Is chronic peripheral vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?

Author

Collier, Jayde

Published

2022-11-22

Thesis Type

Thesis (Masters)

School

School of Pharmacy & Med Sci

DOI

10.25904/1912/4859

Is chronic peripheral vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?

Jayde Alana Collier
BExSc, MPhty
School of Health Sciences and Social Work
Griffith University

Submitted in fulfilment of the requirements of the degree
Master of Medical Research (MMR)

Primary supervisor: A/Prof Benjamin Weeks
Co-supervisor: Prof Belinda Beck

Submitted 15th July 2022

Abstract

Background

Impaired functioning of the peripheral vestibular system, known as peripheral vestibular dysfunction (PVD), is relatively prevalent amongst older populations. Sufferers often experience imbalance and vertigo, which increase the likelihood of falling. For this reason, PVD is typically viewed as a fall-related risk factor for fracture. However, fracture risk is also influenced by factors that impair the structural integrity and strength of bone (bone-related risk factors). It is unknown whether PVD is associated with poorer bone-related indices of fracture risk. Thus, the primary objective of the current study, was to investigate bone-related and fall-related indices of fracture risk in older adults with PVD. Secondary aims of the project were to evaluate health-related quality of life of people living with PVD and to explore correlations between the indices of fracture risk.

Methods

Community-dwelling healthy older people (60 years and older) and those with diagnosed PVD (aged 74.6 ± 7.1 years), were recruited to the study. Bone mineral density (BMD) was determined from dual energy x-ray absorptiometry (DXA) at the left femoral neck (FN) and lumbar spine (L1-4). Geometric and volumetric parameters of bone strength were evaluated using peripheral quantitative computed tomography (pQCT) at the 4% and 38% left tibia sites. Sarcopenia was evaluated using whole body DXA and pQCT (66% tibia site) estimates of appendicular skeletal muscle mass (ASM), calf muscle cross-sectional area (CSA) and calf muscle density. Lifestyle factors with the potential to influence bone health, including physical activity participation and calcium intake were assessed using the Bone-specific Physical Activity Questionnaire (BPAQ) and AusCal questionnaire, respectively. A series of clinical measures of strength and balance, including Timed Up and Go (TUG) test, Dynamic Gait Index (DGI), grip strength, and five times sit-to-stand test (FTSTS) were used to evaluate fall-related indices of fracture risk. Health-related quality of life (HR-QoL) was examined using the 36-Item Short Form Survey (SF-36). Independent samples t-tests, Mann-Whitney U tests, and Fisher's exact tests were used to examine differences between the PVD and healthy groups across the outcome variables. Spearman correlation analyses were conducted to explore associations between outcome variables within each group.

Results

A total of 42 community-dwelling healthy participants (aged 73.7 ± 4.6 years) and 22 participants with diagnosed PVD (aged 74.6 ± 7.1 years) participated in the study. There were no differences in BMD between the PVD and healthy groups at FN ($t = 1.827$, $p = 0.073$) or L1-4 ($t = 1.711$, $p = 0.093$) sites. However, the PVD group demonstrated a general trend for lower BMD at both skeletal sites. Female sub-group analysis revealed that women with PVD had lower FN BMD than healthy women (0.74 ± 0.13 g/cm^2 versus 0.83 ± 0.10 g/cm^2, $p = 0.027$). The proportion of participants with FN T-scores reflective of osteopenia or osteoporosis was greater in the female PVD group than the healthy female group (92.9% vs. 59.4% respectively, $p = 0.035$).

Apart from endocortical circumference, there were no between-group differences in pQCT derived geometric or volumetric indices of bone strength. The PVD group had significantly lower endocortical circumference when compared to the healthy group (36.4 mm vs. 40.2 mm respectively, $p = 0.025$). There were no between-group differences in bone-related lifestyle factors (exercise and calcium). Whilst PVD participants had lower scores on the Dynamic Gait Index compared to their healthy counterparts (18.9 ± 5.4 vs. 22.4 ± 2.24 respectively, $p < 0.001$), there were no between-group differences for any other fall-related outcome.

The PVD group reported lower HR-QoL than the healthy group across vitality, emotional role limitations, social functioning, and general health sub-domains of the SF-36. Positive associations were observed between FES-I and TUG, FTSTS and TUG and L1-4 BMD and FN BMD in both groups. DGI was negatively related to TUG and FTSTS in both healthy and PVD groups.

Conclusion

Contrary to previous reports, the current study did not observe generalised differences in BMD or other indices of bone strength between healthy older adults and those with PVD. However, PVD was associated with poorer BMD in post-menopausal women. As such, post-menopausal women with PVD, may be more vulnerable to osteoporosis and fracture than the general older population. With a view to reduce fracture incidence, these findings suggest that osteoporosis screening and intervention may be beneficial adjuncts to standard PVD management.

Statement of originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Table of Contents

List of abbreviations

aBMD	Areal bone mineral density
ADLs	Activities of daily living
AP	Antero-posterior
ASM	Appendicular skeletal muscle mass
BLSA	Baltimore longitudinal study of ageing
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BPAQ	Bone-specific physical activity questionnaire
BPPV	Benign paroxysmal positional vertigo
BSI	Bone strength index
BVH	Bilateral vestibular hypofunction, partial and complete loss of function
CNS	Central nervous system
COVID-19	Coronavirus
CRM	Canal repositioning manoeuvre
CSA	Cross-sectional area
cVEMP	Cervical vestibular evoked myogenic potential
DGI	Dynamic gait index
DHI	Dizziness handicap inventory
DHP	Dix-hallpike
DXA	Dual-energy X-ray absorptiometry
ENT	Ear, nose, and throat
EWGSOP	European Working Group on Sarcopenia in Older People
FES-I	Falls efficacy scale international
FN	Femoral neck
FRAX	Fracture risk assessment tool
FTSTS	Five times sit-to-stand
GCUH	Gold Coast University Hospital
GP	General Practitioner
GUHREC	Griffith University Human Research Ethics Committee

HC	Horizontal canal
HR	Hormone replacement therapy
HR-QoL	Health-related quality of life
HREC	Human Research Ethics Committee
IGF-I	Insulin-like growth factor
IL-6	Interleukin 6
L1-4	Lumbar spine vertebra 1-4
MANOVA	Multivariate analysis of variance
MD	Meniere's disease
MTF	Minimal trauma fracture
PA	Physical activity
PC	Posterior canal
pQCT	Peripheral quantitative computed tomography
PTH	Parathyroid hormone
PVD	Peripheral vestibular dysfunction
QoL	Quality of life
RT	Romberg test
SCC	Semicircular canal
SD	Standard deviation
SF-36	36-Item Short Form Survey
SNS	Sympathetic nervous system
SSA	Site specific application
SSI	Strength-strain index
SSIp	Polar strength-strain index
TUG	Timed Up and Go test
UVH	Unilateral vestibular hypofunction, partial and complete loss of function
vBMD	Volumetric bone mineral density
VH	Vestibular hypofunction
VN	Vestibular neuritis
VRT	Vestibular rehabilitation therapy
WB	Whole body
WHO	World Health Organisation

List of figures

List of tables

List of appendices

Statement of acknowledgement

Firstly, I would like to acknowledge the wonderful work of my supervisors, Ben and Belinda. I am so fortunate to have had the opportunity to work with such dedicated and inspiring academics. I would like to thank Ben and Belinda for supporting me throughout this journey into the research world – it has been such a great experience. They have invested so much of their time and effort into educating me, and for that, I am forever grateful.

Working with Ben and Belinda has reignited my passion for the physiotherapy. I am excited to implement what I have learnt into clinical practice, so that I can deliver better patient care. I am excited by the opportunities they have presented along the way – teaching, conferences, and projects. I would like to thank them for opening so many doors, that I never knew existed. I am looking forward to working together again in the future!

Secondly, I would also like to acknowledge the vestibular physiotherapists at GCUH (Vicky Stewart, Shelly Kwan), Equilibrium Rehab (Meg Richards), Bayside Balance (Emma Warner) and LGH (Ethan Marrinan, Leia Barnes, Jac Foster) for supporting me with recruitment. Sarah and Deb, my lovely dizzy physi friends from Cairns, are deserving of a very special mention. Deb and Sarah have taught me everything I know about vestibular rehabilitation. I want to thank them for inspiring me to do this project!

Finally, I must thank my beautiful family, friends and my amazing partner Dylan. They have provided constant emotional support and motivation throughout this project. They have all had to listen to me talk about the vestibular system for the last 18 months, it's probably sent them dizzy! I am so lucky to have these special people in my life.

Introduction

Background

Osteoporosis is a common age-related skeletal disorder, affecting approximately 1.2 million older Australians (Cosman et al., 2014; Watts et al., 2013). The pathophysiological hallmark of osteoporosis is deficient bone mineral density (BMD) and deterioration of bone microarchitecture, arising from an imbalance in bone remodelling processes (Cosman et al., 2014; Meyer et al., 2019). Impairment in the structural integrity and strength of bone, increases its susceptibility to fracture. However, bone fragility in and of itself does not necessarily lead to fracture. Rather, fracture occurs when osteoporotic bone becomes overloaded by minimal trauma (i.e., fall from standing height), whereby, it is referred to as a fragility or minimal trauma fracture (MTF) (Cosman et al., 2014). Thus, factors contributing to an increasing propensity to fall (i.e., poor balance, slow gait speed and sarcopenia) and factors contributing to bone fragility (i.e., low bone mass, bone microarchitectural deterioration and unfavourable geometry) must be considered concurrently, in the evaluation of fracture risk (Bouxsein & Karasik, 2006; Cosman et al., 2014; Cozadd et al., 2021).

Peripheral vestibular dysfunction (PVD) describes the pathological impairment of the inner ear balance sensory system. As the vestibular system plays an integral role in the maintenance of balance, PVD greatly increases the odds of falling (Agrawal et al., 2009; Marchetti et al., 2011). The propensity to fall is increased by dizziness and disequilibrium (common symptoms of PVD), which result from impaired perception of verticality, linear acceleration, and/or angular velocity (Herdman et al., 2014).

As the prevalence of some vestibular disorders also increases with advancing age, previous literature has largely focused on fall-related indices of fracture risk in PVD populations (Agrawal et al., 2009). Recent literature, however, has focused on the investigation of bone-related indices of fracture risk within this patient group. More specifically, some vestibular disorders have been found to be associated with a reduction in bone mineral density (BMD) – an important determinant of bone strength (Byun et al., 2019; Shupak & Faranesh, 2020; Talaat et al., 2015). The mechanisms underlying this association are not well understood. Some authors have hypothesised that the function of the vestibular organs may be influenced by age-related changes in systemic calcium homeostasis (Walther et al., 2014). Reduced calcium bioavailability is thought to contribute to the degradation of otoconia (calcium carbonate crystals) within the inner ear, which may in turn,

lead to dysfunction (Walther et al., 2014; Zhang et al., 2021). Noting the clinical implications of fracture, the association warrants further investigation in the PVD population – a population who are likely to be older and have an increased propensity to fall. This study provides a novel contribution to the literature, as fall-related and bone-related indices of fracture risk were investigated concurrently, in older adults with PVD.

Significance

According to data from the Australian Institute of Health and Welfare, fractures are the most common fall-related injury sustained by elderly Australians (Pointer et al., 2019). Fractures impart a significant cost burden upon the health care system. In fact, hip fractures alone cost the Australian economy $1 billion annually (Tatangelo et al., 2019). Such cost may be attributed to hospitalisation, surgical management, and rehabilitation. Over the long-term, fracture-related morbidity may also contribute to health care expenditure, through its association with functional decline and poor health-related quality of life (HR-QoL) – factors which become catalysts for increased health care utilisation.

With an ageing population, fracture incidence is expected to rise substantially. In light of the predicted economic fallout, fracture has been recognised as a public health priority. Accordingly, government investment in preventative care, aims to alleviate the socioeconomic burden (Cosman et al., 2014; Tatangelo et al., 2019). However, effective fracture prevention is dependent upon a thorough understanding of all risk factors (bone-related and fall-related) to enable the early identification and timely management of high-risk populations.

Although older people with PVD may be predisposed to fracture through an increased propensity to fall, fracture risk may also be compounded by an associated reduction in BMD. Furthermore, there is an increased prevalence of both osteoporosis and vestibular dysfunction with advancing age (Liao et al., 2015). Thus, ageing with comorbid PVD may further compound the age-related increase in fracture risk. With regard to clinical practice, peripheral vestibular disorders are highly treatable (Herdman et al., 2014). Therefore, it may be possible to positively influence bone-related and fall-related risk factors for fracture through the management of PVD. Such treatment may be a low-cost, high value adjunct to fracture prevention. Outcomes of this study may therefore, inform fracture prevention programs and the clinical management of older persons suffering from PVD.

Aims and Objectives

The primary aim of the current study was to investigate whether there were any differences in fall-related and bone-related indices of fracture risk, between healthy older adults and those with chronic PVD. The specific objectives of the project are:

1. to determine whether there were differences in bone-related indices of fracture risk (BMD, bone strength and geometric indices, calcium intake, and bone-relevant physical activity participation) between older adults with and without chronic PVD;
2. to determine whether there were differences in fall-related indices of fracture risk (sarcopenia indices, dynamic balance, fear of falling, falls history) between older adults with and without chronic PVD;
3. to determine whether there were differences in health-related quality of life (HR-QOL) between older adults with and without chronic PVD; and
4. to explore associations between indices of fracture risk in each group.

Hypotheses

Null hypothesis 1: There will be no differences in bone-related indices of fracture risk (BMD, geometric and volumetric parameters of bone strength) between older adults with and without PVD.

Alternative hypothesis 1: Older adults with PVD will have poorer bone-related indices of fracture risk (BMD, geometric and volumetric parameters of bone strength) compared to those without.

Null hypothesis 2: There will be no differences in fall-related risk factors for fracture (sarcopenia parameters, fear of falling, dynamic balance, falls history) between older adults with and without PVD.

Alternative hypothesis 2: Fall-related indices of fracture risk (sarcopenia parameters, dynamic balance, fear of falling, falls history) will be poorer in older adults with PVD compared to those without.

Null hypothesis 3: There will be no difference in HR-QoL between older adults with PVD and those without.

