplay between Cd-induced renal dysfunction and bone deterioration.

Contrary to our initial hypothesis, we did not observe elevated urinary calcium concentrations in women with osteopenia or osteoporosis. However, it is important to acknowledge that participants in all groups included women who were receiving calcium supplementation either

preventatively or therapeutically, which may have influenced our findings.

To mitigate the adverse health effects of Cd exposure, various approaches have been employed to estimate urinary Cd thresholds for Cd-induced renal tubular damage, revealing substantial variability across populations from different regions (0.3–10 µg/g creat) (Hu et al. 2014; Nishijo et al. 2014; Suwazono et al. 2011; Wang et al. 2016; Woo et al. 2015). Notably, higher UCd thresholds are often derived from studies in Asian populations, where environmental Cd pollution is significantly high. A recent meta-analysis, focusing exclusively on data from countries with typical environmental Cd levels, provided a more refined estimate (Smereczański & Brzóska 2023). This study identified a LOAEL (Lowest Observed Adverse Effect Level) for Cd-induced nephrotoxicity at UCd > 0.27 µg/g creat. This threshold is lower than the median UCd concentrations observed among the study participants, emphasizing the current low-level Cd exposure being of concern to renal risk in susceptible populations, potentially contributing to CKD.

We also identified several well-established risk factors for osteoporosis. As anticipated, age was a significant (unmodifiable) risk factor across all measured bone sites. Prolonged bed rest was associated with an increased risk of osteoporosis at the lumbar spine, consistent with previous studies showing that bed rest promotes bone resorption through elevated osteoclast activity (Baecker et al. 2003). No similar relationship was found at the femoral neck or total hip, suggesting that the lumbar spine is more susceptible to the effects of prolonged bed rest, likely due to reduced mechanical loading in this area (Marmonti et al. 2017). Conversely, a higher BMI was associated with a reduced risk of osteoporosis, likely because the increased mechanical load on the skeleton, which stimulates osteoblast activity and promotes bone strength (Heidari et al. 2015).

Despite the significant insights gained from this study, there are some limitations that should be acknowledged. First, the cross-sectional design precludes the establishment of causal relationships between Cd exposure and health outcomes. Secondly, the reliance on noninvasive urinary biomarkers as the primary exposure metric limited our ability to assess blood biomarkers, such as estimated glomerular filtration rate (eGFR), which would have provided a more comprehensive assessment of renal function and CKD diagnosis. Third, the results related to smoking status should be interpreted with caution due to the small number of smokers in the study population. Nevertheless, this low prevalence is consistent with national data (VIGITEL 2023) and likely reflects the effectiveness of Brazil's stringent tobacco control policies (Romer 2021). Finally, medication use among participants—particularly given their advanced age and associated comorbidities—may have influenced certain variables, including urinary Ca concentrations in patients taking calcium supplements. Future research involving larger, longitudinal cohorts is needed to validate these findings and to further elucidate the long-term effects of dietary Cd exposure on kidney and bone health.

Conclusions

This study demonstrates that even low-level environmental Cd exposure is associated with early signs of renal tubular dysfunction in postmenopausal women, as indicated by increased urinary β2-microglobulin. Importantly, these effects were observed at Cd concentrations below national reference thresholds, suggesting that current safety limits may underestimate risks, particularly for vulnerable populations.

While a non-linear association was found between Cd exposure and BMD in our study population, women with the highest urinary Cd levels exhibited notably reduced femoral neck BMD. This pattern points to a possible threshold effect, where Cd's impact on bone health becomes clinically significant only beyond a certain exposure level. The independent association between urinary Cd and urinary calcium further suggests a potential mechanistic link between Cd-related renal dysfunction and altered calcium metabolism.

In light of these findings, there is a clear need for stricter environmental controls, enhanced population biomonitoring, and prospective studies to better define Cd's long-term effects. Given the dual public health burdens of CKD and osteoporosis in aging populations, early identification of subclinical toxicity may be critical to effective prevention and intervention strategies.

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Author Contributions Carlos T. Kunioka contributed toward writing—original draft, visualization, methodology, investigation, and formal analysis. Jonas C. Cruz contributed toward writing—review & editing, software, methodology, and formal analysis. Vanessa C. O. Souza contributed toward writing—review & editing and Methodology. Bruno A. Rocha contributed toward writing—review & editing and validation. Fernando B. Jr contributed toward writing—review & editing and resources. Luís Belo contributed toward writing—review & editing, supervision, validation, and formal analysis. Maria C. Manso contributed toward writing—review & editing, supervision, validation, conceptualization, and formal analysis. Márcia Carvalho contributed toward writing—review & editing, supervision, formal analysis, data curation, project administration, and conceptualization.

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Data Availability The datasets generated during the current study are not publicly available due to ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Research Ethics Committee of Fernando Pessoa University (Porto, Portugal), Western Paraná State University (Cascavel, Brazil), and Plataforma Brasil (approval number: 2.636.746). All individual participants provided written informed consent.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

SUPPLEMENTARY MATERIAL

Low-Level Environmental Cadmium Exposure and Its Effects on Renal and Bone Health in Brazilian Postmenopausal Women: A Cross-Sectional Study

Journal: Exposure and Health

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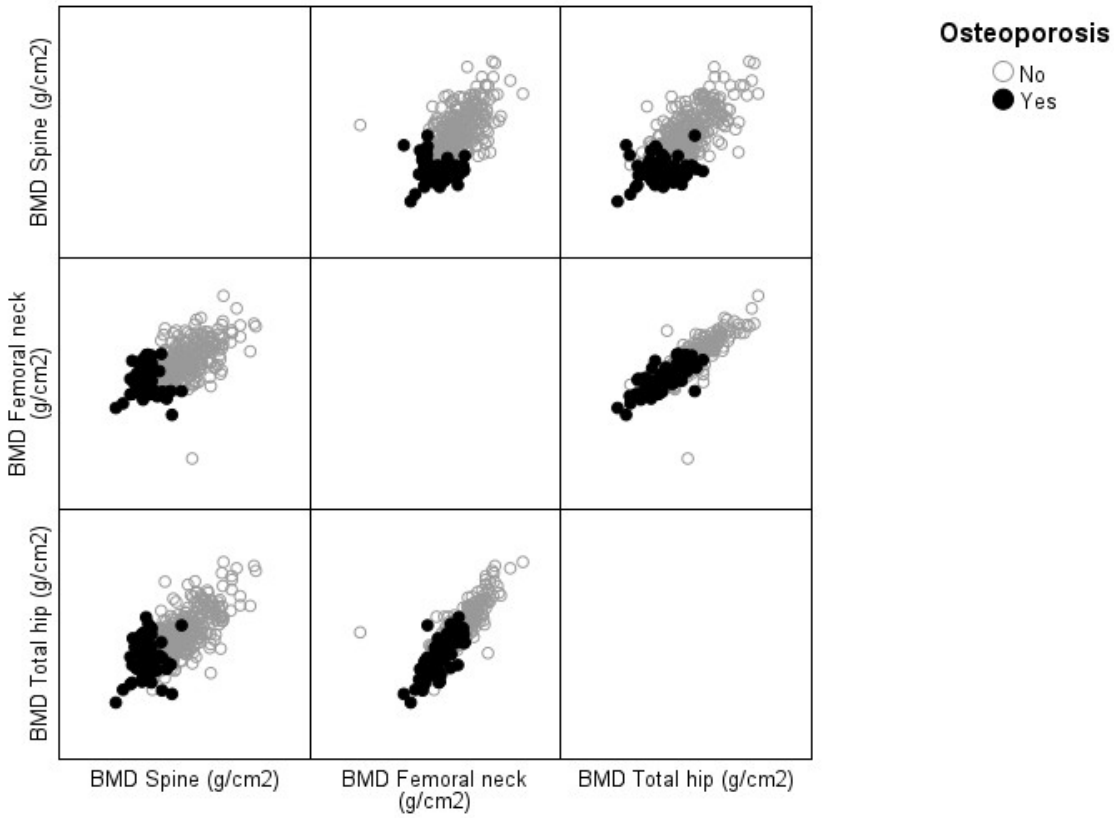
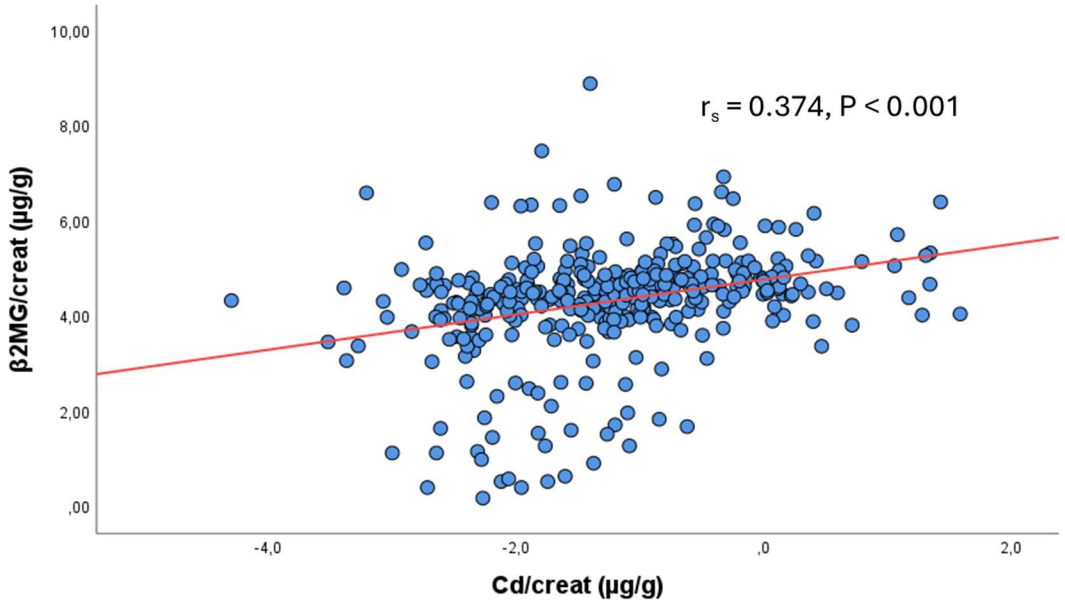
Figure S1. Correlation between bone mineral density (BMD) values obtained at different bone sites (lumbar spine, femoral neck and total hip).



		LnBMD Lumbar Spine	LnBMD Femoral Neck	LnBMD Total Hip
LnBMD Lumbar Spine	Pearson correlation	1	0.525	0.697
	Sig. (two-tailed)		<0.001	<0.001
	N	380	380	380
LnBMD Femoral Neck	Pearson correlation	0.525	1	0.743
	Sig. (two-tailed)	<0.001		<0.001
	N	380	380	380
LnBMD Total Hip	Pearson correlation	0.697	0.743	1
	Sig. (two-tailed)	<0.001	<0.001	
	N	380	380	380

Figure S2. Correlation between creatinine-adjusted urinary β2-microglobulin (β2-MG/creat) and creatinine-adjusted urinary cadmium (Cd/creat) levels (variables ln-transformed) in postmenopausal women. r_s, Spearman's rank correlation coefficient; $P < 0.05$ was considered as statistically significant.



Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

CAPÍTULO III. ASSOCIAÇÃO DO CÁDMIO E ANTIMÓNIO URINÁRIOS COM O RISCO DE OSTEOPOROSE EM MULHERES BRASILEIRAS PÓS-MENOPÁUSICAS: EVIDÊNCIAS DE UM ESTUDO DE BIOMONITORIZAÇÃO DE 20 METAIS/METALOIDES

Este capítulo apresenta um estudo transversal realizado com o objetivo de investigar os níveis urinários de 20 metais e metaloides, bem como a sua relação com a DMO e o risco de osteoporose, numa amostra de mulheres brasileiras pós-menopáusicas.

O conteúdo deste capítulo corresponde, na íntegra, ao artigo científico que se apresenta abaixo, na sua forma final publicada em revista.

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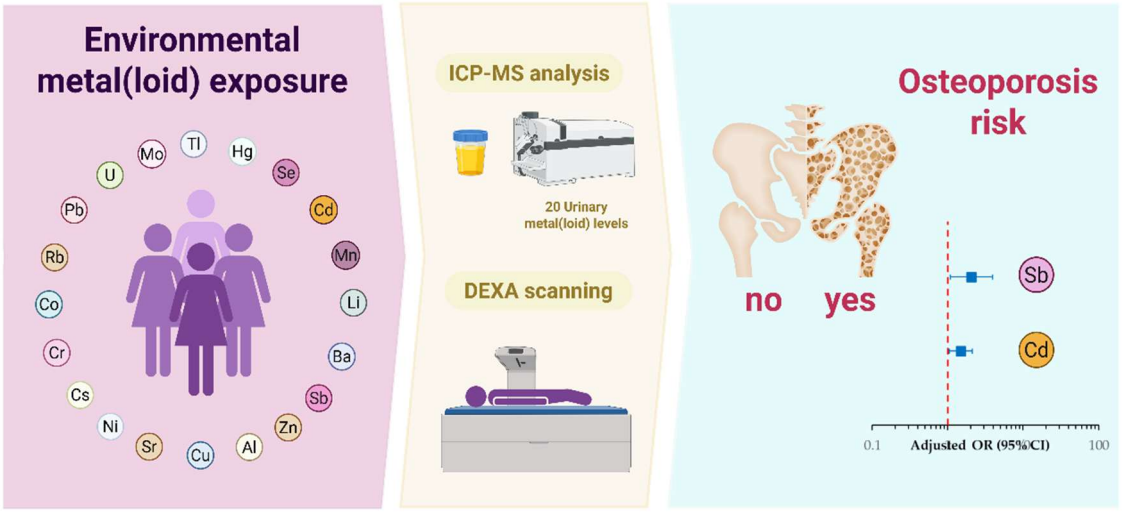
Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

Graphical Abstract



Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

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Article

Association of Urinary Cadmium and Antimony with Osteoporosis Risk in Postmenopausal Brazilian Women: Insights from a 20 Metal(loid) Biomonitoring Study

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Abstract: Osteoporosis is a major public health concern, particularly among postmenopausal women. Environmental exposure to metals has been proposed as a potential contributor to osteoporosis, but human data remain limited and inconsistent. This study investigated changes in urinary concentrations of 20 metal(loid)s in patients with osteoporosis, as well as the association of these elements with bone mineral density (BMD), in a cohort of 380 postmenopausal women aged 50–70 years from Cascavel, Paraná, Brazil. Demographic, lifestyle, and clinical data were collected, and urinary concentrations of aluminum (Al), barium (Ba), cadmium (Cd), cobalt (Co), cesium (Cs), copper (Cu), mercury (Hg), lithium (Li), manganese (Mn), molybdenum (Mo), nickel (Ni), lead (Pb), rubidium (Rb), antimony (Sb), selenium (Se), tin (Sn), strontium (Sr), thallium (Tl), uranium (U), and zinc (Zn) were measured by inductively coupled plasma mass spectrometry. BMD was assessed at the lumbar spine, femoral neck, and total hip using dual-energy X-ray absorptiometry. Osteoporosis was diagnosed in 73 participants (19.2%). Osteoporotic women had significantly higher urinary concentrations of Cd, Mn, Pb, Sb, Sn, and Zn ($p < 0.05$). Statistically significant negative correlations were observed between BMD and urinary concentrations of Al, Cd, Hg, Mn, Sb, and U. After adjustment for confounders, elevated urinary concentrations of Cd, Mn, Pb, and Sb remained independently and significantly associated with higher odds of osteoporosis, with Cd (aOR = 1.495; $p = 0.026$) and Sb (aOR = 2.059; $p = 0.030$) showing the strongest associations. In addition, women with urinary concentrations above the 90th percentile for both Cd and Sb had a significantly higher prevalence of osteoporosis compared to those with lower levels (44.4% vs. 18.0%; $p = 0.011$). Longitudinal studies are needed to confirm causality and inform prevention strategies.

Keywords: metals; metalloids; environmental exposure; bone mineral density; women; aging; osteoporosis

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1. Introduction

Osteoporosis is a highly prevalent osteometabolic disorder characterized by a reduction in bone mass and the deterioration of bone microarchitecture, resulting in increased bone fragility and risk of fracture [1,2]. This condition is recognized as a major public health concern worldwide, particularly among postmenopausal women [3], driven by the dual impact of estrogen deficiency and aging on bone health [4]. Estrogen plays a key role in regulating bone remodeling by inhibiting osteoclast-mediated bone resorption and supporting osteoblast function. Following menopause, the abrupt decline in estrogen levels disrupts this balance, resulting in accelerated bone loss [4,5]. Concurrently, aging contributes to a gradual decline in bone formation due to reduced osteoblast activity, impaired calcium absorption, and changes in bone microarchitecture [6,7]. This combination of hormonal and age-related factors synergistically increases the risk of osteoporotic fractures, especially those affecting the hip and spine, leading to significant morbidity, long-term disability, reduced quality of life, and increased mortality [8].

Osteoporosis affects an estimated 500 million people worldwide, with women facing a lifetime risk of osteoporotic fractures between 30–50%, compared to 15–30% in men [9]. According to the Global Burden of Disease Study 2019, low BMD was responsible for 438,000 deaths and 16.6 million disability-adjusted life years (DALYs) worldwide [1]. That same year, 178 million new fractures were recorded, contributing to 25.8 million years lived with disability (YLDs) [10]. As global populations continue to age, the global burden of osteoporosis is projected to rise sharply, creating significant challenges to healthcare systems. This issue is further compounded by the feminization of aging, as, on average, women live longer than men and are disproportionately affected by the disease.

In Brazil, osteoporosis also poses a significant and growing public health challenge. Recent national surveys estimate the prevalence of osteoporosis among Brazilian women over the age of 50 to range between 15% and 33%, depending on the diagnostic criteria and region studied [11]. The aging demographic profile of the Brazilian population, combined with lifestyle factors such as sedentary behavior, sub-optimal nutrition, and low vitamin D concentrations, has contributed to an increasing incidence of osteoporotic fractures. Hip fractures, in particular, have shown a rising trend in hospitalization rates, imposing significant costs on the Brazilian Unified Health System (SUS) and affecting patients' functional independence and quality of life [8].

Given its significant clinical and socioeconomic impact, understanding the modifiable risk factors for osteoporosis is essential to guide public health interventions and preventive strategies. While traditional determinants, including age, sex, hormonal status, calcium and vitamin D intake, and physical activity, are well established [12], growing evidence suggests that environmental exposures to toxic metals, such as lead, cadmium, and arsenic, may also play a significant role in bone health and the development of osteoporosis [13–15], and this warrants further investigation.

Metals and metalloids are ubiquitous in the environment due to both natural and anthropogenic activities, and humans can be exposed through inhalation, ingestion, or dermal contact [16,17]. Several studies have investigated the influence of essential and toxic elements on bone health, revealing complex and sometimes contradictory effects. Essential trace elements, such as copper (Cu), manganese (Mn), selenium (Se), zinc (Zn), and cobalt (Co), are essential for maintaining normal physiological functions, including bone metabolism [18]. However, studies have shown that high levels of manganese (Mn) exposure may be associated with an increased risk of osteoporosis [19]. Zn has been shown to promote osteoblast proliferation and differentiation and bone matrix formation [20]. Selenium (Se), recognized for its antioxidant properties, may protect against oxidative stress [21,22], a factor that has been implicated in bone loss, and cobalt (Co) is involved in

vitamin B12 metabolism, which may indirectly influence bone health [23]. However, both deficient and excessive intakes of these essential metals can have adverse effects [18,23].

Numerous epidemiological studies have highlighted the detrimental effects of exposure to toxic metals, particularly cadmium (Cd) and lead (Pb), on BMD and fracture risk [24–26]. Cd has been consistently linked to adverse skeletal outcomes. In a recent systematic review and meta-analysis conducted by our group, we demonstrated that even low-level environmental Cd exposure is linked to an increased risk of osteoporosis in postmenopausal women [27]. Similarly, low-level Pb exposure has been implicated in bone demineralization and disturbances in calcium homeostasis [28]. The effects of mercury (Hg) on bone health are less well defined. Although human data are lacking, some studies link Hg exposure to altered calcium homeostasis and increased osteoclast activity [29], while others report inconsistent findings [30]. Furthermore, elements such as antimony (Sb) and thallium (Tl) have been shown to induce oxidative stress [31–33], a process detrimental to bone integrity. However, their specific roles and underlying mechanisms in bone metabolism remain poorly understood and warrant further investigation.

Other less common elements, such as lithium (Li) and strontium (Sr), present more complex or even contradictory effects, depending on the exposure level and the population studied [34]. Lithium has been suggested to promote bone formation through the activation of the Wnt/β-catenin signaling pathway [35,36], a critical signaling pathway in osteogenesis [37], while Sr, although used therapeutically in osteoporosis management, may impair normal bone mineralization when present at high environmental levels [18,38,39]. Uranium (U) and cesium (Cs) are radioactive elements that may also interfere with calcium homeostasis in bone [40–42], though their effects in human populations remain poorly understood.

This cohort study seeks to address existing knowledge gaps by investigating the associations between exposure to a broad range of metals and metalloids—including aluminum (Al), barium (Ba), Cd, Co, Cs, Cu, Hg, Li, Mn, molybdenum (Mo), nickel (Ni), Pb, rubidium (Rb), Sb, Se, tin (Sn), Sr, Tl, U, and Zn—and BMD in postmenopausal women. By biomonitoring urinary metal(loid) levels, this study offers novel insights into how environmental exposure to these metals may affect bone health and contribute to osteoporosis risk.

2. Methods

2.1. Study Design and Population

We conducted a cross-sectional study using a cohort of 380 postmenopausal women. Ethical approval for the study was granted by the Research Ethics Committees of the State University of Western Paraná (Unioeste), Plataforma Brasil (approval number: 2.636.746), and Fernando Pessoa University in Porto, Portugal. Prior to participation, all individuals provided written informed consent.

Data collection spanned from March 2022 to February 2024. Participants were recruited through announcements disseminated via social media platforms, universities, medical clinics, health centers, hospitals, and both regional and municipal health departments. The inclusion criteria specified women between 50 and 70 years of age who were postmenopausal, defined retrospectively as experiencing at least 12 consecutive months without menstruation, and who had been residing in the study region for a minimum of 10 years. Exclusion criteria included the presence of serious active medical conditions such as advanced hepatic or renal insufficiency and cancer, a medically confirmed diagnosis of secondary osteoporosis—including but not limited to hyperparathyroidism, malignancies, or chronic corticosteroid therapy—as well as any history of occupational exposure to metals through industrial employment.