Alternative hypothesis 3: Older adults with PVD will have poorer HR-QoL in comparison to healthy older adults.

Null hypothesis 4: There will be no associations between the indices of fracture risk.

Alternative hypothesis 4: Associations will be observed between the indices of fracture risk.

Approach

To test the hypotheses, an observational study was designed. Two groups of community-dwelling older adults were recruited – one group comprising healthy participants, the other comprising participants diagnosed with PVD. A series of clinical measurements pertaining to the bone-related and fall-related indices of fracture risk were undertaken and comparisons were made between the groups to detect potential differences.

Literature review

Minimal trauma fracture (MTF) from osteoporosis poses a major public health challenge. Having significant associated morbidity and mortality, MTF imparts a heavy economic burden on global health care systems (Cosman et al., 2014; Watts et al., 2013). Population ageing will increase incidence of fragility fracture and associated expenditure. Early implementation of fracture prevention strategies in high-risk individuals, will minimise this cost burden. As such, it is important to have a thorough understanding of fracture risk factors and high-risk groups.

Predisposition to fracture is determined by the combination of fall-related and bone-related indices of fracture risk. Bone-related indices of fracture risk include low bone mineral density (BMD) and poor bone geometry and/or microarchitecture that impede bone strength. Fall-related indices of fracture risk include balance impairment, fear of falling and sarcopenia (Cosman et al., 2014).

Peripheral vestibular dysfunction (PVD) is associated with greatly increased odds of falling, secondary to balance impairment and vertigo (Herdman et al., 2014). Increased prevalence of PVD in older populations, may co-exist with an age-associated decline in bone health, thereby, compounding fracture risk (Liao et al., 2015). Whilst the association between PVD and fall-related risk factors for fracture is well-established, further investigation of bone-related risk factors is required to properly characterise fracture risk in this patient population. As such, this review will summarise the relevant literature pertaining to the indices of fracture risk, in the context of PVD.

Osteoporosis and minimal trauma fracture in the older person

Affecting approximately 1.2 million older Australians, osteoporosis is a chronic skeletal disease, characterised by low BMD and deterioration of bone microarchitecture (Kanis et al., 2008; Watts et al., 2013). These age-associated changes compromise the strength of bone, increasing its susceptibility to fracture (Cosman et al., 2014). As a result, fracture can transpire in the setting of a minimal trauma, for example, a fall from standing height (Health & Welfare, 2022; Santy-Tomlinson et al., 2018). Notably, half of all fall-related injuries in older Australians involve a MTF (Health & Welfare, 2021). Whilst the hip is implicated in 30% of cases, the wrist, lumbar spine and pelvis are also common skeletal sites for MTF (Health & Welfare, 2020).

Impacts of fracture

Fragility fracture imparts a substantial burden upon the individual and the economy, through its association with increased morbidity and mortality. Of all fracture types, hip fracture is associated with the highest mortality rate. It is estimated that 25% of older Australians who suffer a fractured hip will die prematurely within 12 months following the incident (Hallen, 2021; Health & Welfare, 2018; Watts et al., 2013). Reduced life expectancy may be attributed to postoperative complications (i.e. chest infection, embolism), frailty, and poor physiological reserve (Panula et al., 2011). Poor mobility, chronic pain, and loss of independence are key contributors to fracture-associated morbidity (RACGP, 2010). With many unable to return to their pre-morbid level of function and independence, in-home support services or residential aged care may be required to facilitate participation in activities of daily living (ADLs). Disability may also foster the development of chronic illnesses which can contribute to poorer health-related quality of life (HR-QoL) and repeated hospitalisation (Conley et al., 2020; Dyer et al., 2016).

Expenditure related to the management of osteoporosis and MTF within Australia is currently estimated to be 3.4 billion dollars annually. Whilst these costs reflect the hospitalised fracture cases, the true economic burden of MTF is likely far greater, as non-hospitalised fracture management remains unaccounted for (Tatangelo et al., 2019; Watts et al., 2013). Additionally, the cost burden may be compounded by delayed identification and management of osteoporosis, resulting in missed opportunity to prevent MTF (Watts et al., 2013).

Population ageing is expected to foster a rise in the prevalence of fracture. As the economic toll is set to follow a similar trajectory, MTF and osteoporosis have been recognised as major public health issues. Investments in cost-effective, preventative strategies that focus on risk reduction, are necessary to minimise the future economic impact of MTF. Within Australia, strategies aimed at reducing fracture risk may include:

- Early identification and management of high-risk groups/individuals
- Expansion of programs that aim to prevent secondary fracture
- Education provided across the lifespan, to raise awareness of osteoporosis and fracture
- Improved access to allied health professionals for longer-term support (i.e. exercise intervention, falls prevention) (RACGP, 2010).

Underpinning the effectiveness of preventative strategies, is a thorough understanding of the risk factors for fracture. Given the prevalence of PVD and fracture increases with age, we sought to investigate the indices of fracture risk in an aging PVD population.

Fracture risk and evaluation of bone strength

Predisposition to fracture is driven by factors that reduce bone strength (bone-related indices of fracture risk) in addition to, factors or conditions that increase the likelihood of falling (fall-related indices of fracture risk) (Cosman et al., 2014; Cozadd et al., 2021). Fracture risk is normally assessed in clinical practice using Dual-energy X-ray Absorptiometry (DXA) (Osterhoff et al., 2016). DXA obtains two-dimensional images that provide an estimate of BMD as a function of bone mineral content (BMC) divided by bone area (areal BMD; aBMD). Although bone strength is multifaceted, BMD is the most widely reported surrogate estimate of bone strength (Osterhoff et al., 2016). Osteoporosis is defined by the World Health Organisation (WHO) as a BMD T-score below -2.5 standard deviations from a young adult reference population mean. Osteopenia, a precursor to the development of osteoporosis, is defined by a T-score between -1.0 and -2.5 standard deviations from the reference population mean (WHO, 1994).

Peripheral quantitative computed tomography (pQCT) may be used as an adjunct to DXA in the evaluation of bone strength, due to its three-dimensional imaging capability. As such, pQCT provides a more sophisticated analysis of bone strength by accounting for bone size and geometry. It is also able to distinguish cortical from trabecular bone for the evaluation of microarchitecture (Choksi et al., 2018). Therefore, it was advantageous to utilise both imaging modalities (pQCT and DXA), in the investigation of bone-related determinants of fracture risk in the current study.

Bone-related indices of fracture risk

Non-modifiable risk factors

Age

The skeletal system deteriorates with age. Across the lifespan, skeletal integrity and calcium homeostasis is maintained through the bone remodelling process (Florencio-Silva et al., 2015; Osterhoff et al., 2016; Santos et al., 2017). Bone remodelling involves the coupled action of osteoclasts (bone resorption cells) and osteoblasts (bone deposition cells), such that, bone resorption and bone formation are relatively balanced. Whilst bone remodelling is

influenced by many factors (i.e. biochemical signals, mechanical loading, nutrient availability), ageing beyond the fourth decade is associated with an imbalanced and accelerated remodelling process, in which bone resorption surpasses bone formation (Boskey & Coleman, 2010; Osterhoff et al., 2016). As a result, there is an age-associated deterioration in the structure and mass of bone, which reduces bone strength and resistance to fracture (Osterhoff et al., 2016; Santos et al., 2017). More specifically, increased cortical bone porosity, loss of trabecular connectivity, and endocortical thinning, constitute the pathophysiological hallmarks of osteoporosis (Figure 1) (Weaver et al., 2016). Such skeletal changes across the lifespan, account for the increased prevalence of osteoporosis amongst elderly populations (Boskey & Coleman, 2010; Seeman, 2013; Weaver et al., 2016).

Figure 1. Age-related changes in bone geometry (Weaver et al., 2016)

Genetics

Much of the variation in BMD (50-85%) can be explained by genetics (Ralston & Uitterlinden, 2010; Weaver et al., 2016). Genes that encode for factors involved in bone metabolism (i.e. interleukin-6 (IL-6), insulin-like growth factor (IGF-I)), are associated with BMD. Genetic variants or abnormalities may, therefore, influence an individual's genetic predisposition to osteoporosis (Pouresmaeili et al., 2018). Additionally, the identification of

genes associated with increased fracture risk independent of BMD, suggests a potential role of genetics in other predictors of bone strength, such as geometry and microarchitecture (Ralston & Uitterlinden, 2010).

Sex

Sex-related differences in bone metabolism, mass, and geometry, may account for the increased prevalence of osteoporosis and MTF amongst women compared to men (Choi et al., 2021; De Martinis et al., 2021; Duan et al., 2003). Whilst some sex differences emerge as early as childhood, they are more prominent after puberty. Notably, peak bone mass which is generally attained by the third decade of life, is higher in males than females. As females achieve lower peak bone mass than males, age-associated bone loss is more likely to result in osteoporosis or osteopenia in females (Figure 2) (Duan et al., 2003; Santos et al., 2017; Weaver et al., 2016). Similarly, long bone geometry differs between sexes. Young adult males have larger long bone diameter and cortical thickness than females at the completion of the growth period. Such geometry is favourable in terms of bone strength, as greater displacement of the cortex from the neutral axis generates greater bending resistance (Figure 3) (Duan et al., 2003). Persistence of these sex-related differences into older age may increase female susceptibility to fracture (Duan et al., 2003).

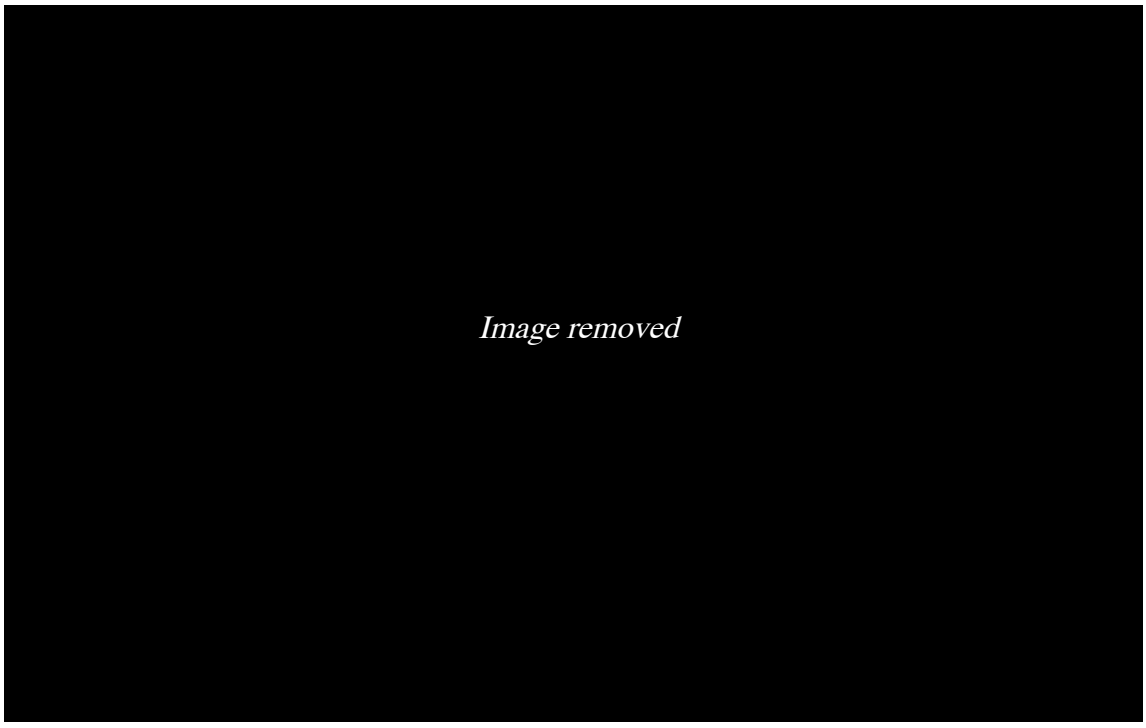


Figure 2. Sex-related differences in bone mass across the lifespan (Weaver et al., 2016)

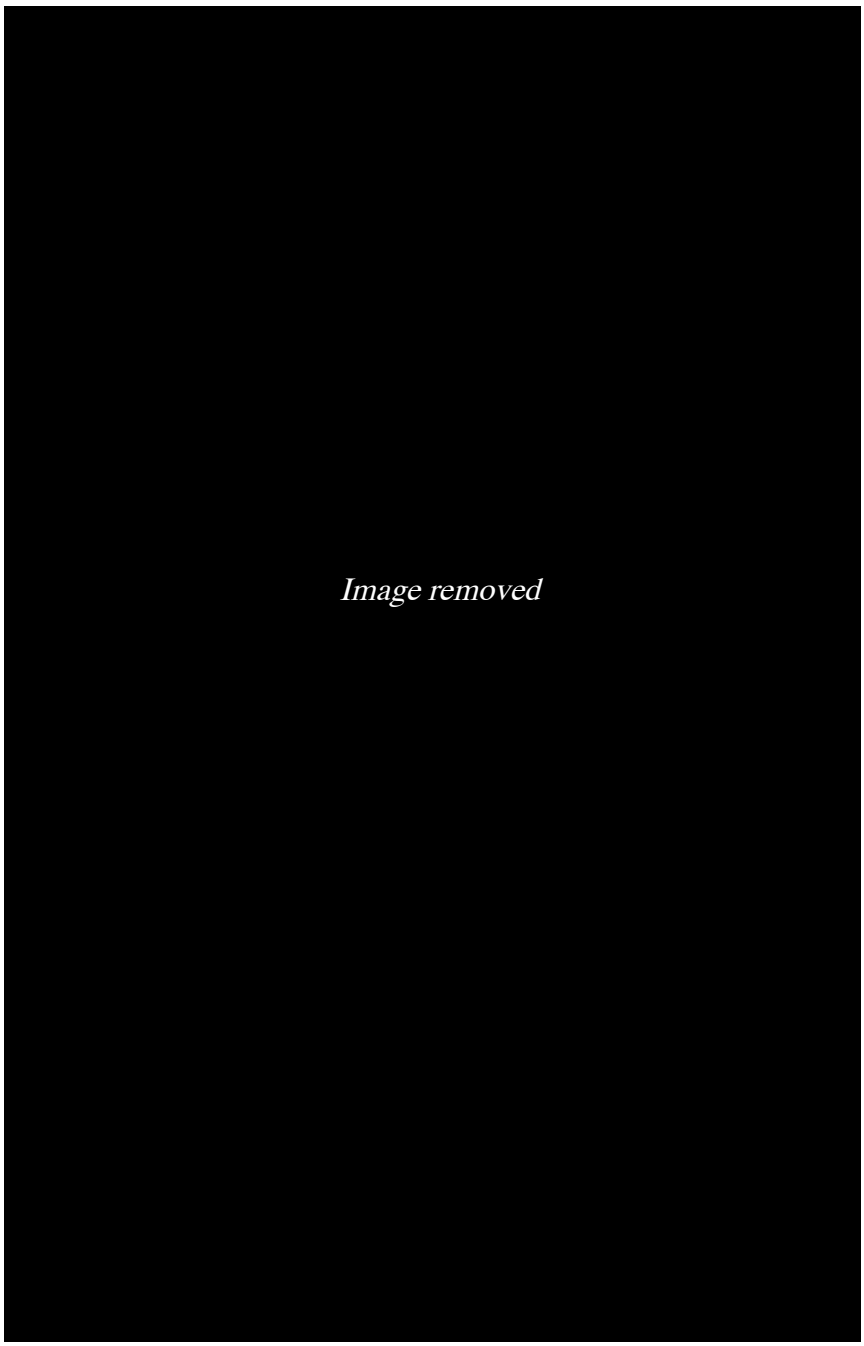


Figure 3. Sex-related differences in long bone geometry across the lifespan (Duan et al., 2003)

Sex hormones also contribute to sex differences in fracture risk. For women, menopause heralds the reduction in circulating oestrogen – a powerful protector of bone health. As oestrogen deficiency accelerates bone turnover through the disinhibition of osteoclasts, the percentage rate of bone loss is reported to be 1.5-2.0 times greater in postmenopausal women than men of similar age (Daly et al., 2013). Thus, menopause is viewed as a significant contributing factor in female predisposition to osteoporosis and MTF.