After obtaining informed consent, participants completed a structured questionnaire designed to collect data on osteoporosis risk factors, potential dietary and occupational metal exposures, as well as relevant sociodemographic and health-related variables. Prolonged bed rest was defined as a duration of 28 days or more, while insufficient physical activity was classified as engaging in less than 30 min of exercise per day. Following the questionnaire, trained research staff measured each participant's body weight and height, from which body mass index (BMI) was calculated. The research team then coordinated the scheduling of urine sample collection and bone mineral density (BMD) assessments for all participants.

2.2. BMD Measurement

Bone mineral density (BMD) assessment was conducted for all participants using dual-energy X-ray absorptiometry (DEXA). The examinations were performed within the same radiology department utilizing the HOLOGIC Horizon-A model device. Measurements were obtained at standardized anatomical locations, specifically the lumbar spine, femoral neck, and total hip. The classification of bone health status followed the guidelines established by the World Health Organization (WHO). According to these criteria, osteoporosis is diagnosed when BMD is reduced by 2.5 SD or more at any of the evaluated bone sites.

2.3. Measurement of Urinary Metal(loid) Concentrations

First-morning urine samples were collected in metal-free tubes and stored at −20 °C until analysis. Urinary metal and metalloid concentrations were performed using inductively coupled plasma mass spectrometry (ICP-MS), equipped with a quadrupole ion deflector (NexION® 2000, PerkinElmer, Shelton, CT, USA) and operated with high-purity argon gas (99.999%, Air Liquide, São Paulo, Brazil), following the analytical protocol previously established in the laboratory [43]. All reagents employed were of analytical grade (Sigma-Aldrich, St. Louis, MO, USA). Nitric acid (HNO_3) used in sample preparation was further purified through sub-boiling distillation in a quartz distillation apparatus (Kürner Analysentechnik).

For each element analyzed, calibration curves with matrix matching were constructed using standard solutions ranging from 0 to 200 µg/L, prepared with a diluent composed of 0.5% HNO_3 and 0.01% Triton X-100. Method accuracy and precision were evaluated using certified reference urine samples provided by the Institut National de Santé Publique du Québec (INSPQ) (QM-U-Q1509, Quebec, Canada). A 200 µL aliquot of each urine sample was diluted to a final volume of 5 mL with the prepared diluent, and all measurements were conducted in triplicate. Urinary element concentrations falling below the limit of detection (LOD) were estimated by assigning a value equal to the LOD divided by the square root of two ($LOD/\sqrt{2}$).

Urinary creatinine concentrations were determined using the alkaline picrate method on the Atellica® CH analyzer (Siemens, São Paulo, Brazil). Metal and metalloid concentrations were then normalized to creatinine concentrations in urine and expressed as µg/g creatinine.

All procedures were performed at the Analytical and Systems Toxicology Laboratory (ASTox), Ribeirão Preto School of Pharmaceutical Sciences, University of São Paulo.

2.4. Statistical Analysis

Categorical variables were summarized as absolute and relative frequencies (n, %) and compared using the chi-square test or Fisher's exact test, as appropriate. Quantitative variables were presented as medians with interquartile ranges (IQRs; Q1–Q3) and compared between groups using the Mann–Whitney U test due to non-normal distributions.

Associations between key variables were assessed using Spearman's rank or Pearson correlation coefficients, with ln-transformation applied when necessary. A heatmap based on Spearman's correlation values (selected due to non-normality) was used to visualize relationships among urinary concentrations of the analyzed elements.

Multiple linear regression with stepwise selection was used to identify independent variables associated with BMD; variables were ln-transformed when needed to meet model assumptions. Additionally, binary logistic regression was performed to evaluate the association between potential predictors and osteoporosis risk. Odds ratios (ORs) were adjusted for age, BMI, duration of menopause, smoking status, and prolonged bed rest.

All analyses were performed using IBM SPSS Statistics version 30.0. A two-tailed p-value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the Study Population

The sociodemographic characteristics, health habits, and clinical data of the postmenopausal women included in this study are summarized in Table 1. The median age of the 380 participants was 60 years. The median BMI was 27 kg/m^2, with 75% of the women presenting a BMI above the upper-normal cutoff of 25 kg/m^2. The majority of participants (93.7%) reported never having smoked or being former smokers, and only one woman reported current alcohol consumption. The overall prevalence of osteoporosis in the study population was 19.2%.

Table 1. Clinical and sociodemographic characteristics of participants, presented overall and according to osteoporosis diagnosis.

Variables	Overall n = 380	No Osteoporosis n = 307	With Osteoporosis n = 73	p-Value [1]
Age (years)	60.0 (56.0; 65.8)	60.0 (56.0; 65.0)	62.0 (59.0; 66.0)	**0.011**
BMI (kg/m^2)	27.0 (24.4; 30.2)	27.6 (24.8; 30.8)	26.1 (23.4; 28.1)	**<0.001**
Length of menopause (years)	13.0 (7.3; 19.0)	12.0 (7.0; 18.0)	16.0 (10.5; 21.5)	**0.002**
Prior fracture (yes)	109 (28.7%)	84 (27.4%)	25 (34.2%)	0.252
Arthritis (yes)	72 (18.9%)	62 (20.2%)	10 (13.7%)	0.246
Vitamin D intake (yes)	183 (48.2%)	149 (48.5%)	34 (46.4%)	0.795
Corticoids (yes)	88 (23.2%)	70 (22.8%)	18 (24.7%)	0.758
Prolonged bed rest (yes)	28 (7.4%)	21 (6.8%)	7 (9.6%)	0.454
No exercise (yes)	135 (35.5%)	112 (36.5%)	23 (31.5%)	0.497
Calcium intake (yes)	100 (26.3%)	68 (22.1%)	32 (43.8%)	**<0.001**
Alcohol intake (yes)	1 (0.3%)	1 (0.3%)	0 (0%)	1.000
Smoking (yes)	24 (6.3%)	16 (5.2%)	8 (11.0%)	0.333
Antiresorptive medications				**<0.001**
Bisphosphonates	10 (2.6%)	4 (1.3%)	6 (8.2%)	
Bisphosphonates and HRT	1 (0.3%)	0 (0%)	1 (1.4%)	
HRT	45 (11.8%)	33 (10.7%)	12 (16.4%)	
No	324 (85.3%)	270 (87.9%)	54 (74.0%)	
Lumbar spine				
BMD (g/cm^2)	0.92 (0.82; 1.06)	0.97 (0.88; 1.08)	0.74 (0.70; 0.77)	**<0.001**
T-score	−1.10 (−2.00; 0.10)	−0.70 (−1.50; 0.40)	−2.80 (−3.10; −2.50)	**<0.001**
Diagnosis of osteoporosis	61 (16.1%)	0 (0%)	61 (83.6%)	**<0.001**
Femoral neck				
BMD (g/cm^2)	0.73 (0.65; 0.83)	0.75 (0.68; 0.86)	0.63 (0.56; 0.71)	**<0.001**

Table 1. *Cont.*

Variables	Overall n = 380	No Osteoporosis n = 307	With Osteoporosis n = 73	*p*-Value [1]
T-score	−1.10 (−1.78; −0.20)	−0.90 (−1.50; 0.10)	−2.00 (−2.65; −1.35)	**<0.001**
Diagnosis of osteoporosis	25 (6.6%)	0 (0%)	25 (34.2%)	**<0.001**
Total hip				
BMD (g/cm^2)	0.87 (0.78; 0.96)	0.90 (0.81; 0.98)	0.74 (0.69; 0.84)	**<0.001**
T-score	−0.60 (−1.30; 0.10)	−0.40 (−1.00; 0.30)	−1.60 (−2.05; −0.90)	**<0.001**
Diagnosis of osteoporosis	10 (2.6%)	0 (0%)	10 (13.7%)	**<0.001**
Urinary creatinine (mg/dL)	52.7 (29.0; 90.9)	52.8 (31.1; 93.1)	52.5 (22.2; 85.4)	0.090

Results are presented as median (first quartile; third quartile), unless otherwise indicated; [1] Mann–Whitney test; Statistically significant differences are shown in bold. Abbreviations: BMD, Bone mineral density; BMI, Body mass index; HRT, Hormone replacement therapy. Statistically significant *p*-values are shown in bold.

Table 1 also shows a comparison of these variables between women with and without a diagnosis of osteoporosis. Statistically significant differences were observed between the two groups in terms of age, BMI, menopausal duration, and calcium intake. Specifically, women diagnosed with osteoporosis were slightly older, had a lower BMI, experienced a longer postmenopausal period, and reported higher calcium intake. Additionally, a significantly higher proportion of women with osteoporosis reported using antiresorptive medication ($p < 0.001$).

As expected, bone mineral density (BMD) and T-scores at the lumbar spine, femoral neck, and total hip were significantly lower in women with osteoporosis compared to those without osteoporosis ($p < 0.001$).

3.2. Urinary Concentrations of Metals and Metalloids in Brazilian Postmenopausal Women

Table 2 depicts the urinary concentrations of 20 metals and metalloids for the entire study cohort, as well as separately for women with and without an osteoporosis diagnosis. After adjusting for age, BMI, duration of menopause, smoking status, and prolonged bed rest, statistically significant differences in median urinary concentrations were identified between the two groups for Cd, Mn, Pb, Sb, Sn, and Zn. Specifically, women with osteoporosis had higher median urinary concentrations of Cd (0.38 µg/g creatinine vs. 0.30 µg/g creatinine, $p = 0.012$), Mn (7.0 µg/g creatinine vs. 4.1 µg/g creatinine, $p = 0.014$), Pb (4.8 µg/g creatinine vs. 3.7 µg/g creatinine, $p = 0.020$), Sb (0.27 µg/g creatinine vs. 0.17 µg/g creatinine, $p = 0.015$), Sn (0.70 µg/g creatinine vs. 0.49 µg/g creatinine, $p = 0.046$), and Zn (860 µg/g creatinine vs. 777 µg/g creatinine, $p = 0.004$) compared to women without osteoporosis.

Table 2. Urinary concentrations (expressed in µg/g creatinine) of metals and metalloids, presented overall and according to osteoporosis diagnosis.