Medical factors

Other hormones released by the endocrine system also contribute to the maintenance of bone health and calcium homeostasis (Eller-Vainicher et al., 2019; Pouresmaeili et al., 2018). Parathyroid hormone (PTH) for example, drives the release of skeletal calcium stores through increased remodelling rates and improved intestinal absorption of calcium. Similarly, thyroid hormone and cortisol increase osteoclast activity to drive bone resorption. Endocrine disorders that affect circulating levels of these endogenous hormones (i.e. diabetes, hyperparathyroidism, Cushing's syndrome) are associated with increased risk of fracture, through induction of secondary osteoporosis (Eller-Vainicher et al., 2019).

Modifiable risk factors

Medication

Some medications such as glucocorticoids (steroid hormones) which are commonly used in the management of chronic obstructive pulmonary disease and inflammatory conditions, may induce secondary osteoporosis through inhibition of osteoblast differentiation and reduced intestinal calcium absorption. Contrarily, pharmacological interventions such as hormone replacement therapy (HR), bisphosphonates, and monoclonal antibodies (i.e. Denosumab) aim to reduce bone resorption and maintain bone mass and are commonly used in the treatment of osteoporosis (Pouresmaeili et al., 2018).

Smoking

Smoking is regarded as a risk factor for osteoporosis because of its association with increased PTH and reduced vitamin D levels (Pouresmaeili et al., 2018). Additionally, osteoblasts contain nicotine receptors, that when activated by the presence of high nicotine levels, reduce osteoblastic bone formation (Choi et al., 2021). In combination, these factors contribute decreased bone formation and increased risk of osteoporosis and MTF. As such, smoking cessation is encouraged in the management of osteoporosis.

Calcium and vitamin D

Calcium absorption from the gut relies on adequate levels of serum vitamin D. When serum calcium is decreased, the body aims to restore calcium homeostasis through activation of vitamin D. Vitamin D increases absorption of dietary calcium through the intestine and raises PTH levels to allow calcium stores to be released from bone. As such, vitamin D deficiency (as with reduced sun exposure or dietary intake), may contribute to reduced

calcium absorption and increased bone turnover. Low dietary calcium intake can also have negative implications for bone health. As calcium is required for healthy functioning of the heart, muscles and nerves, low dietary calcium intake may trigger the withdrawal of calcium from skeletal stores. Over time, reduced nutrient bioavailability may contribute to a decline in bone mass and resultant rise in osteoporosis risk (Pouresmaeili et al., 2018). In such cases, supplementation is a necessary, but not entirely sufficient, therapeutic strategy for osteoporosis.

Physical activity

Mechanical loading (i.e. physical activity (PA)) is necessary for optimal bone strength. Osteocytes within the bone matrix, sense and distribute information about mechanical load to the osteoclasts and osteoblasts. Elaborate communication between the bone cells facilitates adaptive bone remodelling, enabling bone to withstand increased mechanical demands (Boskey & Coleman, 2010; Florencio-Silva et al., 2015). Bone loading in PA is the product of pulling forces generated by muscle contractions and ground reaction forces generated through weightbearing (Santos et al., 2017; Weeks & Beck, 2020). Unsurprisingly, high-intensity, high-impact resistance exercise has been found to be highly effective in improving bone strength and bone-related indices of fracture risk in older people with low bone mass (Kistler-Fischbacher et al., 2021). On the contrary, physical inactivity and mechanical unloading (i.e. bed rest) which are particularly prevalent in frail populations, are catalysts for bone loss and increased fracture risk (Vignaux et al., 2015).

Fall-related indices of fracture risk

Sarcopenia

Despite their morphological differences, muscle and bone are interconnected structurally and functionally. Both tissues are responsive to changes in hormone levels, mechanical load (exercise), and nutrient bioavailability (Edwards et al., 2013; Patel et al., 2018). They also follow similar temporal profiles for age-related changes in their health. For example, a progressive decline in muscle strength and mass beyond the fourth decade of life, is normally accompanied by a decline in bone density and strength (A. Cruz-Jentoft et al., 2019; Weeks & Beck, 2020). Fat infiltration, reduced muscle fiber number, reduced cross-sectional area, and satellite cell loss (muscle precursor cells), constitute the age-associated changes in muscle health which characterise the pathophysiology of sarcopenia (Edwards et al., 2013; Patel et al., 2018). Clinically, sarcopenia manifests in reduced muscle strength,

mass and function, which may explain its association with adverse health outcomes such as poor HR-QoL, frailty and fracture (A. J. Cruz-Jentoft et al., 2019; Weeks & Beck, 2020).

Since adequate muscle strength and function are necessary for the maintenance of balance, sarcopenia may contribute to fracture risk through increased falls. Older people with severe sarcopenia are more than three times as likely to suffer falls, than those without the condition or those with sarcopenia (Gadelha et al., 2018). Reduced mechanical strain from sarcopenia may also contribute to poor bone health and increased fracture risk (Sepúlveda-Loyola et al., 2020). Although in isolation sarcopenia is seen to increase fracture risk, the co-existence of osteoporosis and sarcopenia (osteosarcopenia), is associated with far greater fracture risk (Sepúlveda-Loyola et al., 2020). Since PA is capable of targeting osteoporosis and sarcopenia concomitantly due to its mutually beneficial effects on bone and muscle health, it constitutes an efficient strategy for fracture prevention.

Balance impairment

Balance impairment is strongly associated with ageing. Cumulative effects of advancing age and subsequent deterioration of multiple body systems, contribute to the multifactorial aetiology of balance dysfunction in older populations (presbystasis) (Değer et al., 2019; Montero-Odasso, 2016). Maintenance of balance relies on the complex neural integration and interpretation of input from vestibular, visual, and proprioceptive sensory systems. Dysfunction in any of these systems, whether the result of ageing or disease, can reduce the reliability of body orientation and environmental information that is received by the brain. Unreliable balance information can elicit inaccurate postural responses within the musculoskeletal system, increasing the likelihood of falling (Montero-Odasso, 2016; Rasman et al., 2018). Despite sensory balance system dysfunction, functional balance may be recovered through exercise and vestibular rehabilitation, subsequently reducing the risk of falling. Underpinning the effectiveness of these strategies, is the ability of the central nervous system (CNS) to compensate for dysfunction (Herdman et al., 2014).

History of falls and fear of falling

History of a previous fall is strongly predictive of future falls and fracture (Cozadd et al., 2021). In fact, frequent fallers who fall more than once within a 12-month period, are twice as likely to suffer fracture when compared with non-fallers (Afrin et al., 2020). However, the widely applied fracture risk assessment tool (FRAX), does not account for previous falls in its risk factor algorithm (Cosman et al., 2014). Falls are often traumatic

events that may lead to a fear of falling. Consequently, older people may restrict their mobility or participation in PA, thereby, driving a negative cycle of deconditioning and further deterioration of bone and muscle health. Overall, these problems will further increase the likelihood of experiencing a fall or fracture (Marchetti et al., 2011; Montero-Odasso, 2016). Fear of falling may be alleviated through balance exercise and falls prevention programs, which build balance confidence (Herdman et al., 2014).

Polypharmacy

Polypharmacy represents a common modifiable risk factor for falls in elderly populations. Longitudinal studies suggest that the prescription of ≥ 4 medications in chronic disease management, is associated with an 18% increase in the rate of falls (Dhalwani et al., 2017). Medications may contribute to falls by virtue of drug-induced side effects. For example, psychotropic medications and narcotics can have a sedative effect which results in reduced reaction times or alertness (Cosman et al., 2014; Montero-Odasso, 2016). In addition, interactions between multiple medications may amplify drug-related side effects (Montero-Odasso, 2016). However, the relationship between polypharmacy and falls is likely confounded by the presence of multiple underlying comorbidities.

Overall, there are numerous modifiable risk factors for fracture, both bone-related and fall-related. Altering exposure to such risk factors is a key strategy in the prevention of MTF. As PVD is amenable to treatment, it might represent a modifiable risk factor for fracture.

Peripheral vestibular dysfunction

Peripheral vestibular dysfunction is an umbrella term that encapsulates pathologies of the peripheral portion of the vestibular system – semicircular canals (SCCs), otolith organs, and the vestibular nerve (Figure 4). Impaired functioning of this sensory balance system greatly increases the odds of falling, which may in turn, contribute to an increased fracture risk (Agrawal et al., 2009).

PVD is distinct from central vestibular dysfunction, which encompasses problems with the processing of vestibular information within the CNS (Herdman et al., 2014). The current work focuses specifically on PVD, as it tends to be more amenable to treatment (i.e. vestibular rehabilitation) than central dysfunction and may offer a potential therapeutic target in the prevention of MTF. High treatability of PVD can be attributed to redundancies within the peripheral vestibular system. Firstly, bilateral pairing of peripheral vestibular organs allows the brain to receive input from the intact organ in the event of unilateral dysfunction

(Fetter, 2016). Secondly, recovery from peripheral dysfunction is possible through central compensation by the CNS. Therefore, most peripheral disorders induce temporary vestibular dysfunction. Longer-term dysfunction may be present in disorders that cause permanent damage to the vestibular organs (i.e. Meniere's disease). Similarly, older populations may be more likely to suffer persistent impairment because of an age-associated degradation of central circuitry and sensory systems, which impedes central compensation (Allen et al., 2017). In contrast to peripheral disorders, central vestibular dysfunction is less treatable by virtue of a lack of redundancy within the central vestibular system (Han et al., 2011). As such, individuals suffering from central vestibular disorders may be faced with the prospect of ageing with this dysfunction.

Figure 4. Peripheral vestibular system (Herdman et al., 2014)

Anatomy and physiology of the peripheral vestibular system

The unique anatomy and physiology of the peripheral vestibular end organs, enables the system to sense head movement, as well as spatial and postural orientation with respect to gravity (Agrawal et al., 2009). The SCCs are aligned to three planes of angular head

movement, whilst the otolith organs are oriented about horizontal and vertical axes (Figure 4). Such anatomical arrangement allows for motion detection in all directions, which is vital for the maintenance of gaze stability and balance (Agrawal et al., 2009; Herdman et al., 2014). Hair cells within SCCs and otolith organs constitute the sensory receptors of the vestibular system. Semicircular canal hair cells deflect according to the direction of endolymphatic fluid flow, generated by angular head motion (Figure 5C) (Swenson, 2017). Deflection towards the longest process of the hair cells produces an excitatory signal and deflection away from the longest process produces an inhibitory signal (Figure 5B). Coplanar pairing of canals enables the system to generate equal and opposite signals in the right and left paired canals, for any given head movement (Herdman et al., 2014). Coplanar pairing also allows for redundancy within the system. Compensation for the impaired canal is provided by the contralateral intact canal, enabling the CNS to receive input regarding the angular velocity within the plane of the impaired canal. Otolith hair cells are embedded within a gelatinous otolithic membrane. Weighting of this membrane from overlying calcium carbonate crystals (otoconia), allows the hair cells to sense gravity. Acceleration, deceleration, and gravity forces cause the shearing of otoconia atop of the otolithic membrane. Resultant hair cell deflection enables the transduction of static tilt and linear acceleration (Figure 5D) (Herdman et al., 2014; Swenson, 2017).

Figure 5. Schematic of hair cells within the vestibular system. (A) Hair cell structure (B) Direction of hair cell deflection determines excitatory or inhibitory signalling. (C) Sensory receptor of the SCC. (D) Sensory receptor of the otolith organ.

Peripheral vestibular disorders

PVD arises following pathological insult to the vestibular end organs or the vestibular nerve. Underactivity or overactivity within the end organs can result in the relay of erroneous sensory information to the CNS, which can induce dizziness and disequilibrium (common symptoms of PVD) (Herdman et al., 2014). Similarly, the transmission of vestibular information to the CNS, may be disrupted by vestibular nerve pathology (S. H. Jeong, H. J. Kim, et al., 2013 2013). Whilst there are numerous disorders under the PVD umbrella, this review will focus on the more common presentations including Benign Paroxysmal Positional Vertigo (BPPV), vestibular neuritis (VN), vestibular hypofunction (VH), and Meniere's disease (MD).

Benign Paroxysmal Positional Vertigo

Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular disorder, accounting for 20-30% of all presentations of peripheral vertigo (Dhameliya et al., 2020; Hülse et al., 2019; Lindell et al., 2021). Lifetime prevalence is widely reported to be 2.4%, however, it appears to affect older populations most frequently (von Brevern et al., 2007).

Whilst a consensus on the pathogenesis of BPPV is yet to be reached, it is thought to arise from otoconial debris (from otolith organ) entering the endolymph-filled SCC. As the calcium carbonate crystal moves through the endolymph with respect to gravity, there is a transient, pathological rise in neural firing from the impaired canal. Although BPPV can affect any canal, posterior canal (PC) BPPV is the most common variant, accounting for approximately 80% of cases. Sufferers often experience episodic vertigo and nausea that is precipitated by gravity-dependent head movement (Herdman et al., 2014). Most cases are considered idiopathic in origin, however, head trauma (i.e. from a fall) and osteoporosis are known risk factors for the development and recurrence of BPPV (Chen et al., 2020; Karataş et al., 2017; von Brevern et al., 2007). As these factors affect elderly populations, they may contribute to the increased prevalence of BPPV with advancing age.

Whilst spontaneous resolution of this condition is possible, in some cases, symptoms persist (chronic BPPV) or may re-present (recurrent BPPV). Treatment involves canal repositioning manoeuvres (CRM), commonly performed by physiotherapists and medical professionals to treat BPPV (Baloh et al., 2010). Theoretically, CRM utilises gravity and head movement to guide debris out of the canal, back towards the otolith organs. Although current management approaches are beyond the scope of this review, there is evidence supporting the efficacy of canal repositioning treatment in reducing symptoms, falls and improving QoL. Thus, BPPV is a largely modifiable risk factor for falls (Ganança et al., 2010; Herdman et al., 2014).

Meniere's disease

The second most common peripheral vestibular disorder is Meniere's disease. The exact prevalence of this disorder is difficult to ascertain as MD is challenging to diagnose. However, it's prevalence is thought to be highest between 40 and 60 years (Baloh et al., 2010). MD frequently manifests as spontaneous attacks of vertigo with fluctuating hearing loss, tinnitus, severe unsteadiness, and nausea/vomiting (Baloh et al., 2010; Herdman et al.,

2014). Symptoms can fluctuate over time and are often highly variable between individuals, which explains the difficulty in achieving a diagnosis. Whilst the aetiology of MD is not well understood, genetics and infective processes are thought to play a role in its development (Baloh et al., 2010; Herdman et al., 2014).

The pathophysiological hallmark of this condition is thought to be endolymphatic hydrops, in which, there is a transient increase in endolymph volume and pressure during the episodic attack. Over time, repeated attacks may result in permanent loss of vestibular function, also known as Vestibular Hypofunction. At this stage, patients may be amenable to vestibular rehabilitation therapy (VRT), which involves exercises that foster central compensation (Han et al., 2011; Herdman et al., 2014). However, many patients are faced with the prospect of ageing with MD because of limited treatment options and low treatment efficacy (Baloh et al., 2010).

Vestibular Neuritis

Vestibular Neuritis is thought to arise from a benign inflammatory insult to the vestibular nerve (S. H. Jeong, H. J. Kim, et al., 2013 2013). Inflammation is suspected to cause damage and disruption to the vestibular nerve pathway, resulting in partial or complete loss of vestibular function (VH). In most cases, viral infection is the likely precipitant. Sufferers often present to a medical professional within the first 24 hours of onset, as symptoms of vertigo, nausea and significant unsteadiness rapidly worsen (Baloh et al., 2010). Over the following weeks, gradual recovery is achieved through central compensation. As VN mostly affects younger people, the vast majority will recover within three months. However, some people (particularly the elderly), may develop chronic symptoms related to vestibular asymmetry (chronic VH). Reduced capability for central adaptation in an ageing brain and vestibular system, may explain why older people are more susceptible to chronic symptoms (S. H. Jeong, H. J. Kim, et al., 2013).

Ageing of the peripheral vestibular system

Age-related reduction in hair cells, neuronal cells and otoconia within the vestibular end organ/s, may contribute to impaired vestibular function in older age (Allen et al., 2017; Ji & Zhai, 2018; Walther et al., 2014). For these reasons, the prevalence of vestibular dysfunction may increase with advancing age. The age-related decline in vestibular function may be distinct from pathological dysfunction induced by inner ear disorders. Nevertheless,

age-related changes in the inner ear may predispose older individuals to vestibular disorders (Allen et al., 2017).

PVD and fall-related risk factors for MTF

PVD and balance impairment

Balance dysfunction in those with PVD, occurs secondary to a loss of gaze stability and postural control (Agrawal et al., 2009). Environmental conditions that diminish the reliability of information obtained from visual or proprioceptive systems (i.e. darkness, uneven surfaces) or tasks involving head movement, present a significant challenge to the impaired vestibular system. Such conditions reduce the ability of the CNS to compensate for the vestibular loss through substitution of other sensory inputs, thereby increasing the risk of falls (Herdman et al., 2014). Dynamic balance and falls risk in vestibular populations may be assessed using the Dynamic Gait Index (DGI), as it incorporates some of these challenging conditions. Elderly vestibular populations have recorded a mean DGI score of 15, in comparison with a mean score of 22.8 in healthy older adults. Scores less than 19 are indicative of high falls risk, which suggests that PVD populations are more likely to fall than healthy populations (Herman et al., 2009). Static balance in PVD may be assessed using the Romberg test (RT) because it involves balance conditions that progressively increase the demand on the vestibular system. Standing with feet together and eyes closed on a compliant surface is particularly demanding for those with vestibular impairment, as the reliability of sensory information obtained from visual and proprioceptive sensory systems is decreased. In fact, failure of this test has been used in large population-based studies as a diagnostic proxy for PVD, where cost and time constraints have rendered formal vestibular function testing unfeasible (Agrawal et al., 2009; S. Y. Kim et al., 2020).

Fear of falling in PVD

In addition to physical sequalae, balance impairment and falls can also have negative psychological consequences such as, fear of falling (Marchetti et al., 2011). Fear of falling is a prominent problem amongst older populations, particularly those with PVD, as it is related to balance impairment and dizziness. In vestibular patients, higher levels of fear of falling are associated with poorer performance on clinical measures of balance including the DGI and TUG (Marchetti et al., 2011). As such, fear of falling may be considered a risk factor for falls. Dizziness may also play a role in the development of fear of falling in those with PVD. Among patients with VH, worse dizziness severity is associated with worse fear of falling.

High fear of falling may also translate to difficulty performing activities of daily living (ADL) such as dressing, walking, and completing household duties (Song & Lee, 2020). Thus, fear of falling may foster avoidance behaviours that negatively impact participation in PA and VRT. This is particularly concerning given VRT and exercise are known to be effective in reducing falls and MTF (Herdman et al., 2014; Song & Lee, 2020).

Sarcopenia and PVD

Physical activity is also crucial for muscle health and the prevention of sarcopenia. As sarcopenia is associated with reduced postural control, co-existence of PVD and sarcopenia may compound the risk of fracture in this population (A. J. Cruz-Jentoft et al., 2019). Although sarcopenic PVD populations have not been formally examined in the literature, older people with sarcopenia are 1.3 times more likely to suffer postural instability under conditions where visual cues are removed, than older adults who do not have sarcopenia (A. Y. Kim et al., 2020). Given balance impairment was evaluated by failure of condition four of the RT and this same test has been used as a diagnostic surrogate for vestibular impairment, it could be inferred that sarcopenia may have an increased prevalence amongst PVD populations. Actual prevalence, however, remains to be elucidated.

PVD and bone-related risk factors

Osteoporosis and PVD

Risk of fracture may also be increased in PVD populations, by virtue of associations between vestibular impairment and bone-related indices of fracture risk. Due to the high prevalence of BPPV relative to other vestibular disorders, and the fact that advancing age is a shared risk factor for the development of BPPV and osteoporosis, the literature largely focuses on the association between these two conditions (Choi et al., 2019; H.-J. Kim et al., 2020; von Brevern et al., 2007).

Current understanding of BPPV pathophysiology is assumed to relate to dislodgment of otoconia from the otolithic membrane. As otoconia are comprised of calcium carbonate, it is thought that their structure and adherence to the otolithic membrane may be influenced by altered calcium homeostasis (i.e. osteoporosis). Indeed, electron microscopy images of human otoconia, have revealed that older specimens exhibit an age-associated, degenerative morphology. Otoconial degeneration was characterised by fissuring, enlarged pore formation, and fragmentation, which may predispose otoconia to dislodgment (Figure 6). To date, this study has provided the most convincing evidence to support the proposed pathophysiology of

BPPV (Walther et al., 2014). Systemic disturbances in calcium homeostasis are thought to affect endolymphatic calcium supply, which may influence the health of otoconia. As such, many studies have begun to investigate osteoporosis and bone turnover in BPPV populations.

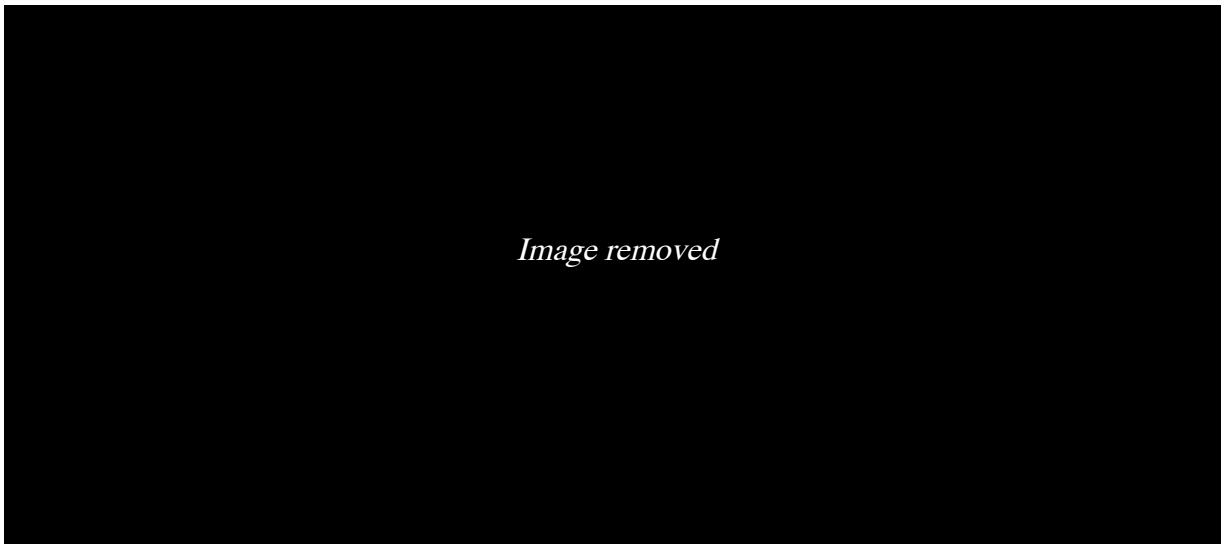


Figure 6. Human otoconia. (A) Intact otoconia from younger specimen. (B) Otoconia with enlarged pores and fissures from older specimen (Walther et al., 2014)

Osteoporosis is considered a risk factor for the development and recurrence of BPPV (Byun et al., 2019; Jang & Kang, 2009). BPPV incidence has been reported as being nearly twice as high in osteoporotic cohorts than non-osteoporotic controls (Byun et al., 2019; Chan et al., 2017). Similarly, rates of BPPV recurrence are also far greater in those with osteoporosis, suggesting a strong link between the two conditions (Byun et al., 2019; Jang & Kang, 2009).

BPPV also demonstrates a sex-related predominance for females, as does osteoporosis. Female sex may be considered an independent risk factor for BPPV because females are more likely to develop BPPV than males, irrespective of underlying osteoporosis (Byun et al., 2019). However, one study did not observe female sex to be a risk factor for BPPV, potentially due to smaller sample size and 1:4 matching, as opposed to the larger sample sizes and 1:1 matching used in the Byun et al. (2019) (Chan et al., 2017). BPPV incidence also appears to peak in the 6th decade, which corresponds with post-menopause for females (Liu et al., 2017). Post-menopause reflects a period whereby oestrogen deficiency contributes to accelerated bone turnover and increased susceptibility to osteoporosis (Daly et

al., 2013). Furthermore, the use of oestrogen for the management of menopause is not only protective for bone health, but also negatively associated with BPPV occurrence (Liu et al., 2017). As BPPV shares similar temporal and sex risk profiles to osteoporosis, older women with BPPV may constitute a higher risk population for fracture. Importantly, the post-menopausal and age-associated increase in fracture risk may be further compounded by comorbid BPPV.

It is also possible that the association between BPPV and osteoporosis may be bi-directional in nature. Irrespective of age and sex, those with BPPV demonstrate lower hip and spine BMD than healthy controls (Jeong et al., 2009). Fracture prevalence is also increased in BPPV patient populations, particularly those over 65 years – although this may reflect the increased number of falls in this population (Liao et al., 2015).

Aside from BPPV, a reduction in BMD has also been found in other types of vestibular dysfunction. For example, the Baltimore Longitudinal Study of Ageing (BLSA) examined vestibular function and BMD in their cohort of community-dwelling older adults. Saccular function formed the focus of this study, as the saccule (otolith organ) is capable of gravity perception and gravity perception is important for bone loading. Saccular function was measured using cervical vestibular evoked myogenic potentials (cVEMPs), with absent responses indicative of PVD. Interestingly, older individuals with PVD had lower hip BMD than those with preserved vestibular function. Spine BMD however, remained similar between the two groups (Bigelow et al., 2016). As such, these findings suggest that the association between vestibular dysfunction and reduced BMD, may be specific to weight-bearing bones. The clinical relevance of this finding may be questioned, as the study did not compare T-scores between groups at each skeletal site.

Similar site-specific findings have been reproduced within a Meniere's disease patient population (Shupak & Faranesh, 2020). However, unlike the BLSA study, 74% of patients with MD were found to have T-scores indicative of osteoporosis/osteopenia. Despite some convincing evidence of an association between osteoporosis and PVD, the cross-sectional nature of most studies in this area precludes the establishment of causality.