Elements (µg/g creat)	Overall n = 380	No Osteoporosis n = 307	With Osteoporosis n = 73	*p*-Value [1]
Al	217 (108; 448)	202 (106; 425)	340 (129; 638)	0.273
Ba	16.5 (8.3; 29.0)	15.4 (8.0; 27.8)	19.7 (9.0; 36.8)	0.127
Cd	0.30 (0.15; 0.55)	0.30 (0.14; 0.49)	0.38 (0.16; 0.71)	**0.012**
Co	0.23 (0.09; 0.46)	0.22 (0.08; 0.46)	0.26 (0.13; 0.66)	0.543
Cs	7.9 (4.0; 14.0)	7.7 (4.0; 13.5)	8.2 (4.6; 15.5)	0.419
Cu	93.6 (53.1; 172.9)	92.0 (52.9; 169.9)	98.4 (57.6; 184.7)	0.148
Hg	0.99 (0.41; 2.07)	0.97 (0.40; 1.93)	1.03 (0.55; 2.91)	0.501
Li	6.9 (3.2; 14.9)	6.7 (3.2; 14.8)	8.5 (3.9; 17.0)	0.578

Table 2. *Cont.*

Elements (µg/g creat)	Overall n = 380	No Osteoporosis n = 307	With Osteoporosis n = 73	*p*-Value [1]
Mn	4.4 (1.7; 9.7)	4.1 (1.7; 8.8)	7.0 (2.4; 15.7)	**0.014**
Mo	17.0 (8.6; 33.4)	17.0 (8.6; 32.3)	16.5 (9.3; 37.7)	0.378
Ni	16.0 (8.1; 30.9)	15.8 (8.0; 28.9)	17.5 (9.1; 35.9)	0.219
Pb	4.0 (2.1; 8.1)	3.7 (2.1; 7.4)	4.8 (2.7; 11.7)	**0.020**
Rb	3105 (1567; 5742)	3026 (1557; 5627)	3636 (1649; 6220)	0.570
Sb	0.19 (0.10; 0.39)	0.17 (0.10; 0.36)	0.27 (0.13; 0.52)	**0.015**
Se	11.7 (5.9; 24.4)	12.0 (6.0; 25.6)	10.8 (5.5; 22.9)	0.439
Sn	0.52 (0.23; 1.09)	0.49 (0.22; 0.92)	0.70 (0.24; 1.86)	**0.046**
Sr	76.4 (40.7; 179.3)	75.8 (38.5; 178.7)	87.9 (51.3; 215.3)	0.100
Tl	0.22 (0.11; 0.46)	0.21 (0.11; 0.45)	0.26 (0.12; 0.54)	0.076
U	0.017 (0.005; 0.041)	0.016 (0.005; 0.038)	0.021 (0.008; 0.056)	0.109
Zn	808 (458; 1548)	777 (460; 1510)	860 (456; 1882)	**0.004**

Results are presented as median (first quartile; third quartile); [1] Generalized Linear Model (GLM) of the ln-transformed elements adjusted for age (years), BMI (Kg/m^2), length of menopause (years), smoking, and prolonged bed rest. Statistically significant differences are shown in bold. Abbreviations: Al, aluminum; Ba, barium; Cd, cadmium; Co, cobalt; Cs, cesium; Cu, copper; Hg, mercury; Li, lithium; Mn, manganese; Mo, molybdenum; Ni, nickel; Pb, lead; Rb, rubidium; Sb, antimony; Se, selenium; Sn, tin; Sr, strontium; Tl, thallium; U, uranium; Zn, zinc. Statistically significant *p*-values are shown in bold.

3.3. Intercorrelations Between Metal(loid) Concentrations in Urine

Figure 1 presents the heatmap generated from Spearman correlation coefficients calculated for all measured metal(loid) concentrations in urine of the study population. Notably, several strong positive correlations were observed between creatinine-adjusted element concentrations. The strongest correlations in decreasing order were between Rb and Cs (0.955, $p < 0.01$), Tl and Rb (0.904, $p < 0.01$), Se and Cs (0.892, $p < 0.01$), Tl and Cs (0.890, $p < 0.01$), Mn and Al (0.871, $p < 0.01$), Ni and Ba (0.869, $p < 0.01$), Se and Rb (0.866, $p < 0.01$), Zn and Ni (0.858, $p < 0.01$), Mo and Cs (0.850, $p < 0.01$), Ni and Cu (0.849, $p < 0.01$), Zn and Cu (0.847, $p < 0.01$), Cu and Cs (0.845, $p < 0.01$), Zn and Ba (0.843, $p < 0.01$), Ba and Al (0.840, $p < 0.01$), Rb and Mo (0.832, $p < 0.01$), Zn and Cu (0.828, $p < 0.01$), Cu and Ba (0.826, $p < 0.01$), Sr and Cs (0.820, $p < 0.01$), Rb and Cu (0.816, $p < 0.01$), Pb and Ba (0.814, $p < 0.01$), Sb and Ni (0.811, $p < 0.01$), Pb and Al (0.808, $p < 0.01$), and Sb and Ba (0.805, $p < 0.01$).

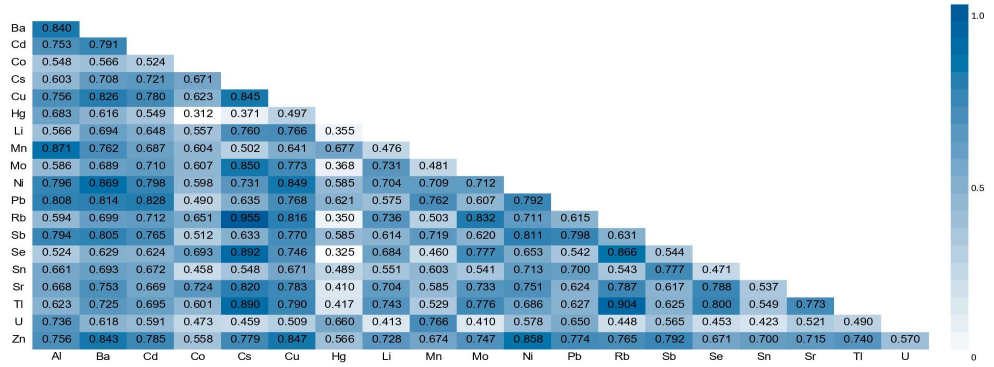

Figure 1. Heatmap plot showing correlation between the elements in urine. Spearman's rank correlation coefficients (R).

3.4. Association of Studied Variables (Clinical and Analytical) with BMD

The statistically significant associations obtained between BMD at the lumbar spine, femoral neck, and total hip and age, BMI, menopause length, and urinary metal(loid) concentrations are presented in Table 3. Age and menopause length showed negative correlations with BMD at all three sites, while BMI showed positive correlations. Among the metals and metalloids, weak but statistically significant negative correlations were observed between BMD and urinary concentrations of Al (lumbar spine, total hip), Cd (lumbar spine, total hip), Hg (total hip), Mn (lumbar spine), Sb (lumbar spine, total hip), and U (lumbar spine, femoral neck, total hip).

Table 3. Statistically significant associations between ln-transformed bone mineral density (BMD) at the lumbar spine, femoral neck, and total hip and ln-transformed age, BMI, menopause length, and urinary metal(loid) concentrations.

		BMD Lumbar Spine	**BMD Femoral Neck**	**BMD Total Hip**
BMD Lumbar Spine	r	1	0.525	0.697
	p		**<0.001**	**<0.001**
BMD Femoral Neck	r	0.525	1	0.743
	p	**<0.001**		**<0.001**
BMD Total Hip	r	0.697	0.743	1
	p	**<0.001**	**<0.001**	
Age	r	−0.182	−0.256	−0.278
	p	**<0.001**	**<0.001**	**<0.001**
BMI	r	0.301	0.311	0.456
	p	**<0.001**	**<0.001**	**<0.001**
Menopause Length	r	−0.247	−0.220	−0.271
	p	**<0.001**	**<0.001**	**<0.001**
Al	r	−0.112	−0.062	−0.104
	p	**0.030**	0.227	**0.042**
Cd	r	−0.102	−0.064	−0.128
	p	**0.048**	0.215	**0.013**
Hg	r	−0.084	−0.062	−0.128
	p	0.101	0.226	**0.012**
Mn	r	−0.128	−0.072	−0.097
	p	**0.012**	0.159	0.058
Sb	r	−0.106	−0.068	−0.104
	p	**0.039**	0.186	**0.044**
U	r	−0.107	−0.103	−0.116
	p	**0.036**	**0.044**	**0.023**

r, Pearson correlation coefficient; Abbreviations: Al, aluminum; BMD, bone mineral density; BMI, body mass index; Cd, cadmium; Hg, mercury; Mn, manganese; Sb, antimony; U, uranium. Statistically significant *p*-values are shown in bold.

Given that lumbar spine was the bone site where most cases of osteoporosis were diagnosed, we sought to determine the primary determinants of BMD at this location. Multiple linear regression analysis identified ln-transformed BMI as the strongest positive predictor of lumbar spine BMD, while ln-transformed menopause length, smoking, and prolonged bed rest were significant negative predictors (Table 4). No metals or metalloids were included as significant predictors of lumbar spine BMD in this model.

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Table 4. Main variables associated with bone mineral density at the lumbar spine, by multiple linear regression analysis.

Dependent Variable	Model	Unstandardized Coefficients		Standardized Coefficients	t	*p*-Value
		Beta (95% CI)	Std. Error	Beta		
Ln BMD	(Constant)	−0.956 (−1.277; −0.636)	0.163		−5.863	**<0.001**
	Ln BMI	0.310 (0.214; 0.405)	0.049	0.299	6.366	**<0.001**
	Ln menopause Length	−0.052 (−0.072; −0.032)	0.010	−0.242	−5.140	**<0.001**
	Smoking	−0.024 (−0.045; −0.004)	0.010	−0.111	−2.358	**0.019**
	Prolonged bed rest	−0.067 (−0.129; −0.004)	0.032	−0.099	−2.096	**0.037**

Abbreviations: BMD, bone mineral density; BMI, body mass index. Statistically significant *p*-values are shown in bold.

3.5. Association Between Urinary Metal(loid) Concentrations and Osteoporosis Risk

Independent adjusted odds ratios (aORs) for osteoporosis outcome associated with ln-transformed urinary metal and metalloid variables are presented in Figure 2. After adjusting for age, BMI, length of menopause, smoking, and prolonged bed rest, urinary Cd (aOR = 1.495, 95% CI: 1.048; 2.131, $p = 0.026$), Mn (aOR = 1.014, 95% CI: 1.001; 1.028, $p = 0.040$), Sb (aOR = 2.059, 95% CI: 1.073; 3.950, $p = 0.030$), and Zn (aOR = 1.00027, 95% CI: 1.00006; 1.00048, $p = 0.012$) were significantly associated with osteoporosis outcome. However, only Cd and Sb showed clinically meaningful associations, as the odds ratios for Mn and Zn were very close to 1.

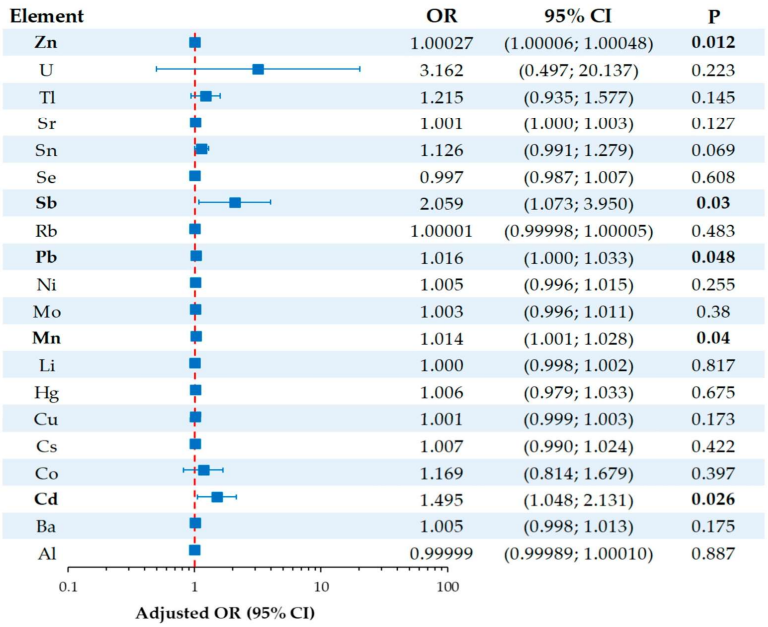

Figure 2. Forest plot showing the independent adjusted odds ratios (aORs) for osteoporosis outcomes associated with metal(loid) exposure. ORs were adjusted for age, BMI, length of menopause, smoking, and prolonged bed rest. Statistically significant *p*-values are shown in bold.