It would appear from the literature, that the association between poor bone health and PVD may be bi-directional. Poorer bone health may contribute to the development of PVD and vice versa, PVD may contribute to the development of osteoporosis or osteopenia.

However, an explanation for these associations remains to be elucidated and currently, there is not enough quality evidence to confirm the direction of these associations.

PVD and bone metabolism

In an attempt to unravel the association between low BMD and vestibular dysfunction, some researchers have investigated several parameters of bone metabolism. Of all the bone metabolism markers, vitamin D is most widely researched because of its role in calcium homeostasis and prevention of bone loss. As some peripheral vestibular disorders (i.e. BPPV, Meniere's disease) are associated with an increased risk of osteoporosis, it may be possible that the two conditions may be related by virtue of reduced vitamin D bioavailability. Indeed, there are consistent reports within the literature of decreased serum vitamin D levels amongst patients with BPPV and VN (S.-H. Jeong et al., 2013; Wu et al., 2019; Zhang et al., 2021). Although Goldschagg et al. (2021) had contested this notion when investigating vitamin D levels in BPPV and "other" vestibular disorders, they did not use an appropriate control group. Rather, patients with neurological disease were used for comparison. Therefore, caution must be exercised when interpreting the contradictory findings of this study or lack thereof. To date, it remains to be elucidated whether other peripheral vestibular disorders outside of BPPV and VN, are associated with lower serum vitamin D.

Adding weight to the notion that adequate vitamin D levels may be important for the function of the vestibular system, is the fact that the vestibular organs express vitamin D receptors (Zhang et al., 2021). Furthermore, a recent randomised control trial found that BPPV recurrence could be mitigated through vitamin D supplementation (Jeong et al., 2020). Whilst the mechanism for its effectiveness remains to be elucidated, physical inactivity (a common problem in PVD populations) may act as a confounding factor, as low levels of vitamin D are also associated with minimal sun exposure (S.-H. Jeong et al., 2013; Song & Lee, 2020). With respect to other markers of bone metabolism in PVD, high-quality studies in this area are lacking. However, a single study of males with and without BPPV revealed no between-group differences in serum procollagen type 1 N propeptide (bone formation marker) and β-isomerised carboxy-terminal telopeptide of type 1 collagen (bone resorption marker) (Yunqin Wu et al., 2018).

Physical inactivity and PVD

Reduced PA participation has long been associated with adverse health outcomes, particularly osteoporosis and MTF. Individuals with PVD may restrict their participation in PA in an effort to avoid an exacerbation of their dizziness and/or disequilibrium symptoms. Despite the known influence of PA on bone health, most studies investigating bone-related indices of fracture risk in vestibular populations, have failed to account for PA participation (Morimoto et al., 2019; Song & Lee, 2020). However, a recent study using accelerometer data, has revealed that patients with chronic UVH spend less time in an upright position and take fewer steps per day than healthy controls. Furthermore, the UVH group also demonstrated less energy expenditure related to vigorous ADLs such as sweeping and walking up/down stairs, suggesting that avoidance behaviours may be at play (Alessandrini et al., 2021). In addition to having a negative impact on bone health, PA avoidance may also hamper vestibular compensation/rehabilitation because the vestibular system is not being exposed to the necessary stimulus required to overcome dysfunction (Herdman et al., 2014). Consequently, chronic symptoms and reduced QoL may drive further activity restriction in PVD populations (Shiozaki et al., 2021). As regular PA is protective against age-related bone loss and falls, fracture risk may be compounded in PVD by virtue of decreased participation in PA (Santos et al., 2017).

Sympathetic nervous system, bone and vestibular impairment

Gravity perception is an important role played by the vestibular system (Herdman et al., 2014). As vestibular nuclei (central vestibular system) share anatomical projections with autonomic areas of the brainstem, the vestibular system is capable of modulating sympathetic nervous system (SNS) outflow (i.e. blood pressure, heart rate, breathing) in response to changes in position relative to gravity. Modulation occurs via the vestibulosympathetic reflex (Vignaux et al., 2013; Vignaux et al., 2015). As bone is richly innervated with autonomic receptors (alpha and beta), attention has turned to investigating the vestibulosympathetic reflex in relation to bone remodelling. Rodent models of bilateral vestibular loss demonstrated significantly reduced BMD at the femur, compared to rats without vestibular impairment at 1 month following vestibular loss. This was despite finding that locomotor activity (ie. physical activity) was greater in the rats with vestibular loss. Rats were then administered propranolol (non-selective beta blocker) in a follow-up study to confirm involvement of the SNS in vestibular-related bone loss. Whilst propranolol did not affect bone mass in rats with normal vestibular function, the decrease in BMD was attenuated by

the beta blocker in rats with bilateral loss. This finding was accompanied by a blunted reduction in osteoblast surface/bone surface parameters in rats with vestibular loss. Overall, these findings suggest that the association between PVD and bone loss may be mediated by the SNS (Vignaux et al., 2013).

To date, SNS activity has not been investigated in human PVD populations. Although beta blockers were investigated previously as a potential therapy for osteoporosis and the prevention of fracture, these studies have been of poorer quality and yielded conflicting results that require further investigation (Langerhuizen et al., 2022).

Summary

In summary, there is evidence that PVD is associated with bone-related and fall-related risk factors for fracture. As such, older people with PVD may represent a high-risk group for MTF. Whilst most literature has examined bone-related or fall-related indices of fracture risk in isolation, our study bridges an important gap by examining both determinants of fracture risk concurrently. With the goal of reducing fracture risk, the outcomes of this study may provide support for PVD screening and management in osteoporotic populations. Likewise, it may be beneficial to screen and treat osteoporosis in PVD populations, should we observe an increased risk of fracture.

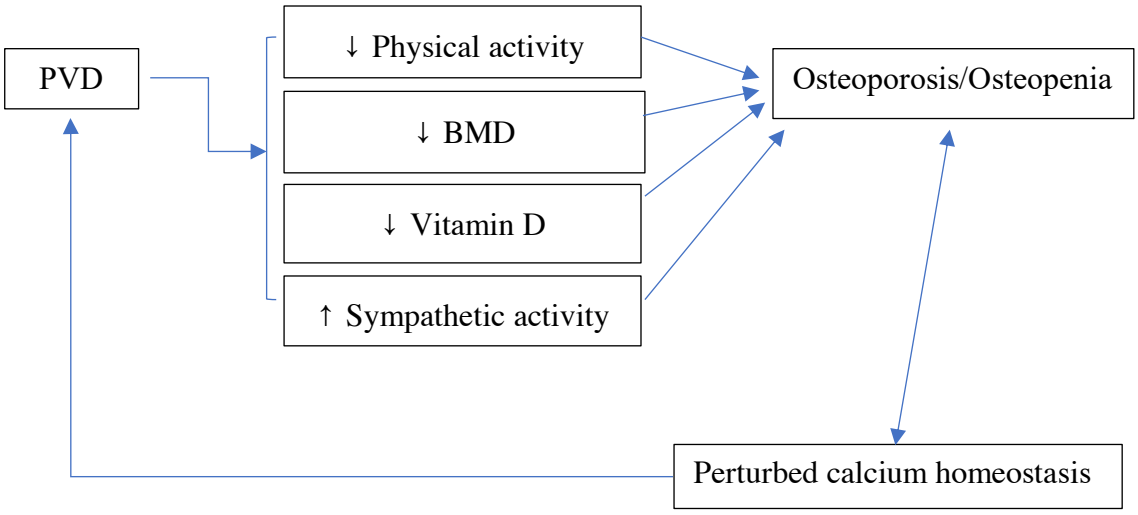


Figure 7. Summary of bone-related risk factors for fracture and their association with PVD

Methods

Experimental design

This study adopted a cross-sectional design, to compare indices of fracture and falls risk between older adults with and without vestibular impairment. Two groups of older adults were recruited to the study – one group of healthy participants and one group of participants diagnosed with chronic PVD. During a single visit (~2 hours), each participant completed various questionnaires, densitometry, and clinical tests. Testing was conducted in the Bone Densitometry Research Laboratory, Griffith University, Gold Coast campus, Australia.

Ethics

Initial ethics approval for the study was granted on 19/05/2021 by the Griffith University Human Research Ethics Committee (GUHREC) (GU Ref No: 2021/333) (Appendix A, i). Written approval from Metro South Health HREC (Appendix B) and Gold Coast Health HREC (Appendix A, ii) was obtained following GUHREC approval. This enabled the distribution of recruitment flyers within these health services, without the need for Site Specific Application (SSA). A subsequent variation request was approved on 12/10/2021, which allowed a battery of vestibular screening tests to be performed on participants. This request also included an updated flyer and consent package to reflect the inclusion of the screening tests (Appendix A, iii). Further variations were submitted to the GUHREC to include the use of a Facebook page to advertise the study and a flyer mail-out to vestibular physiotherapy waitlisted patients at Gold Coast University Hospital (GCUH) (Appendix A, v).

Participants

The target population was community-dwelling residents of South-East Queensland, aged 60 years and over. At initial phone contact, anyone that reported an underlying neurological condition (i.e. Parkinson's disease, stroke), recent fracture, recent radiation exposure or that they were unable to mobilise independently, were excluded from the study. Participants were also screened for metal prostheses that may have prevented scanning. Participants using hormone replacement therapy (HR), steroids and/or osteoporosis medication were not excluded from the study. Similarly, those with an endocrine disorder (i.e. diabetes) were not excluded to ensure that our sample was representative of a typical elderly population.

Healthy participants were those who were asymptomatic of dizziness and balance dysfunction and denied a medical history of PVD. Healthy participants were excluded if they

had any metal prostheses that prevented scanning of the lumbar spine and at least one hip. To reduce the possibility of including healthy participants with underlying PVD, each participant was screened for posterior and horizontal canal BPPV, using the Dix-Hallpike and Supine Roll tests respectively (please see vestibular screening process below). Those who had a positive response to testing (i.e. diagnostic nystagmus), were removed from the healthy group and included in the PVD group analysis. Participants with mixed central/peripheral disorders (i.e. vestibular migraine) were initially included in the study to improve statistical power. However, these participants were later removed from statistical analysis, as their diagnoses were not purely peripheral in nature and may have confounded the results.

PVD participants were those who had been formally diagnosed with a peripheral vestibular disorder by an Ear, Nose and Throat (ENT) Specialist, trained Vestibular Physiotherapist, or Audiologist. Participants were only included in the study if their symptoms (i.e. vertigo, imbalance) were chronic, meaning they had persisted for at least six weeks prior to enrolment. They were not excluded on the basis of current treatment. Unlike healthy participants, PVD participants were not excluded from this study for having metal prostheses that precluded the use of DXA, for the purpose of improving statistical power of other outcomes.

Sample size

Sample size was estimated based on priori data from a study by Y. Wu et al. (2018) which examined BMD in older women with and without BPPV. In anticipation of unequal group numbers, the power analysis was based off unequal group means. Accordingly, to discriminate lumbar spine aBMD (g/cm^2) group means of 0.813 g/cm^2 and 0.941 g/cm^2 with a standard deviation of 0.184 g/cm^2 and 0.119 g/cm^2 respectively, a total sample size of 44 was required (power = 80%, $\alpha = 0.05$). When adjusted for the observational study (+ 20%), the total sample size required was 54 (27 in each group).

Recruitment

Healthy participants were recruited through flyers displayed at various retirement villages, and senior community groups in the Gold Coast and Brisbane regions (Appendix A, vi). Flyers were also electronically distributed via University of the Third Age e-newsletters.

PVD participants were recruited from the community in addition to, various public and private vestibular physiotherapy clinics, with an updated flyer (Appendix A, vii). A public Facebook page designed to attract older individuals with dizziness and a flyer mail-

out to patients on the GCUH waitlist for vestibular physiotherapy, were additional methods of recruitment for the PVD group.

Vestibular screening process

A series of simple positional tests were employed to screen all participants for the presence of BPPV, including those that had already been diagnosed with PVD. The Dix-Hallpike (DHP) positional test was used to identify the presence of posterior canal (PC) BPPV, as the most common form of BPPV (Herdman et al., 2014). Neck range of movement and vertebrobasilar insufficiency were screened prior to all positional testing to ensure participants were safe and comfortable with the testing procedures. All tests were performed by a registered physiotherapist (JC). Participants were asked to assume a long sitting position on the DXA scanning bed. The left PC was assessed with the head rotated 45 degrees towards the left. With the head supported posteriorly in this position, participants were asked to swiftly assume a supine position. Given neck stiffness was a prominent issue in this age group, a pillow was placed at the level of the scapulae to facilitate neck extension and thus, maximise the effect of gravity within the canal. Participants were held in the supine position for 60 seconds. Test results were considered positive (for PC BPPV) where upbeat torsional nystagmus, lasting < 60 seconds, was observed by the physiotherapist. The same procedure was repeated with right head rotation.

The supine head roll test was used to identify the presence of horizontal canal (HC) BPPV (Herdman et al., 2014). Participants remained in the supine position following the DHP. After a brief rest period, in a neutral head position, their head was supported by the physiotherapist in 20 degrees of neck flexion (to bias the HC). Holding this flexed position, participants were guided swiftly into full left neck rotation. After 60 seconds, they returned to neutral head rotation and the procedure was repeated for the right side. A positive test was indicated by the presence of direction-changing horizontal nystagmus.

Participants who were initially recruited to the healthy group but were found have BPPV during testing (n = 5), were included in the PVD group. Given these participants were asymptomatic (unless when in test position), there was no way of determining exactly how long they had suffered BPPV. It was assumed that they had chronic BPPV. Detection of BPPV during this screening process did not prevent the participant from performing the outcome measures within a single session, as BPPV only affects the vestibular apparatus when the head is in a gravity-dependent position.

To further confirm that healthy participants did not have underlying PVD, we had initially employed the Romberg test (RT) on foam with eyes closed to screen all participants for underlying impairment. Failure of this balance condition (standing for < 30 seconds with feet together, eyes closed on compliant surface) had been used by other researchers in large population-based studies as a surrogate for vestibular impairment (Agrawal et al., 2011). However, it was later decided that the results from the RT were not to be used to identify PVD participants, as this would compromise the quality of the study and accuracy of results.

Outcomes

Anthropometrics

Participant height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Model 216; Seca, Hamburg, Germany). Weight was measured to the nearest 0.1 kg using a mechanical beam scale (Model 700; Seca, Hamburg, Germany). All measurements were taken in light clothing without shoes. Body mass index (BMI) was calculated from weight/height^2 (Kg/m^2).

Demographics and PVD characteristics

To better understand the characteristics of participants in the PVD group, questions relating to time of diagnosis, length of symptoms, treatment methods, and type of vestibular disorder were included on the questionnaire. Basic demographic information was also obtained from this questionnaire such as sex, age, physical activity participation, hospital admission history (5 years) and current level of function in community.

Self-perceived handicap

Disability associated with symptoms of PVD was quantified using the Dizziness Handicap Inventory (DHI) (Appendix D). This 25-item questionnaire measures self-perceived disability associated with dizziness/vertigo/imbalance across a 3-point scale (4 – always, 2 – sometimes, 0 – no). Scores were aggregated across emotional, physical, and functional components, with higher scores indicative of higher perceived disability associated with vestibular symptoms (Jacobson & Newman, 1990). This measure was included in the study as it is widely used in the clinical evaluation of PVD populations and is also associated with functional performance (Whitney et al., 2004).

Medical factors

A screening questionnaire was administered, to obtain an overview of each group regarding their medical history and to account for potential confounding factors. Participants were asked to report their smoking history, past medical history of endocrine disorder and use of medications that are known to potentially affect bone metabolism (i.e. HT, osteoporosis medication, steroids, beta blockers) and vestibular function (i.e. Stemetil).

Bone-related indices of fracture risk

Dual energy X-ray absorptiometry

Left femoral neck (FN) and lumbar spine (L1-4) BMD and appendicular skeletal muscle mass (obtained from whole body (WB) scan) were examined using DXA (Norland Elite, Swissray, Edison, NJ, USA) in the Bone Densitometry Research Laboratory, Griffith University, Gold Coast campus, Australia. All DXA scans were performed by a single technician with a Queensland Health radiation use license (JC). A standardised protocol was employed, in accordance with the Radiation Safety Act 1999 (Qld). Daily calibration of the scanner was performed according to manufacturer standards. Participants were positioned in supine for all scans, as the projections were taken in the antero-posterior (AP) plane. Standard patient positioning and anatomical markers were used for each scan. Whole body scans were performed with forearms pronated and lower limbs slightly abducted. Lumbar spine scans were performed with hips and knees flexed, supported on a foam block to eliminate lumbar lordosis. Hip scans required the participants' left lower limb to be fixed in a positioning device such that, hip internal rotation and abduction were maintained throughout scanning. Where metal prostheses prevented the scanning of the left femoral neck, the right femoral neck was scanned. Lumbar spine scans were also not undertaken for participants with metalware in this region. The presence of bilateral hip replacements and lumbar internal fixation together, precluded the use of DXA.

Scan analyses were performed using host software (Norland Illuminatus version 4.7.6) by a trained DXA operator (JC) in accordance with standard procedures and areal BMD (g/cm^2) reported, as it is strongly associated with fracture risk (Chalhoub et al., 2016). Additionally, BMD T-scores were used to characterise the groups in a clinically relevant manner. As per WHO definitions, BMD was considered normal if the T-score was greater than -1.0. Osteopenia was identified by a T-score of between -1.0 and -2.5, while

osteoporosis was defined by a T-score of -2.5 or below (Kanis, 1994). The Geelong reference database was used for the conversion of BMD to T-scores.

pQCT

Peripheral Quantitative Computed Tomography (pQCT, XCT-3000, Stratec Medizintechnik, Pforzheim, Germany) scans of the left tibia were used to examine tibial geometry and strength. Tibial length was measured from the distal tip of the medial malleolus and proximal border of the medial tibial plateau with an anthropometric ruler (No. 9065; Standardgraph, Germany). Participants were seated facing the device, with their left lower limb positioned in full knee extension, on a plastic holder inside the gantry. Velcro straps were used to secure the limb to reduce movement artefact. A scout scan of the ankle joint was used to obtain the anatomical reference point (tibial endplate) for the location of imaging, prior to scanning. A trained technician (JC) performed all scans using a standard four-slice protocol, with images acquired at 4%, 14%, 38% and 66% of tibial length from the distal tibial endplate. Analyses were performed by the same technician using host software (version 6.20, Stratec Medizintechnik, Pforzheim, Germany). Volumetric BMD (vBMD, mg/cm^3), cortical thickness (mm), and polar strength-strain index (SSI_p, mm^3) were determined at the 38% site (Sheu et al., 2011). Trabecular vBMD was derived at the 4% site. Where the left lower limb was unable to be scanned due to the presence of metalware, the right lower limb was examined. Trained technicians performed daily machine calibration with standard, cone, and cortical phantoms.

Other risk factors for poor bone health

Calcium intake

Dietary calcium intake was estimated using the AusCal, a calcium-specific questionnaire designed and validated for the Australian diet (Appendix B) (Beck et al., 2011). Participants recorded approximate serving size and frequency of consumption (per day, week, or month) of calcium-rich foods and calcium supplementation was documented. Average calcium intake (mg) was obtained via data entry into FoodWorks nutritional analysis software (Version 10, Xyris Software, Brisbane, Australia) by a single investigator (JC). Calcium intake was examined in this study, as it is known to influence bone health (Weeks & Beck, 2020).

Bone-relevant physical activity participation

Physical activity is another lifestyle factor known to influence bone health. To account for this, the Bone-Specific Physical Activity Questionnaire (BPAQ) was used to estimate participation in bone-relevant physical activity across the lifespan (Appendix C) (Weeks & Beck, 2008). Current BPAQ scores were calculated based upon physical activity type and frequency of participation (per week) reported for the preceding 12 months. Past BPAQ scores were calculated from physical activity participation reported across the lifespan, excluding the previous 12 months. Past and current BPAQ scores were averaged to derive total BPAQ scores. All analyses were performed using a customised calculator available online (http://www.fithdysign.com/BPAQ/). The calculator uses an algorithm to assign a weighting to each physical activity, which accounts for mechanical load. Higher BPAQ scores reflect participation in activities that generate larger mechanical loads. This bone-relevant tool has been used to assess physical activity in populations across the lifespan and was therefore, appropriate for this study of the older population.

Fall-related indices of fracture risk

Sarcopenia

As per the revised European Working Group on Sarcopenia in Older People (EWGSOP2) recommendations, muscle strength, quantity and physical performance were incorporated into the study as parameters of sarcopenia (A. Cruz-Jentoft et al., 2019).

The five-times sit to stand test (FTSTS) was used as an index of lower extremity muscle strength. Participants were seated in a standard chair (height 45 cm) and asked to cross their arms over their chest. They were instructed to move from sitting to standing as quickly as possible, for five repetitions. Time to complete the task was recorded. Scores >15 seconds are indicative of sarcopenia (A. Cruz-Jentoft et al., 2019). Dominant hand grip strength was used to estimate upper extremity strength. A hand-held dynamometer (JAMAR, Hatfield, PA, USA) was used, whilst in a seated position with the elbow supported at 20 degrees of shoulder abduction on a table. Participants were given an opportunity to trial two grip sizes and select one that felt most comfortable, prior to the formal trials. Participants were asked to squeeze the dynamometer with maximal effort over three trials. The trial average was compared with cut-off values for probable sarcopenia (<27 kg males, <16 kg females) (A. Cruz-Jentoft et al., 2019).

Muscle quantity and quality were examined using pQCT and DXA to confirm the presence of sarcopenia. Calf muscle cross-sectional area (CSA, cm^2) was determined by pQCT at the 66% tibial site (Cesari et al., 2006). Additionally, Appendicular Skeletal Muscle Mass (ASM) was calculated as the sum of lean mass (g) within the extremities, obtained from WB DXA scans. ASM was adjusted for body size using ASM/h^2. Cut-off values (< 7 kg/m^2 males, < 5.5 kg/m^2 females) were used to confirm the presence of sarcopenia (A. J. Cruz-Jentoft et al., 2019). Muscle density was also obtained from pQCT at the 66% tibial site as a surrogate of muscle quality and adiposity (Cesari et al., 2006).

The Timed Up and Go (TUG) test was used to examine physical performance. Participants were asked to rise from a standard chair without upper limb support, walk briskly for three metres, turn at the marked line on the floor, and return to their starting position. Time was recorded from the moment their buttocks lost contact with the chair, until they returned to the seated position. TUG time > 20 seconds was used to identify severe sarcopenia (if all other diagnostic criteria were met), which is indicative of increased risk of fall and fracture (A. J. Cruz-Jentoft et al., 2019).

Falls history

Falls history was obtained via the screening questionnaire. Participants reported the number of falls they had suffered in the preceding 12 months. A fall was defined as any event where they unintentionally came to rest on the ground or a lower level (WHO, 2007).

Fear of falling

Fear of falling was examined using the Falls Efficacy Scale – International (FES-I). Participants were asked to rate their concern for falling on a 4-point scale (not at all concerned, somewhat concerned, fairly concerned, very concerned) across 16 functional activities. Scores were summed, with higher scores indicative of higher fear of falling (Delbaere et al., 2010).

Dynamic balance

The Dynamic Gait Index (DGI) was used to assess dynamic balance and falls risk. Participants were asked to follow standardised verbal instructions for eight dynamic balance tasks. Their performance was marked on a scale from 0 (severe impairment) to 3 (no impairment) by the same assessor (JC). Scores were summed, where higher scores reflected

better dynamic balance. A cut-off score of < 19/24 was used to indicate increased falls risk (Whitney et al., 2000).

Health-related Quality of Life

Health-related quality of life (HR-QoL) was evaluated via the 36-Item Short Form Survey (SF-36) version 1 (RAND Corporation). Scoring was performed in accordance with standard procedures (Hays et al., 1995). Individual item categorical scales were transformed into quantitative scores between 0 (worst health state) and 100 (best health state) using a free online calculator (https://orthotoolkit.com/sf-36/) (Petri et al., 2017). Scores were then aggregated across eight health subdomains: physical function, role limitations physical, role limitations emotional, vitality, mental well-being, social function, pain, and general health as per standard procedures (Hays et al., 1995).

Scan quality assurance

A quality assurance check was undertaken prior to data analysis to improve the accuracy of results. Results obtained from poor quality scans secondary to movement artefact or incorrect positioning, were removed from the data set. A standardised visual inspection rating scale (a Likert scale ranging from 1 – none to 5 – extreme) was used to rate movement artefact for pQCT scan quality (Blew et al., 2014). Scans that scored 4-5 (severe to extreme) were excluded from the data analysis. To avoid overestimation of FN BMD, DXA scans were removed if there was sub-optimal hip internal rotation, such that lesser trochanter was clearly visible. Similarly, lumbar spine scans were removed if quality was poor or there was ambiguity surrounding the identification of vertebral levels (Watts, 2004). A record of the scans removed can be found in (Appendix E).

Data analysis

SPSS software version 28.0 (SPSS, Chicago, Illinois, USA) was used for all statistical analyses. Descriptive statistics were used to present participant characteristics and anthropometric data. Univariate analyses including Fisher's exact test and independent samples t-tests were used to examine between-group differences across categorical and normally distributed quantitative variables respectively. Fisher's exact test was used instead of chi-square because of the reduced sample size and risk of introducing statistical error with chi-square. Categorical variables were determined as having two levels to support the use of Fisher's exact 2 x 2 contingency table. Results for normally distributed variables were presented as mean (standard deviation (SD)). Non-parametric data was analysed using Mann-

Whitney U test and the results were presented as median (min, max). Spearman correlation analyses to examine the association between outcomes within each group. Strength of correlation was interpreted based upon the cut-off *r*-values published by Dancey and Reidy (2007). Statistical significance was set to $p < 0.05$ for all analyses.

Sub-group analyses

As a result of low sample size in the male group, we were unable to perform a male sub-group analysis. However, female sub-group analysis was performed for each outcome, to further investigate possible sex-related differences.

Participant reporting

Participants were provided with their DXA results and a letter that summarised the outcomes of their testing session (Appendix F). Participants with DXA-derived T-scores indicative of osteopenia or osteoporosis, were encouraged to seek medical advice from their General Practitioner (GP). Similarly, participants who were found to have underlying BPPV were provided with details of local physiotherapists, qualified in treating this condition. Participants deemed at high risk of falling indicated by poor performance on the TUG and DGI, were provided with basic falls prevention education (i.e., appropriate lighting, footwear, clear environment) and encouraged to seek physiotherapy for balance exercise.

Results

Participant characteristics

A total of 73 individuals volunteered for the study, of whom, 64 were eligible and included based on inclusion and exclusion criteria. Forty-two were classified as healthy and 17 had been diagnosed with PVD. The PVD group was comprised of 12 participants who had been diagnosed with PVD by a trained physiotherapist, ENT specialist or audiologist. Five additional healthy participants who had tested positive for BPPV during the vestibular screening process were included in the PVD group. Mean ages for the healthy and PVD groups were 73.7 ± 4.6 years and 75.6 ± 6.8 years, respectively. There were no between-group differences in sex distribution, age, height, weight, BMI, 5-year hospital admission history, or daily medication use. However, there were many more females in each group than there were males (female: male ratio approximately 4:1). Less than 20% of participants in each group were subject to polypharmacy (≥ 4 medications daily) (Table 1).