Given that Cd and Sb demonstrated the strongest and most clinically meaningful associations with increased osteoporosis risk, we further analyzed their combined effects. Women were categorized based on whether their urinary concentrations of both elements were below or at/above the 90th percentile thresholds (1.079 μg/g creatinine for cadmium and 0.729 μg/g creatinine for antimony; see Supplementary Table S1). Notably, women with elevated urinary concentrations exhibited significantly lower BMD at all measured bone sites and a higher prevalence of osteoporosis (44.4% vs. 18.0%; $p = 0.011$).

4. Discussion

This cross-sectional study investigated the association between urinary concentrations of 20 metal(loid)s and osteoporosis in a cohort of postmenopausal Brazilian women. Several significant associations were identified. Consistent with established risk factors for osteoporosis, women diagnosed with the disease were generally older, had a lower BMI, and experienced a longer time since menopause onset. Moreover, increased urinary concentrations of aluminum, cadmium, mercury, manganese, antimony, and uranium were correlated with decreased BMD. Notably, this study is the first to demonstrate a significant association between elevated urinary concentrations of both cadmium and antimony and an increased risk of postmenopausal osteoporosis, even after adjusting for potential confounders. In light of the increasing environmental burden of these elements from industrial, mining, and vehicular sources [44], our findings reinforce the importance of further human and environmental monitoring studies.

Biomonitoring studies are crucial for assessing population-level exposure to environmental metals and metalloids, identifying vulnerable groups, and informing risk mitigation efforts. Beyond characterizing exposure–outcome relationships, biomonitoring provides an essential tool for evaluating the effectiveness of regulatory policies over time [45,46]. Urine is widely recognized as a suitable biological matrix for such assessments, owing to its non-invasive collection and its reliability for specific metals. For elements such as cadmium, cobalt, cesium, molybdenum, nickel, antimony, strontium, thallium, and uranium, urinary concentrations serve as robust biomarkers of exposure due to their relatively stable excretion profiles [47]. In contrast, for metals such as lead, mercury, manganese, aluminum, copper, and zinc, urinary levels are considered less reliable indicators of exposure [48]. This limitation arises from alternative primary excretion routes (e.g., biliary or fecal pathways) or tight homeostatic regulation, which can obscure the relationship between exposure and urinary elimination.

In our study, urinary concentrations of two essential trace metals—manganese and zinc—and of four toxic metal(loid)s—cadmium, lead, tin, and antimony—were higher in osteoporotic women compared with non-osteoporotic controls (Table 2). Both Mn and Zn were reported to present a U-shaped curve in terms of their toxicity and effect on bone health. This means that, at low levels, they are essential and beneficial for bone formation and mineralization, whereas, at excessively high levels, they become toxic, leading to impaired bone metabolism and bone loss [18]. Therefore, the increased urinary excretion of Mn and Zn observed in the osteoporosis group may reflect heightened environmental exposure but could also result from osteoporosis-induced loss of essential trace elements, as previously described [49]. This loss may further exacerbate deficiencies that are critical for maintaining bone health. Conversely, the elevated urinary concentrations of Cd, Pb, Sn, and Sb are more likely attributable to increased environmental exposure to these toxic metals, which are known to interfere with bone remodeling and mineralization, thereby potentially contributing to osteoporosis risk [14]. Among them, in the present study only cadmium and antimony showed significant negative correlations with BMD (Table 3), implicating a potential role in bone deterioration. However, the observed correlation

coefficients were modest, indicating weak predictive value when considered individually. This was corroborated by multiple linear regression analysis, which failed to identify any of the metals as independent predictors of lumbar spine BMD (Table 4).

Nevertheless, potential adverse effects may become more pronounced at higher exposure levels, as we recently demonstrated for Cd in Brazilian postmenopausal women [50], or in scenarios involving co-exposure to multiple metal(loid)s. In our study, women with urinary cadmium and antimony concentrations above the 90th percentile exhibited a significantly higher prevalence of postmenopausal osteoporosis (Supplementary Table S1). This finding underscores the possible additive or synergistic effects of Cd and Sb on bone degradation, in agreement with previous reports on the combined impact of metal mixtures on BMD reduction [51]. Notably, both cadmium and antimony tend to accumulate in soil and crops due to industrial emissions and agricultural practices [52,53], increasing the likelihood of concurrent human exposure through dietary intake or shared environmental sources. This co-exposure scenario is further supported by the strong positive correlation observed between urinary concentrations of these metals in our cohort ($p = 0.765$; Figure 1).

Substantial epidemiological evidence indicates that chronic exposure to cadmium is associated with impaired bone metabolism, reduced BMD, and increased risk of osteopenia and osteoporosis [14,27,54,55]. Cadmium exerts its deleterious effects through multiple mechanisms, including renal dysfunction, disruption of calcium homeostasis, oxidative stress, and inflammation. Specifically, cadmium inhibits osteoblast differentiation while enhancing osteoclast activity, partly through interference with Wnt/β-catenin signaling and upregulation of RANKL expression [15,56]. Cadmium-induced oxidative stress activates NF-κB and increases proinflammatory cytokines such as IL-6 and TNF-α, further contributing to bone resorption [57]. Additionally, cadmium disrupts calcium metabolism by impairing gastrointestinal absorption, renal reabsorption, and vitamin D receptor-mediated synthesis of 1,25-dihydroxyvitamin D [58]. Proteomic and metabolomic analyses have also revealed cadmium-related alterations in osteogenic gene expression, bone matrix protein production, and mineralization pathways, further implicating cadmium in skeletal fragility [59]. In contrast, data on antimony remain limited. Given its chemical similarity to arsenic, a recognized osteotoxicant, antimony may exert analogous effects, including oxidative stress induction and disruption of osteoblast function [33]. Some experimental studies have linked high antimony levels to redox imbalance and increased bone loss [60]. However, the evidence remains sparse and inconsistent, highlighting the need for additional in vivo and in vitro studies to elucidate antimony's role in bone demineralization and osteoporosis risk.

The adjusted odds ratios provided deeper insight into the independent relationships between metals and metalloid exposure and osteoporosis risk (Figure 2). Antimony demonstrated the strongest association (aOR = 2.059), suggesting that higher urinary antimony concentrations are associated with more than a two-fold increase in the odds of developing osteoporosis. Cadmium was also associated with an increased risk (aOR = 1.495), indicating a moderate but clinically meaningful effect. Statistically significant associations were observed for manganese and zinc as well; however, their effect sizes were minimal, as indicated by the low odds ratios. The significance for manganese and zinc likely reflects the large sample size and narrow confidence intervals rather than a meaningful biological impact.

To the best of our knowledge, only two studies to date have investigated the associations between urinary concentrations of multiple metallic elements and BMD loss or osteoporosis risk in older and/or postmenopausal women. The first study, based on data from the U.S. National Health and Nutrition Examination Survey (NHANES) 2005–2010, supports our findings by identifying urinary cadmium, along with arsenic and tungsten,

as negatively associated with BMD [61]. A more recent analysis of NHANES 2017–2020 data found no statistically significant associations between BMD in women and any of the 11 examined metal(loid)s (Ba, Cd, Co, Cs, Mo, Mn, Pb, Sb, Sn, Tl, and W) after adjusting for potential confounders. However, a consistent negative trend was observed for all elements except manganese. This may reflect the impact of successful public health interventions that have substantially reduced environmental exposures in the U.S. population over time [62]. As a result, current exposure levels may be below the biological threshold needed to influence bone health. Notably, the NHANES 2017–2020 study reported a sex-specific effect of antimony: urinary antimony levels were negatively associated with femoral BMD in women but positively associated in men [63]. These findings, consistent with our data, suggest that antimony exposure may represent a sex-specific risk factor for bone loss in women. Further research is needed to confirm these associations and elucidate the biological mechanisms underlying antimony toxicity.

Although the observed associations underscore the potential role of chronic low-level metal exposure as a modifiable risk factor for postmenopausal osteoporosis, the following limitations warrant consideration. First, the cross-sectional design precludes causal inference, and reverse causation, whereby osteoporosis influence on metal and metalloid excretion cannot be completely excluded. Second, the study population consists of postmenopausal women from a specific region of Brazil, which may limit the generalizability of the results. Third, although creatinine adjustment was applied to ensure comparability with previous studies, it may introduce bias due to variability in muscle mass [64]. This limitation should be acknowledged when interpreting the results. Finally, we did not assess dietary intake or other potential sources of metal and metalloid exposure (e.g., traffic emissions), which could also influence the observed associations.

Future longitudinal studies are essential to confirm these associations and to elucidate the underlying mechanisms. Additionally, identifying the primary sources of exposure would further support the development of effective prevention strategies.

5. Conclusions

This study adds to the growing body of evidence that environmental exposure to metals and metalloids is significantly associated with reduced BMD and increased odds of osteoporosis in postmenopausal women. Antimony demonstrated the strongest association with osteoporosis risk, while cadmium was linked to a moderate yet clinically relevant risk. While causality cannot be established, the findings highlight the need to address environmental metal exposure as part of broader strategies to preserve bone health. Future longitudinal and mechanistic studies are essential to confirm these associations and to inform risk assessment and mitigation efforts.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/toxics13060489/s1, Table S1: Comparison of participants with urinary concentrations of both Cd and Sb below and at or above the 90th percentile (P90; 1.079 and 0.729 µg/g creatinine for Cd and Sb, respectively).

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Fernando Pessoa University (Porto, Portugal), Western Paraná State University (Cascavel, Brazil), and Plataforma Brasil (approval number: 2.636.746). All individual participants provided written informed consent.

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

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy restrictions.

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

Abbreviations

The following abbreviations are used in this manuscript:

aOR	Adjusted odds ratio
BMI	Body mass index
DALYs	Disability-adjusted life years
DEXA	Dual-energy X-ray absorptiometry
ICP-MS	Inductively coupled plasma–mass spectrometry
HRT	Hormone replacement therapy
NHANES	U.S. National Health and Nutrition Examination Survey
WHO	World Health Organization
YLDs	Years lived with disability

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Supplementary Table S1. Comparison of participants with urinary concentrations of both Cd and Sb below and at or above the 90th percentile (P90; 1.079 and 0.729 µg/g creatinine for Cd and Sb, respectively).

Variables	Overall n = 380	Cd and Sb < P90 n = 362	Cd and Sb ≥ P90 n = 18	*p*-value[1]
Age (years)	60.0 (56.0; 65.8)	60.0 (56.0; 65.3)	63.5 (58.5; 66.0)	0.182
BMI (kg/m^2)	27.0 (24.4; 30.2)	27.2 (24.8; 30.4)	24.3 (20.9; 26.6)	**0.003**
Length of menopause (years)	13.0 (7.3; 19.0)	13.0 (7.0; 19.0)	16.0 (9.3; 21.0)	0.310
Prolonged bed rest	28 (7.4%)	27 (7.5%)	1 (5.6%)	1.000
Smoking	24 (6.3%)	24 (6.6%)	0 (0%)	0.266
Urinary Cd (µg/g creat)	0.30 (0.15; 0.55)	0.29 (0.14; 0.49)	1.44 (1.18; 2.98)	**<0.001**
Urinary Sb (µg/g creat)	0.19 (0.10; 0.39)	0.18 (0.10; 0.35)	1.17 (0.86; 1.58)	**<0.001**
Lumbar BMD (g/cm^2)	0.92 (0.82; 1.06)	0.93 (0.83; 1.06)	0.81 (0.72; 0.92)	**0.005***
Femoral BMD (g/cm^2)	0.73 (0.65; 0.83)	0.74 (0.66; 0.83)	0.64 (0.59; 0.68)	**<0.001***
Total hip BMD (g/cm^2)	0.87 (0.78; 0.96)	0.88 (0.79; 0.96)	0.76 (0.69; 0.84)	**<0.001***
Osteoporosis (Yes)	73 (19.2%)	65 (18.0%)	8 (44.4%)	**0.011**

Results are presented as median (first quartile; third quartile); [1]Mann-Whitney test; Statistically significant differences are shown in bold. Abbreviations: BMD, Bone mineral density; BMI, Body mass index; Cd, Cadmium; Sb, antimony. *, Statistical significance was kept after adjustment for BMI (P<0.05). Bold p-values indicate significant differences.

Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

CAPÍTULO IV. DISCUSSÃO GERAL

O presente capítulo tem como objetivo apresentar uma discussão integrada dos resultados obtidos nos diferentes estudos que constituem esta tese de doutoramento, centrando-se na associação entre a exposição ambiental a metais e metaloides e o risco de osteoporose e de disfunção renal em mulheres pós-menopáusicas. A progressão dos trabalhos, iniciados com uma revisão sistemática e meta-análise da relação entre a exposição ao Cd e a osteoporose, culminando numa abordagem de biomonitorização mais abrangente, envolvendo múltiplos metais e metaloides, permitiu uma compreensão mais aprofundada dos impactos destes elementos na saúde óssea e renal.

4.1. Cádmio e Risco de Osteoporose em Mulheres Pós-menopáusicas: Perspetiva Global e na População Brasileira

A revisão sistemática e meta-análise apresentada no primeiro artigo (**Capítulo I**) demonstrou que a exposição ambiental ao Cd, mesmo em níveis baixos, constitui um fator de risco relevante para o desenvolvimento de osteoporose em mulheres pós-menopáusicas. Este estudo, de carácter pioneiro pela sua abrangência a nível global, consolidou a evidência de uma associação significativa entre a exposição ao Cd e o aumento do risco de osteoporose. Especificamente, verificou-se que mulheres pós-menopáusicas expostas a níveis ambientalmente baixos de Cd apresentavam um risco 1,95 vezes superior de desenvolver osteoporose (OR = 1,95; IC 95%: 1,39–2,73; $p <$ 0,001), em comparação com grupos que apresentam menores concentrações de Cd urinário (UCd). De forma congruente, nos grupos expostos a níveis mais elevados de Cd, o risco aumentou para 1,99 vezes (OR = 1,99; IC 95%: 1,04–3,82; $p = 0,040$).

A consistência dos resultados observada entre os grupos com exposição baixa e elevada, embora com heterogeneidade significativa no grupo de alta exposição, reforça a noção de que o Cd representa um fator de risco para a osteoporose, mesmo em concentrações geralmente consideradas como ambientalmente seguras (baixas).

As variações nas concentrações de UCd entre as populações incluídas nos estudos analisados foram substanciais, com os países asiáticos a apresentarem níveis aproximadamente dez vezes superiores aos registados na Europa e na América do Norte. Esta disparidade geográfica poderá ser explicada, em grande medida, por diferenças nas

fontes de exposição, particularmente ao nível da dieta. Em populações não fumadoras, a ingestão de alimentos contaminados, como cereais e vegetais folhosos, constitui a principal via de exposição ao Cd. A contaminação do solo e da água em várias regiões asiáticas, decorrente de atividades industriais, exploração mineira e da aplicação de fertilizantes com elevado teor de Cd, tem favorecido uma maior bioacumulação deste metal em culturas alimentares. Entre estas, o arroz destaca-se como um dos principais veículos de exposição dietética ao Cd, dada a sua elevada capacidade de absorção e o papel central que desempenha na alimentação dessas populações (Lu et al., 2019).

De salientar que, até à data da presente investigação, não existiam estudos publicados sobre a exposição ao Cd e os seus efeitos na saúde óssea em populações da América Latina, nomeadamente do Brasil. Esta lacuna foi colmatada através do segundo estudo (**Capítulo II**) incluído nesta tese, um estudo transversal conduzido com 380 mulheres pós-menopáusicas residentes em Cascavel-PR, Brasil, uma região fortemente agrícola. A prevalência de osteoporose nesta população (19,2%) encontra-se em consonância com os dados nacionais reportados por Marinho et al. (2014), situando-se dentro da média global estimada para a respetiva faixa etária e perfil demográfico (Xiao et al., 2022). A mediana das concentrações de UCd na amostra foi de 0,30 μg/g de creatinina, indicativa de uma exposição crónica de baixo nível. Contrariamente ao expectável dado que se trata de uma população residente numa região marcadamente agrícola, estes valores são comparáveis aos registados em países como a Suécia e a Austrália, e substancialmente inferiores aos verificados em regiões asiáticas com elevada contaminação ambiental por Cd (Wang et al., 2015; La-Up et al., 2021).

Apesar dos níveis relativamente baixos de exposição, verificou-se que as mulheres situadas no percentil 95 das concentrações de UCd (≥ 1,1 μg/g de creatinina) apresentavam uma redução acentuada da DMO, bem como uma maior prevalência de osteoporose, sobretudo ao nível da coluna lombar e do colo femoral. Embora as análises de regressão linear múltipla ajustadas não terem identificado uma associação independente estatisticamente significativa entre UCd e DMO na amostra global, observaram-se tendências sugestivas de efeito adverso em níveis mais elevados de exposição. Nomeadamente, registaram-se associações limítrofes entre o UCd e a presença de osteopenia na região do colo femoral (p = 0,073), bem como com osteoporose na coluna lombar (p = 0,109).

Estes padrões foram corroborados pela aplicação da regressão bayesiana com máquina de

kernel (BKMR), a qual evidenciou uma relação não linear entre os níveis UCd e a DMO. A análise indicou que, em concentrações mais baixas, o impacto do Cd na densidade óssea é pouco expressivo, mas que, a partir de determinados limiares, se verifica um declínio mais acentuado da DMO, apontando para um possível efeito dose-dependente com relevância clínica.

Os mecanismos biológicos subjacentes à toxicidade do Cd no tecido ósseo são complexos e ainda não estão totalmente elucidados. O Cd possui uma semivida excecionalmente longa no organismo humano (estimada entre 10 e 30 anos), acumulando-se predominantemente nos rins e nos ossos. A osteoporose associada à exposição a este metal pode resultar, em parte, de disfunção renal induzida pelo Cd, a qual compromete a reabsorção tubular de cálcio e fósforo, elementos fundamentais para a mineralização óssea. Paralelamente, a síntese renal de vitamina D [1,25$(OH)_2$D] é inibida, reduzindo a absorção intestinal de cálcio e agravando o défice mineral.

Para além destes efeitos indiretos mediados pela função renal, diversas evidências apontam para um efeito osteotóxico direto do Cd, independente da nefrotoxicidade. A homeostase óssea depende de um equilíbrio dinâmico entre a formação óssea, mediada por osteoblastos, e a reabsorção óssea, mediada por osteoclastos. O Cd tem sido implicado na perturbação deste equilíbrio, inibindo a diferenciação e função de osteoblastos, estimulando a atividade osteoclástica e comprometendo a síntese de colagénio, resultando numa remodelação óssea desregulada e favorecendo a perda de massa óssea.

A nível molecular, os efeitos deletérios do Cd no osso parecem estar associados a múltiplas vias de toxicidade, incluindo stress oxidativo, lesões no ácido desoxirribonucleico (ADN), disfunção mitocondrial, senescência celular, apoptose e autofagia (Tang et al., 2025; Song et al., 2023). Adicionalmente, o Cd inibe vias de sinalização fundamentais para a osteogénese, como a via canónica Wnt/β-catenina, essencial para a diferenciação osteoblástica e manutenção da arquitetura óssea (Wu et al., 2019). A via PI3K/Akt, que regula vários processos celulares no tecido ósseo, também tem sido identificada como alvo da ação tóxica do Cd, sendo suprimida em modelos de osteoporose induzida por este metal (Song et al., 2023).

Importa ainda sublinhar que as mulheres estão particularmente vulneráveis aos efeitos tóxicos do Cd após a menopausa. Embora a absorção intestinal de Cd ocorra através de transportadores de ferro, diminuindo após a menopausa devido à redução das necessidades de ferro, os efeitos adversos sobre a saúde óssea podem intensificar-se nesse

período, possivelmente devido ao pico acumulativo de Cd renal. Adicionalmente, a depleção estrogénica característica da menopausa constitui um fator determinante na modulação dos efeitos do Cd sobre o osso, aumentando a suscetibilidade desta população aos seus efeitos osteotóxicos.

4.2. Exposição a Múltiplos Elementos e Risco de Osteoporose

Dando continuidade à análise dos efeitos do Cd na saúde óssea, o terceiro artigo (**Capítulo III**) desta tese alargou o âmbito da investigação, avaliando a associação entre a DMO e as concentrações urinárias de 20 metais e metaloides numa amostra da mesma população de mulheres pós-menopáusicas brasileiras. Esta abordagem abrangente permitiu explorar potenciais interações e efeitos combinados entre diversos elementos, proporcionando uma visão mais ampla dos riscos ambientais associados à osteoporose.

Os resultados indicaram que as mulheres com diagnóstico de osteoporose apresentavam concentrações urinárias significativamente mais elevadas de Cd, manganês, Pb, antimónio (Sb), estanho e zinco. Adicionalmente, foram identificadas correlações negativas estatisticamente significativas entre a DMO e os níveis urinários de Al, Cd, Hg, manganês, Sb e urânio, sugerindo um possível efeito tóxico cumulativo destes elementos na massa óssea.

Entre os elementos analisados, o Cd e o Sb destacaram-se por apresentarem associações independentes e clinicamente relevantes com o risco de osteoporose. Após ajuste para potenciais fatores de confusão (idade, índice de massa corporal, duração da menopausa, tabagismo e inatividade física prolongada), verificou-se que concentrações urinárias elevadas de Cd (aOR = 1,495; p = 0,026) e Sb (aOR = 2,059; p = 0,030) estavam associadas a um aumento significativo da probabilidade de ocorrer osteoporose. A associação com o Sb foi particularmente forte, traduzindo-se num risco mais do que duplicado de osteoporose entre as mulheres com maiores concentrações urinárias deste elemento. Embora o manganês e o zinco tenham revelado associações estatisticamente significativas, os seus efeitos foram de pequena magnitude, sugerindo uma relevância biológica limitada no contexto da população estudada.

Um dos resultados mais relevantes foi a identificação de um possível efeito combinado do Cd e do Sb. A prevalência de osteoporose foi significativamente superior nas mulheres com concentrações urinárias elevadas de ambos os elementos (acima do percentil 90),

atingindo 44,4%, comparativamente a 18,0% nas restantes participantes ($p = 0,011$). Esta observação suporta a hipótese da existência de efeitos aditivos ou sinérgicos entre o Cd e o Sb na deterioração da saúde óssea. A forte correlação positiva entre as concentrações urinárias dos dois metais ($r = 0,765$; $p < 0,01$) reforça a possibilidade de uma exposição simultânea, provavelmente resultante de fontes ambientais comuns, como solos e produtos agrícolas contaminados por emissões industriais ou práticas agrícolas intensivas.