Table 1. Participant characteristics

Participant characteristics	**Healthy** **Mean (SD)** **n = 42**	**PVD** **Mean (SD)** **n = 17**	***p*-value**
Age (years)	73.7 (4.6)	75.6 (6.8)	0.285
Height (m)	1.6 (0.1)	1.60 (0.1)	0.313
Weight (Kg)	71.2 (14.8)	65.9 (13.6)	0.211
BMI (Kg/m^2)	26.7 (4.6)	25.4 (4.2)	0.309
Participant characteristics	**Healthy** **N (%)** **n = 42**	**PVD** **N (%)** **n = 17**	***p*-value**
Sex			
Female	34 (81.0)	14 (82.4)	1.00
Male	8 (19.0)	3 (17.6)	
Medication use (daily)			

< 4 medications	36 (85.7)	13 (81.3)	0.696
≥ 4 medications	6 (14.3)	3 (18.8)	
5-year hospital admission history			
< 2 admissions	25 (59.5)	9 (52.9)	0.773
≥ 2 admissions	17 (40.5)	8 (47.1)	

*Note: *p < 0.05, **p < 0.001. SD = standard deviation.*

Fall, fracture, and mobility characteristics are presented in Table 2. There were no differences between groups in falls history and 5-year fracture history. However, more participants in the PVD group required mobility aids to access the community (17.6% vs. 0% respectively, $p = 0.021$) (Table 2).

Table 2. Fall, fracture, and mobility characteristics

Characteristics	**Healthy**	**PVD**	***p*-value**
	N (%)	**N (%)**	
	n = 42	**n = 17**	
Falls last 12 months			
< 2 falls	41 (97.6)	15 (88.2)	0.197
≥ 2 falls	1 (2.4)	2 (11.8)	
Use of mobility aid			
Nil aid	42 (100.0)	14 (82.4)	**0.021***
Uses aid	0 (0.0)	3 (17.6)	
Fracture from fall past 5 years			
No	34 (81.0)	15 (88.2)	0.708
Yes	8 (19.0)	2 (20.0)	

*Note: *p < 0.05, **p < 0.001.*

Clinical characteristics of the PVD group are presented in Table 3. The most prevalent PVD diagnosis was BPPV (70.6%) followed by UVH (11.8%). Other diagnoses included semicircular canal dehiscence (n =1), BVH (n=1) and MD (n=1). The majority of PVD participants had experienced symptoms for > 12 months (58.8%). Physiotherapy was the most common treatment approach, with 35.3% of participants using physiotherapy alone and 29.4% using a combination of physiotherapy and medication to manage their condition. In addition, 35.5% of participants were not receiving treatment for PVD (Table 3).

Table 3. Clinical characteristics of the PVD group (n = 17)

Clinical characteristic	**N (%)**
Clinical diagnosis	
Benign Paroxysmal Positional Vertigo (BPPV)	12 (70.6)
Unilateral vestibular hypofunction (UVH)	2 (11.8)
Bilateral vestibular hypofunction (BVH)	1 (5.9)
Meniere's Disease (MD)	1 (5.9)
Semicircular canal dehiscence	1 (5.9)
Dizziness Handicap Inventory (DHI)	
Asymptomatic	5 (29.4)
Mild	8 (47.1)
Moderate	3 (17.6)
Severe	1 (5.9)
Length of symptoms	
Asymptomatic	5 (29.4)
> 6 weeks	1 (5.9)
> 3 months	1 (5.9)
> 1 year	10 (58.8)
Symptoms in past fortnight	
Yes	10 (58.8)

No	7 (41.2)
Current treatment	
Yes	7 (41.2)
No	10 (58.8)
Treatment type	
Medication alone	0 (0)
Physiotherapy alone	6 (35.3)
Combination of therapies	5 (29.4)
No treatment	6 (35.3)

Note: Combination of therapies = combined medication and physiotherapy.

Bone-related indices of fracture risk

DXA derived measures

DXA derived bone-related indices of fracture risk are presented in Table 4. Although there were no significant differences in BMD between the PVD and healthy groups at either skeletal site, there was a trend for lower BMD at the FN and lumbar spine in the PVD group than the healthy group (Figures 8 and 9). There were no differences between groups in the proportion of participants with healthy T-scores and the proportion of those with T-scores indicative of osteopenia or osteoporosis at either skeletal site (Table 4).

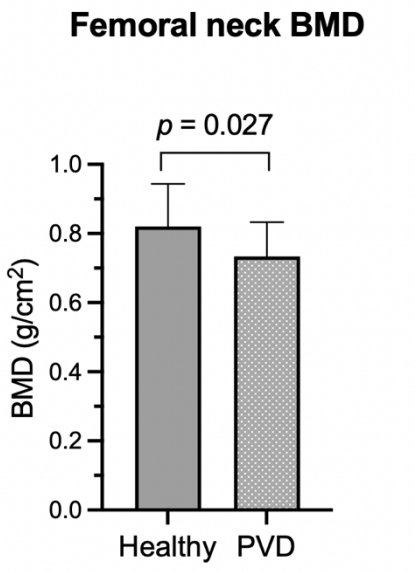


Figure 8. Comparisons of femoral neck BMD between groups. Data presented as Mean BMD; error bars represent standard deviation.

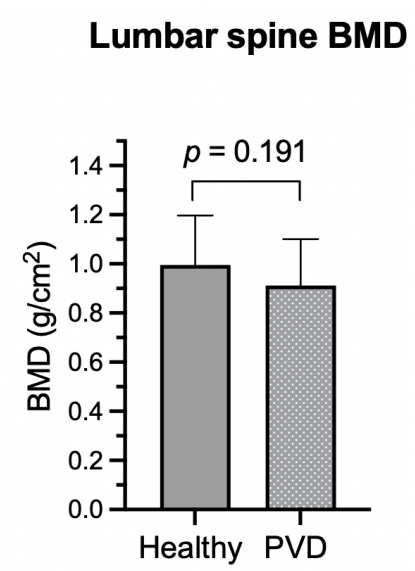


Figure 9. Comparisons of lumbar spine BMD between groups. Data presented as Mean BMD; error bars represent standard deviation.

Table 4. DXA derived indices of fracture risk

Outcome variable	**Healthy (n = 42) Mean (SD)**	**PVD (n = 17) Mean (SD)**	***p*-value**
FN BMD (g/cm^2)	0.81 (0.14)	0.76 (0.12)	0.073
L1-4 BMD (g/cm^2)	1.02 (0.20)	0.92 (0.18)	0.093
Outcome variable	**Healthy (n = 42) N (%)**	**PVD (n =1 7) N (%)**	***p*-value**
T-score L1-4			
Healthy	21 (61.1)	6 (37.5)	0.141

Osteopenia or osteoporosis	14 (38.9)	10 (62.5)	
T-score FN			
Healthy	15 (39.5)	2 (12.5)	0.062
Osteopenia or osteoporosis	23 (60.5)	14 (87.5)	

*Note: *p < 0.05, **p < 0.001. SD = standard deviation, BMD = bone mineral density, L1-4 = lumbar vertebra 1 to 4, FN = femoral neck.*

Although a low male sample size precluded a male sub-group analysis, female sub-group analysis results for DXA parameters are presented in Table 5. There was a difference in FN BMD, where woman with PVD exhibited lower FN BMD than healthy women (0.74 ± 0.10 g/cm^2 vs. 0.83 ± 0.13 g/cm^2 respectively, $p < 0.05$). Similarly, the prevalence of osteoporosis and osteopenia at the FN was greater in women with PVD than those without (92.9% vs. 59.4% respectively, $p < 0.05$).

Table 5. DXA derived indices of fracture risk – female sub-group analysis

Outcome variable	**Healthy (n = 34) Mean (SD)**	**PVD (n = 14) Mean (SD)**	***p*-value**
FN BMD (g/cm^2)	0.83 (0.13)	0.74 (0.10)	**0.027 ***
L1-4 BMD (g/cm^2)	1.02 (0.20)	0.91 (0.15)	0.191
Outcome variable	**Healthy (n = 34) N (%)**	**PVD (n = 14) N (%)**	***p*-value**
T-score L1-4			
Healthy	16 (53.3)	5 (35.7)	0.342

Osteopenia or osteoporosis	14 (46.7)	9 (63.4)	
T-score FN			
Healthy	13 (40.6)	1 (7.1)	**0.035 ***
Osteopenia or osteoporosis	19 (59.4)	13 (92.9)	

*Note: *p < 0.05. SD = standard deviation, BMD = bone mineral density, L1-4 = lumbar vertebra 1 to 4, FN = femoral neck.*

pQCT derived measures

Bone geometry and other indices of bone strength derived from pQCT are displayed in table 6. There were no differences between the PVD and healthy groups in pQCT derived parameters of tibial geometry and strength, apart from endocortical circumference at the 38% tibia site. The PVD group had lower endocortical circumference than the healthy group (36.4 mm vs. 40.2 mm respectively, $p = 0.025$). Female sub-group analysis revealed no between-group differences between groups across any pQCT parameter (Table 7).

Table 6. pQCT derived indices of fracture risk

pQCT parameter	**Healthy (n = 42) Mean (SD)**	**PVD (n = 17) Mean (SD)**	***Z*/*t* (*p*-value)**
4% Tibia total BMC (mg)	257.4 (48.7)	243.5 (40.8)	0.817 (0.419)
4% Tibia total vBMD (mg/cm^3)	258.5 (37.6)	258.6 (34.6)	0.001 (0.999)
4% Tibia total area (mm^2)	1002.8 (170.0)	949.5 (161.3)	0.875 (0.387)
4% Tibia trabecular BMC, (mg)	190.0 (39.7)	175.3 (27.8)	1.086 (0.284)
4% Tibia trabecular vBMD (mg/cm^3)	232.3 (37.1)	228.6 (29.4)	0.293 (0.771)
4% Tibia trabecular area (mm^2)	823.1 (145.2)	775.7 (138.5)	0.910 (0.368)
4% Tibia total BSI (g^2/cm^4)	0.7 (0.2)	0.6 (0.2)	0.581 (0.564)
4% Tibia Trabecular BSI (g^2/cm^4)	0.5 (0.1)	0.40 (0.1)	0.971 (0.338)
38% Tibia vBMD (mg/cm^3)	1123.3 (33.6)	1139.2 (20.4)	-0.901 (0.368)
38% Tibia cortical thickness (mm)	4.6 (0.8)	4.94 (0.58)	-1.367 (0.179)
38% Tibia endocortical circumference (mm)	40.2 (5.2)	36.15 (3.51)	**2.259 (0.029) ***

38% Tibia total BMC (mg)	279.1(54.1)	292.1 (46.6)	-1.270 (0.204)
38% Tibia total area (mm^2)	248.1 (45.1)	256.1 (38.7)	-1.063 (0.288)
38% Tibia periosteal circumference (mm)	68.8 (4.5)	67.2 (4.8)	-0.591 (0.555)
38% Tibia SSI_p (mm^3)	1444.5 (312.1)	1425.9 (285.0)	0.167 (0.868)
38% Tibia polar section modulus (mm^2)	1537.6 (312.7)	1496.9 (285.9)	0.314 (0.706)

*Note: *p < 0.05. BMC= bone mineral content, BSI = bone strength index, SSI_p= polar strength-strain index, vBMD= volumetric bone mineral density.*

Table 7. pQCT derived indices of fracture risk – female sub-group analysis

	Healthy (n = 34) Mean (SD)	**PVD (n = 14) Mean (SD)**	***Z*/*t* (*p*-value)**
4% Tibia total BMC (mg)	246.1 (39.5)	232.8 (37.3)	0.848 (0.403)
4% Tibia total vBMD (mg/cm^3)	257.4 (39.8)	253.5 (37.3)	0.247 (0.806)
4% Tibia total area (mm^2)	965.0 (138.2)	930.3 (174.7)	0.592 (0.558)
4% Tibia trabecular BMC, (mg)	182.4 (35.7)	168.2 (24.7)	1.052 (0.300)
4% Tibia trabecular vBMD (mg/cm^3)	232.3 (39.7)	224.2 (31.9)	0.480 (0.634)
4% Tibia trabecular area (mm^2)	791.2 (118.6)	760.3 (150.4)	0.612 (0.545)
4% Tibia total BSI (g^2/cm^4)	0.6 (0.2)	0.6 (0.2)	0.684 (0.498)
4% Tibia Trabecular BSI (g^2/cm^4)	0.4 (0.1)	0.4 (0.1)	1.002 (0.323)
38% Tibia vBMD (mg/cm^3)	1119.3 (34.1)	1134.7 (12.7)	-1.957 (0.059)
38% Tibia cortical thickness (mm)	4.4 (0.7)	4.8 (0.5)	-1.511 (0.140)
38% Tibia endocortical circumference (mm)	40.4 (5.6)	36.4 (3.4)	1.894 (0.670)

38% Tibia total BMC (mg)	265.1 (41.3)	282.1 (46.8)	-1.446 (0.148)
38% Tibia total area (mm^2)	236.7 (35.2)	248.3 (39.8)	-1.218 (0.223)
38% Tibia periosteal circumference (mm)	67.9 (4.0)	66.6 (5.2)	0.800 (0.429)
38% Tibia SSI_p (mm^3)	1367.6 (247.1)	1382.2 (304.4)	-0.140 (0.889)
38% Tibia polar section modulus (mm^2)	1466.4 (262.7)	1457.4 (306.4)	0.085 (0.933)

*Note: *p < 0.05. BMC = bone mineral content, BSI = bone strength index, SSI_p= polar strength-strain index, vBMD = volumetric bone mineral density.*

Other risk factors for poor bone health

There were no between-group differences in lifestyle factors (BPAQ scores, smoking status, vitamin D supplementation, daily calcium intake) apart from past BPAQ scores. Past BPAQ scores were lower in the PVD group than the healthy group (37.50 ± 33.18 vs. 63.73 ± 65.27, p <0.05). There were no between group differences in medical factors (endocrine disorder, HR, beta-blocker or steroid use and osteoporosis medication use) (Table 8). There were no between-group differences in any lifestyle or medical factors within the female subgroup analysis (Table 9).