Enquanto os efeitos adversos do Cd na saúde óssea estão amplamente documentados, o conhecimento sobre o impacto do Sb permanece limitado. No entanto, é plausível que o Sb exerça mecanismos de toxicidade semelhantes aos descritos como envolvidos na osteoporose, nomeadamente através da indução de stress oxidativo, disfunção mitocondrial e inibição da atividade osteoblástica (Li et al., 2024; Boreiko & Rossman, 2020). Não obstante, a evidência epidemiológica é ainda escassa e inconsistente, realçando a necessidade de estudos adicionais, tanto *in vivo* como *in vitro*, para clarificar o papel do Sb na desmineralização óssea e no risco de osteoporose.

4.3. Fatores de Risco Tradicionais e Emergentes de Osteoporose

Os resultados da presente tese reafirmam a relevância dos fatores de risco tradicionais para a osteoporose, amplamente documentados na literatura científica, salientando paralelamente a necessidade de uma atenção acrescida aos fatores emergentes, em particular à exposição a metais e metaloides, enquanto determinantes potenciais e modificáveis da saúde óssea.

A idade permanece como um dos fatores não modificáveis mais determinantes na redução da DMO, evidenciando uma associação robusta em todas as regiões anatómicas avaliadas (coluna lombar, colo femoral e quadril). O envelhecimento está fortemente associado à perda óssea progressiva, refletindo um desequilíbrio crónico entre os processos de reabsorção e formação óssea (Smit et al., 2024; Chandra & Rajawat, 2021; Aspray & Hill, 2019).

O índice de massa corporal (IMC) demonstrou uma associação inversa significativa com a osteoporose, sugerindo que valores mais elevados de IMC se associam a um menor risco de perda óssea, possivelmente devido ao estímulo osteogénico proporcionado pela carga mecânica (Chiu et al., 2024). Contudo, importa salientar que a obesidade excessiva, particularmente quando associada a inflamação sistémica ou sarcopenia, pode

comprometer a qualidade do tecido ósseo, exigindo uma avaliação mais qualitativa da composição corporal (Chen & Armamento-Villareal, 2024; Hjelle et al., 2021).

O repouso prolongado no leito foi consistentemente associado a um risco acrescido de osteopenia e osteoporose, sobretudo ao nível da coluna lombar, devido à ausência de estímulo mecânico sobre o osso (Rolvien & Amling, 2022; Eimori et al., 2016). De forma surpreendente, a inatividade física revelou, num dos modelos analisados, uma associação inversa com a osteopenia nesta mesma região, um resultado que poderá refletir viés residual, limitações metodológicas ou a influência de fatores de confusão.

A duração da menopausa apresentou uma correlação negativa com a DMO, refletindo o impacto do hipoestrogenismo prolongado na aceleração da reabsorção óssea nas mulheres (de Villiers, 2024). A maior prevalência de suplementação com cálcio e terapêuticas antirreabsortivas entre as mulheres com diagnóstico de osteoporose traduz o reconhecimento clínico da condição, não constituindo um fator causal, mas antes uma consequência do tratamento da doença.

No âmbito dos fatores de risco emergentes, os resultados evidenciaram a exposição a metais e metaloides, destacando-se o impacto já bem documentado do Cd na saúde óssea e apontando, como novidade, o Sb enquanto potencial fator de risco relevante. A evidência crescente sugere que concentrações urinárias elevadas deste metaloide estão associadas a uma maior probabilidade de ocorrência de osteoporose em mulheres pós-menopáusicas. A forte correlação observada entre os níveis de Sb e Cd indica uma possível coexposição ambiental, o que reforça a necessidade de avaliar os efeitos combinados destes elementos na saúde óssea.

A consideração de metais e metaloides como fatores de risco modificáveis representa uma mudança paradigmática na abordagem à osteoporose. Ao contrário de fatores não modificáveis, como a idade ou a menopausa, a exposição a estes elementos pode ser atenuada por meio de políticas públicas eficazes, regulamentação ambiental, alterações comportamentais e estratégias de monitorização biológica. Neste contexto, o aprofundamento da investigação sobre estes elementos revela-se crucial, quer pela sua relevância etiológica, quer pelo seu potencial contributo para a prevenção primária da osteoporose, sobretudo em grupos populacionais mais vulneráveis.

4.4. Lesão Tubular Renal Subclínica Associada à Exposição Ambiental ao Cádmio

Considerando que os rins constituem um dos principais órgãos-alvo da toxicidade induzida pelo Cd, o segundo artigo (**Capítulo II**) desta tese investigou igualmente os efeitos da exposição ambiental a baixos níveis deste metal na função renal de mulheres pós-menopáusicas brasileiras. Os resultados evidenciaram que mesmo níveis reduzidos de exposição ao Cd estão associados a disfunção tubular renal subclínica, traduzida pelo aumento das concentrações urinárias de β2-microglobulina (β2MG).

A análise de regressão linear múltipla demonstrou que o UCd foi um preditor significativo tanto das concentrações de β2MG como dos níveis de cálcio urinário (UCa/creatinina), reforçando a hipótese de que a nefrotoxicidade induzida pelo Cd interfere na homeostase do cálcio. A acumulação de Cd nas células do túbulo proximal poderá comprometer a reabsorção tubular de cálcio, contribuindo para a hipercalciúria observada em indivíduos com maior exposição. Estes achados sugerem um mecanismo pelo qual a disfunção renal pode mediar, pelo menos parcialmente, os efeitos adversos do Cd sobre o tecido ósseo.

A correlação positiva e estatisticamente significativa entre o UCd e a β2MG confirma a existência de lesão tubular renal, mesmo em níveis considerados ambientalmente seguros. Concentrações urinárias de β2MG superiores a 300 μg/g de creatinina são reconhecidas como um marcador clínico de lesão tubular, podendo indicar que o limiar crítico de acumulação renal de Cd foi ultrapassado, aumentando o risco de progressão para comprometimento renal crónico.

4.5. Limitações e Perspetivas Futuras

Esta tese oferece contributos relevantes para o conhecimento sobre os efeitos da exposição ambiental a metais na saúde óssea e renal; ainda assim, importa reconhecer algumas limitações metodológicas e contextuais que condicionam a generalização e interpretação dos resultados.

Em primeiro lugar, o desenho transversal da maioria dos estudos incluídos limita a capacidade de estabelecer relações causais diretas entre a exposição a metais, nomeadamente ao Cd, e os desfechos de saúde avaliados. Embora o UCd seja considerado um biomarcador de exposição a longo prazo, refletindo a acumulação corporal ao longo de anos, não se pode excluir totalmente a possibilidade de causalidade inversa, como a influência da osteoporose na excreção de metais.

A representatividade da amostra é outra limitação relevante. Os estudos transversais basearam-se numa amostragem de mulheres pós-menopáusicas de uma região específica do Brasil, o que poderá restringir a generalização dos achados a outras populações com contextos genéticos, ambientais e sociais distintos. Além disso, a heterogeneidade metodológica observada nos estudos incluídos na meta-análise, designadamente nas técnicas de medição da DMO e nas estratégias de controlo de confundidores, poderá ter influenciado os tamanhos de efeito combinados.

O ajuste das concentrações urinárias de metais pela creatinina, prática comum em estudos de biomonitorização, embora útil para fins comparativos, pode introduzir viés devido à variabilidade interindividual na massa muscular. Esta limitação é particularmente relevante em populações envelhecidas, nas quais a perda de massa muscular é frequente.

A avaliação incompleta da função renal, nomeadamente pela ausência de biomarcadores como a taxa de filtração glomerular estimada, limitou uma caracterização mais abrangente do estado renal das participantes. Acresce que a baixa prevalência de fumadoras nas participantes do estudo poderá ter reduzido o poder estatístico para avaliar adequadamente o impacto do tabagismo como fator de confusão.

Outro aspeto a considerar prende-se com a não inclusão de dados sobre fontes específicas de exposição aos metais analisados, como a dieta ou a proximidade a fontes industriais ou agrícolas. Esta ausência limita a capacidade de identificar vias prioritárias de exposição e, consequentemente, de propor medidas de mitigação mais eficazes. Finalmente, o uso de medicação, particularmente suplementos de cálcio, não foi completamente controlado, podendo ter influenciado variáveis como a excreção urinária de cálcio.

Face a estas limitações, recomendam-se investigações futuras com desenhos longitudinais e prospetivos de elevada qualidade, que permitam confirmar as associações observadas e aprofundar a compreensão dos mecanismos fisiopatológicos envolvidos. Estes estudos deverão incluir coortes mais diversificadas, incorporar biomarcadores renais mais abrangentes e recolher dados detalhados sobre fontes e vias de exposição a metais como o Cd e o Sb. A avaliação dos efeitos combinados de misturas de metais, bem como o seu impacto em subgrupos vulneráveis, como mulheres pós-menopáusicas, deverá também constituir uma prioridade.

CONCLUSÃO

Os estudos desenvolvidos no âmbito deste projeto de investigação permitiram aprofundar o conhecimento sobre a associação entre a exposição ambiental a metais tóxicos e os efeitos adversos na saúde óssea e renal de mulheres pós-menopáusicas, com especial enfoque no Cd e no Sb. As principais conclusões podem ser sintetizadas nos seguintes pontos:

- A exposição ambiental a baixos níveis de Cd em mulheres pós-menopáusicas brasileiras, residentes no município de Cascavel (PR, Brasil), demonstrou estar associado a uma redução da DMO e a um aumento do risco de osteoporose. A relação observada entre o UCd e a DMO apresentou um perfil não linear, em que exposições baixas a moderadas aparentam não provocar alterações relevantes, enquanto concentrações mais elevadas estão associadas a uma redução marcada da DMO. Este efeito é corroborado pelos dados obtidos na meta-análise conduzida à escala global, que demonstraram um risco quase duplicado de osteoporose em mulheres com níveis elevados de UCd.
- Para além dos efeitos sobre o tecido ósseo, o Cd demonstrou ser um marcador preditivo e independente de disfunção renal subclínica, evidenciada pelo aumento da excreção urinária de β2MG para valores superiores de UCd. Embora as participantes com níveis UCd acima dos valores de referência para esta população tenham apresentado concentrações significativamente mais elevadas de β2MG, foi também objetivada uma associação positiva entre UCd e β2MG para concentrações inferiores aos limiares de referência nacionais, indicando que os valores atualmente estabelecidos poderão não ser suficientemente protetores, especialmente em populações vulneráveis.
- A análise conjunta de 20 metais e metaloides permitiu identificar o Sb como um fator de risco emergente na etiologia da osteoporose. Verificaram-se associações estatisticamente significativas e independentes entre os níveis urinários de Sb e o diagnóstico da doença, com este elemento a apresentar uma associação mais robusta com a osteoporose do que o Cd.
- A coexposição a Cd e Sb demonstrou estar significativamente associada a um risco aumentado de osteoporose. A forte correlação positiva entre os níveis urinários destes elementos sugere a existência de efeitos aditivos ou sinérgicos na

sua toxicidade sobre o metabolismo ósseo, representando uma preocupação toxicológica emergente, particularmente no que diz respeito ao Sb, cuja implicação na osteoporose não é tradicionalmente reconhecida.

- A análise de fatores sociodemográficos e clínicos confirmou a idade avançada, o tempo de menopausa e o repouso prolongado como determinantes da perda óssea, enquanto um IMC mais elevado demonstrou efeito protetor na DMO. Estes fatores de risco clássicos devem ser considerados em conjunto com fatores emergentes – como a exposição ambiental a metais/metaloides tóxicos – na avaliação do risco individual de osteoporose.

Em síntese, a investigação aqui desenvolvida reforça a pertinência do Cd como agente osteotóxico e aponta para o Sb como um novo interveniente com impacto potencialmente relevante. A identificação de sinais precoces de lesão renal associada à exposição a metais pode representar uma via promissora para a intervenção preventiva, antecipando complicações renais bem como complicações em outros órgãos e sistemas induzidas pela perda de função renal. A redefinição de limites de exposição e a adoção de medidas ambientais mais rigorosas devem ser prioridades em contextos com risco de contaminação metálica, sobretudo em regiões com populações envelhecidas e frágeis. Investigações futuras, idealmente longitudinais e multidisciplinares, serão essenciais para aprofundar os mecanismos envolvidos, confirmar relações causais e fundamentar estratégias de intervenção mais eficazes e personalizadas na promoção da saúde óssea e renal.

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ANEXO A. Parecer consubstanciado da Comissão de Ética da Universidade Fernando Pessoa

Universidade Fernando Pessoa
www.ufp.pt

Exmo. Senhor
Prof. Doutor Álvaro Monteiro
Director da FCT

Porto, 05 de Março de 2018

Exmo. Senhor Prof. Doutor,

A Comissão de Ética, depois de re-apreciado o projeto de investigação no âmbito do Doutoramento em Ecologia e Saúde de Carlos Tadashi Kunioka, intitulado "Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio", considera nada haver a opor à realização do estudo.

Com os melhores cumprimentos.

A Presidente da
Comissão de Ética da UFP
Susana Teixeira Magalhães
Susana Teixeira Magalhães

ANEXO B. Parecer consubstanciado da Comissão de Ética da Plataforma Brasil.

UNIOESTE - CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE DA UNIVERSIDADE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Osteoporose em mulheres pós-menopáusicas brasileiras e sua associação com a exposição ambiental ao cádmio

Pesquisador: CARLOS TADASHI KUNIOKA

Área Temática: Pesquisas com coordenação e/ou patrocínio originados fora do Brasil, excetuadas aquelas com copatrocínio do Governo Brasileiro;

Versão: 3

CAAE: 83905718.2.0000.0107

Instituição Proponente: hospital universitario do oeste do parana

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.636.746

Apresentação do Projeto:

Reapresentação

Objetivo da Pesquisa:

Reapresentação

Avaliação dos Riscos e Benefícios:

Reapresentação

Comentários e Considerações sobre a Pesquisa:

Reapresentação

Considerações sobre os Termos de apresentação obrigatória:

Atendeu a todos aos elementos obrigatórios

Recomendações:

Aprovação

Conclusões ou Pendências e Lista de Inadequações:

Aprovação

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Endereço: UNIVERSITARIA
Bairro: UNIVERSITARIO **CEP:** 85.819-110
UF: PR **Município:** CASCAVEL
Telefone: (45)3220-3272 **E-mail:** cep.prppg@unioeste.br

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1049271.pdf	04/05/2018 14:00:11		Aceito
Cronograma	cronograma_FINAL.docx	04/05/2018 13:59:31	CARLOS TADASHI KUNIOKA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_final.docx	04/05/2018 13:59:09	CARLOS TADASHI KUNIOKA	Aceito
Declaração de Instituição e Infraestrutura	autorizacaoPMC.pdf	17/04/2018 00:56:01	CARLOS TADASHI KUNIOKA	Aceito
Projeto Detalhado / Brochura Investigador	Cadmio_projeto.docx	17/04/2018 00:32:04	CARLOS TADASHI KUNIOKA	Aceito
Folha de Rosto	folha.pdf	28/02/2018 10:31:19	CARLOS TADASHI KUNIOKA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	termodeciencia.pdf	28/02/2018 10:26:45	CARLOS TADASHI KUNIOKA	Aceito
Declaração de Instituição e Infraestrutura	autorizacao.pdf	28/02/2018 10:25:32	CARLOS TADASHI KUNIOKA	Aceito
Declaração de Pesquisadores	declaracao.pdf	28/02/2018 10:24:35	CARLOS TADASHI KUNIOKA	Aceito
Parecer Anterior	parecer_orientador.pdf	17/01/2018 21:03:30	CARLOS TADASHI KUNIOKA	Aceito
Orçamento	Orcamento.docx	17/01/2018 18:53:06	CARLOS TADASHI KUNIOKA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CASCAVEL, 25 de Maio de 2018

Assinado por:
Dartel Ferrari de Lima
(Coordenador)

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APÊNDICE A. Termo de consentimento livre e esclarecido.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO - TCLE

Título do Projeto: Exposição ao Cádmio na população feminina acima de 50 anos da cidade de Cascavel-PR e sua relação com a osteoporose.

Autor: Prof. Carlos Tadashi Kunioka
e-mail: tadashivi@yahoo.com.br fone: 45 3038 0550

Convidamos **você** a participar de nossa pesquisa que tem o objetivo de **pesquisar a incidência de osteoporose e exposição ao Cádmio, um metal que pode ser tóxico.** Esperamos, com este estudo, **proporcionar o diagnóstico de osteoporose e a possível exposição do seu organismo ao Cádmio.** Para tanto, **você deverá participar de uma entrevista com questionário e exame físico e, em seguida, realizar exames de urina e densitometria óssea.**

Durante a execução do projeto **você se submeterá a questionamentos, exame físico e laboratorial, além da densitometria óssea. Convém salientar que a densitometria é um exame que emite irradiação, e mesmo sendo em baixa dosagem, tem potencial de lesão celular.** No caso de ocorrer **constrangimentos**, ou mesmo dúvidas para a realização dos exames, o pesquisador poderá esclarecê-las ou você poderá desistir de participar da pesquisa, sem que haja qualquer sanção ou ônus.

Sua identidade não será divulgada e seus dados serão tratados de maneira sigilosa, sendo utilizados apenas para fins científicos. Você também não pagará e nem receberá para participar do estudo. Além disso, você poderá cancelar sua participação na pesquisa a qualquer momento. No caso de dúvidas ou da necessidade de relatar algum acontecimento, você pode contatar os pesquisadores pelos telefones mencionados acima ou o Comitê de Ética pelo número 3220-3272.

Este documento será assinado em duas vias, sendo uma delas entregue ao sujeito da pesquisa.

Declaro estar ciente do exposto e **desejo participar** da pesquisa.

Nome:
RG ou CPF:

Eu, **Carlos Tadashi Kunioka,** declaro que forneci todas as informações do projeto ao participante e/ou responsável.

Cascavel, _____ de _____ de 20_.

APÊNDICE B. Questionário aplicado aos participantes do estudo.

Projeto de investigação

"Osteoporose em mulheres pós-menopáusicas na região de Cascavel-PR e sua associação com a exposição ambiental ao cádmio"

CADILLAC- CADmium Investigation in Ladies Living Around Cascavel-PR

Questionário de Osteoporose

1. Qual a sua idade atual? _____ anos completos (à data deste inquérito)
2. Há quantos anos reside na região? _____ anos completos (à data deste inquérito)
3. Foi diagnosticada Osteoporose ao seu pai/mãe? 0. ☐ Não 1. ☐ Sim
4. O seu pai/mãe fraturou o colo do fêmur devido uma queda sem gravidade? 0. ☐ Não 1. ☐ Sim
5. Algum dos seus pais tem cifose dorsal, mais conhecida como corcunda? 0. ☐ Não 1. ☐ Sim
6. Já fraturou algum osso devido a uma pancada ou queda sem gravidade? 0. ☐ Não 1. ☐ Sim
7. Cai com frequência (mais de uma vez por ano) ou tem receio de cair por se sentir enfraquecida?
   0. ☐ Não 1. ☐ Sim
8. Perdeu mais de 3 cm após os 40 anos? 0. ☐ Não 1. ☐ Sim
9. Qual o seu IMC actual? _____ kg/m2
10. Foi sempre demasiada magra (IMC inferior a 19Kg/m2)? 0. ☐ Não 1. ☐ Sim 2. ☐ Não se aplica
11. Tomou corticosteróides durante mais de 3 meses consecutivos (tratamento de asma, artrite reumatoide e outras doenças inflamatórias)? 0. ☐ Não 1. ☐ Sim
12. Sofre de artrite reumatoide? 0. ☐ Não 1. ☐ Sim
13. Sofre de hipertireoidismo ou hiperparatireoidismo? 0. ☐ Não 1. ☐ Sim
14. Sofre de outra doença que exija medicamentos contínuo? 0. ☐ Não 1. ☐ Sim
    a. Se sim, qual? _____
15. Teve alguma vez que ficar acamada por tempo prolongado? 0. ☐ Não 1. ☐ Sim
    a. Quanto tempo? _____ (diga se quantos meses ou anos, conforme adequado)
    b. Por quê? _____
16. Com quantos anos teve início a sua menopausa? _____ anos
17. Teve interrupção da menstruação durante 12 meses consecutivos ou mais (por motivos que não fossem gravidez, menopausa ou histerectomia)? 0. ☐ Não 1. ☐ Sim
    a. Se sim, explique/comente _____
18. Teve necessidade de remover os ovários antes dos 50 anos? 0. ☐ Não 1. ☐ Sim

19. Se respondeu sim na questão anterior, fez reposição hormonal de substituição? 0. ☐ Não 1. ☐ Sim
20. Consome álcool acima dos limites aconselhados (mais de 2 unidades por dia)? 0. ☐ Não 1. ☐ Sim

    Se sim, quanto (nº de copos por tipo de bebida)? _____
21. Fuma ou alguma vez fumou? 1. ☐ Fumador (pelo menos 1 vez/dia) 3. ☐ Não-fumador

    2. ☐ Fumador ocasional (menos de 1 vez/dia) 4. ☐ Ex-fumador

    a. Cigarros _____ nº por dia/semana*

    b. Charutos ou cigarrilhas _____ nº por dia/semana* *(* Riscar o que **não** interessa)*
22. Iniciou o consumo aos _____ anos
23. Se é ex-fumador, parou aos _____ anos
24. Pratica exercícios menos de 30 minutos por dia (incluindo trabalhos domésticos, jardinagem, caminhadas, corridas, etc.)? 0. ☐ Não 1. ☐ Sim
25. Consome alimentos locais como verduras, legumes em geral, milho, soja e derivados? 0. ☐ Não 1. ☐ Sim
26. A água que consome é da Rede Pública-SANEPAR? 0. ☐ Não 1. ☐ Sim
27. A água é de poço local, sem tratamento? 0. ☐ Não 1. ☐ Sim
28. Atividade profissional: trabalha ou trabalhou em atividades metalúrgicas, com baterias, tintas, na agricultura com manipulação/ aplicação de fertilizantes? 0. ☐ Não 1. ☐ Sim
    a. Se sim, diga qual/quais: _____
    b. Quanto tempo? _____ (para cada uma)
29. Evita, não gosta ou é alérgico a leite e derivados (queijos, iogurtes, etc.)? 0. ☐ Não 1. ☐ Sim
30. Toma suplementos de cálcio? 0. ☐ Não 1. ☐ Sim
31. Passa menos de 10 minutos por dia ao ar livre expondo parte do corpo ao sol (braços e pernas)?

    0. ☐ Não 1. ☐ Sim
32. Ingere alimentos ricos em vitamina D (peixes ricos em gordura, ostras, ovos, leite, queijos e fígado)?

    0. ☐ Não 1. ☐ Sim
33. Toma suplementos ricos em vitamina D? 0. ☐ Não 1. ☐ Sim

Data:_____/_____/_____

Nome e contato: _____