Table 8. Lifestyle and medical factors affecting bone health

Lifestyle factors	**Healthy (n = 42) Mean (SD)**	**PVD (n = 17) Mean (SD)**	***p*-value**
BPAQ past	63.7 (65.3)	37.5 (33.2)	**0.047 ***
BPAQ current	0.7 (0, 5.1)	0.8 (0, 8.8)	0.633
BPAQ total	32.5 (32.8)	19.6 (16.8)	0.052
Daily calcium (mg)	831.2 (438.7)	861.8 (327.9)	0.798
Medical factors	**Healthy (n = 42) N (%)**	**PVD (n = 17) N (%)**	***p*-value**
Smoking status			
Non-smoker	30 (71.4)	9 (52.9)	0.228
Ex-smoker	12 (28.6)	8 (47.1)	
History of HR use			
Yes	10 (23.8)	3 (17.6)	0.738

No	32 (76.2)	14 (82.4)	
History chronic steroid use			
Yes	4 (9.5)	1 (5.9)	1.00
No	38 (90.5)	16 (94.5)	
Endocrine disorder			
Yes	11 (26.2)	3 (17.6)	0.737
No	31 (73.8)	14 (82.4)	
Beta blocker use			
Yes	6 (15.4)	5 (31.3)	0.266
No	33 (84.6)	11 (68.8)	
Osteoporosis medication			
Yes	5 (11.9)	3 (17.6)	0.678
No	37 (88.1)	14 (82.4)	
Vitamin D supplement			
Yes	19 (45.2)	8 (47.1)	1.00
No	23 (54.8)	9 (52.9)	

*Note: *p < 0.05, **p < 0.001. HR = hormone replacement therapy, BPAQ = Bone-specific Physical Activity Questionnaire, SD = standard deviation.*

Table 9. Lifestyle and medical factors affecting bone health – female sub-group analysis

Lifestyle factors	**Healthy (n = 34) Mean (SD)**	**PVD (n = 14) Mean (SD)**	***p*-value**
BPAQ past	37.3 (1.1, 282.3)	24.8 (1.2, 117.2)	0.181
BPAQ current	0.70 (0.0, 5.14)	0.71 (0.0, 8.8)	0.901
BPAQ total	20.2 (0.64, 141.7)	14.8 (0.72, 59.3)	0.181
Daily calcium (mg)	821.36 (470.4)	838.3 (347.9)	0.798
Medical factors	**Healthy (n = 42) N (%)**	**PVD (n = 17) N (%)**	***p*-value**
Smoking status			
Non-smoker	25 (73.5)	7 (50.0)	0.178
Ex-smoker	9 (26.5)	7 (50.0)	
History of HR use			
No	24 (70.6)	11 (78.6)	0.728
Yes	10 (29.4)	3 (21.4)	
History chronic steroid use			
No	31 (91.2)	13 (92.9)	1.00
yes	3 (8.8)	1 (7.1)	
Endocrine disorder			
No	24 (70.6)	311 (78.6)	0.728
Yes	10 (29.4)	3 (21.4)	

Beta blocker use			
Yes	3 (9.4)	3 (23.1)	0.334
No	29 (90.6)	10 (76.9)	
Osteoporosis medication			
Yes	4 (11.8)	3 (21.4)	0.400
No	30 (88.2)	11 (18.6)	
Vitamin D supplement			
Yes	17 (50.0)	8 (57.1)	0.756
No	17 (50.0)	6 (42.9)	

*Note: *p < 0.05, **p < 0.001. HR = hormone replacement therapy, BPAQ = Bone-specific Physical Activity Questionnaire, SD = standard deviation.*

Fall-related indices of fracture risk

There were no between-group differences in fear of falling (FES-I), grip strength, height normalised appendicular skeletal muscle mass (ASM/h^2), calf muscle density, calf muscle area, Timed Up and Go (TUG) test time, or Five Times Sit to Stand test (FTSTS) time. Dynamic Gait Index (DGI) scores were lower in the PVD group than the healthy group (Z = -4.30, $p < 0.001$). There were no significant differences in the proportion of participants within each group with probable or confirmed sarcopenia and no sarcopenia ($p > 0.05$) (Table 10). Female subgroup analysis yielded similar results as DGI was lower in the PVD group than the healthy group (Z = -3.776, $p < 0.001$) but no other outcomes differed between-groups (Table 11).

Table 10. Indices of falls risk

Outcome variable	**Healthy (n = 42) Mean (SD)**	**PVD (n = 17) Mean (SD)**	***p*-value**
FES-I scores	21.2 (6.3)	25.8 (12.1)	0.266
TUG (seconds)	6.3 (1.1)	7.6 (2.9)	0.083
DGI score	22.3 (2.1)	19.0 (4.9)	**< 0.001 ****
FTSTS (seconds)	10.9 (3.17)	12.5 (6.5)	0.867
ASM/h^2 (Kg/m^2)	6.92 (1.16)	6.56 (1.42)	0.327
Grip strength (Kg)	22.72 (7.75)	21.37 (8.02)	0.548
Calf muscle area (mm^2)	4795.6 (773.8)	4634.2 (1077.1)	0.604
Calf density (mg/cm^2)	79.0 (2.4)	79.8 (2.0)	0.289
Outcome variable	**Healthy (n = 42) N (%)**	**PVD (n = 17) N (%)**	***p*-value**
Sarcopenia			
No sarcopenia	31 (75.6)	11 (64.7)	0.520
Probable or confirmed	10 (24.4)	6 (35.3)	

*Note: *p < 0.05, **p < 0.001. FES-I = falls efficacy scale international, DGI = Dynamic Gait Index, FTSTS = Five Times Sit to Stand, ASM/h^2 = Appendicular skeletal muscle mass normalised by height, TUG = Timed Up and Go test.*

Table 11. Indices of falls risk – female sub-group analysis

Outcome variable	**Healthy (n = 34) Mean (SD)**	**PVD (n = 14) Mean (SD)**	***p*-value**
FES-I scores	21.5 (6.3)	27.7 (12.1)	0.096
TUG (seconds)	6.3 (1.2)	7.9 (3.1)	0.075
DGI score	22.3 (2.2)	18.8 (5.4)	**< 0.001 ****
FTSTS (seconds)	10.1 (3.3)	12.7 (7.1)	0.586
ASM/h^2 (Kg/m^2)	6.6 (0.9)	6.3 (1.2)	0.339
Grip strength (Kg)	20.1 (5.0)	18.8 (5.6)	0.424
Calf muscle area (mm^2)	4624.2 (662.5)	4336.8 (986.1)	0.340
Calf density (mg/cm^2)	78.2 (2.4)	79.5 (1.9)	0.699
Outcome variable	**Healthy (n = 34) N (%)**	**PVD (n = 14) N (%)**	***p*-value**
Sarcopenia			
No sarcopenia	26 (76.5)	9 (64.3)	0.480
Probable or confirmed sarcopenia	8 (23.5)	5 (35.7)	

*Note: *p < 0.05, **p < 0.001. FES-I = falls efficacy scale international, DGI = Dynamic Gait Index, FTSTS = Five Times Sit to Stand, ASM/h^2 = Appendicular skeletal muscle mass normalised by height, TUG = Timed Up and Go test.*

Health-related quality of life

The PVD group reported lower scores in role limitations emotional, vitality, social functioning, and general health sub-domains of the SF-36 than the healthy group ($p < 0.05$) (Table 12). There were no between-group differences across the remaining sub-domains of the SF-36. There were between-group differences across role limitation emotional, vitality, mental health, social functioning and general health sub-domains of the SF-36 in the female sub-group analysis. Females with PVD reported consistently lower scores than the healthy females in all sub-domains of the SF-36 (Table 13).

Table 12. HR-QoL scores

SF-36 sub-domain	**Healthy (n = 42) Mean (SD)**	**PVD (n = 17) Mean SD)**	***p*-value**
Physical function (%)	75.0 (20.8)	66.8 (27.0)	0.212
Role limitations physical (%)	82.1 (32.3)	57.4 (49.8)	0.071
Role limitations emotional (%)	89.7 (26.0)	72.5 (37.7)	**0.043 ***
Vitality (%)	66.67 (19.6)	55.0 (19.8)	**0.047 ***
Mental health (%)	81.05 (13.1)	72.24 (17.9)	0.079
Pain (%)	79.23 (20.8)	75.44 (18.1)	0.515
Social functioning (%)	91.5 (17.1)	80.8 (22.1)	**0.028 ***
General health (%)	76.90 (17.2)	64.41 (14.1)	**0.010 ***

*Note: *p < 0.05.*

Table 13. HR-QoL scores – female sub-group analysis

SF-36 sub-domain	**Healthy (n = 34) Mean (SD)**	**PVD (n = 14) Mean (SD)**	***p*-value**
Physical function (%)	75.2 (20.8)	66.8 (29.5)	0.270
Role limitations physical (%)	84.6 (28.9)	62.5 (48.7)	0.184
Role limitations emotional (%)	91.2 (23.6)	71.5(38.9	**0.033 ***
Vitality (%)	66.8 (16.4)	56.1 (18.5)	**0.035 ***
Mental health (%)	81.4 (13.0)	71.7 (18.7)	**0.046 ***
Pain (%)	79.7 (19.1)	76.3 (18.9)	0.570
Social functioning (%)	93.6 (12.6)	77.6 (23.1)	**0.007 ***
General health (%)	76.90 (17.2)	64.3 (15.3)	**0.011 ***

*Note: *p < 0.05*.

Association between outcome variables

Healthy group

There were strong positive associations between FTSTS and TUG in the healthy group (r = 0.738, $p < 0.01$). Moderate negative associations were observed between TUG and DGI (r = -0.585, $p < 0.01$), FTSTS and DGI (r = -0.638, $p < 0.01$), FES-I and DGI (r = -0.400, $p < 0.01$) and FES-I and grip strength (r = -0.437, $p < 0.01$). A moderate positive association was evident for ASM/h^2 and grip strength (r = 0.436, $p < 0.01$) and L1-4 BMD and FN BMD (r =0.615, $p < 0.01$). A weak, positive association was observed between FES-I and TUG (r = 0.328, $p < 0.05$) (Table 14).

PVD group

A moderate negative association was observed for the PVD group between FTSTS and DGI ($r = -0.535$, $p < 0.05$), FES-I and grip strength ($r = -0.504$, $p < 0.05$), TUG and grip strength ($r = -0.610$, $p < 0.01$) and TUG and DGI ($r = -0.617$, $p < 0.01$). There were moderate positive correlations between ASM/h^2 and FN BMD ($r = 0.526$, $p < 0.05$), grip strength and DGI ($r = 0.559$, $p < 0.05$) and FES-I and TUG ($r = 0.566$, $p < 0.05$). Strong positive associations were evident for FTSTS and TUG ($r = 0.706$, $p < 0.01$), L1-4 BMD and FN BMD ($r = 0.747$, $p < 0.01$) for the PVD group (Table 15).

Table 14. Correlation coefficients between study variables for the healthy group

Variable	1	2	3	4	5	6	7	8	9	10
1. BPAQ total	1.00									
2. FES-I	-.137	1.00								
3. Daily calcium (mg)	.004	.048	1.00							
4. DGI	.097	**-.400****	-.062	1.00						
5. TUG (sec)	-.145	.328*	.029	**-.585****	1.00					
6.Grip strength (Kg)	.024	**-.437****	.059	.118	-.170	1.00				
7. FTSTS (sec)	-.272	.261	.095	**-.638****	**.738****	-.036	1.00			
8. ASM/h^2 (Kg/m^2)	-.102	-.198	-.086	-.082	.137	**.436****	**.370***	1.00		
9. L1-4 BMD (g/cm^2)	-.153	-.162	-.010	-.006	.060	.150	-.064	.144	1.00	
10. FN BMD (g/cm^2)	-.062	-.170	-.107	.001	.191	-.293	.120	.220	**.615****	1.00

*Note: *p < 0.05, ** p < 0.01. BMD = bone mineral density, BPAQ = bone-specific physical activity questionnaire, FES-I = falls efficacy scale international, DGI = Dynamic Gait Index, FTSTS = Five Times Sit to Stand, ASM/h^2 = Appendicular skeletal muscle mass normalised by height, TUG = Timed Up and Go test.*

Table 15. Correlation coefficients between study variables for the PVD group

Variable	1	2	3	4	5	6	7	8	9	10
1. BPAQ total	1.00									
2. FES-I	.048	1.00								
3. Daily calcium (mg)	.201	.414	1.00							
4. DGI	-.181	-.311	-.185	1.00						
5. TUG	.010	**.566***	.211	**-.617****	1.00					
6.Grip strength	.315	**-.504***	-.036	**.559***	**-.610****	1.00				
7. FTSTS	.365	.439	.152	**-.535***	**.706****	-.375	1.00			
8. ASM/h^2	.321	-.439	-.138	.236	-.541	.446	-.118	1.00		
9. L1-4 BMD	.109	-.321	.787	.367	-.197	.231	.053	.362	1.00	
10. FN BMD	.335	-.130	.326	.157	-.085	.221	.247	**.526***	**.747****	1.00

*Note: *p < 0.05, ** p < 0.01. BMD = bone mineral density, BPAQ = bone-specific physical activity questionnaire, FES-I = falls efficacy scale international, DGI = Dynamic Gait Index, FTSTS = Five Times Sit to Stand, ASM/h^2 = Appendicular skeletal muscle mass normalised by height, TUG = Timed Up and Go test.*

Discussion

The aim of the current project was to determine whether there were any differences in fall-related and bone-related indices of fracture risk, between older adults with chronic peripheral vestibular dysfunction (PVD) and those without. Whilst there was a general trend for lower bone mineral density (BMD) in the PVD group, there were no statistically significant differences found. Sub-group analysis based on sex, revealed females with PVD had lower femoral neck (FN) BMD than healthy females. Older adults with PVD had a lower tibial endocortical circumference than healthy older adults, but no further differences were found in geometric indices of bone strength. With regard to physical activity (PA), past BPAQ scores were significantly lower in the PVD group than the healthy group. Interestingly, there were no between-group differences in current BPAQ scores. There were no differences in fall-related outcomes with the exception of poorer performance on the Dynamic Gait Index (DGI) for the PVD group compared to the healthy group. Those suffering from PVD also demonstrated reduced health-related quality of life (HR-QoL) compared with healthy participants on the 36-Item Short Form Survey (SF-36). There were positive associations between falls efficacy scale international (FES-I) and Timed Up and Go (TUG) test time, five times sit-to-stand (FTSTS) time and, TUG and lumbar spine (L1-4) BMD and, FN BMD in both groups. Dynamic Gait Index (DGI) was negatively correlated with TUG and FTSTS in both healthy and PVD groups.

Bone-related outcomes

Previous research has observed an association between vestibular dysfunction and reduced BMD (Bigelow et al., 2016; Park & Kim, 2016; Shupak & Faranesh, 2020). Much of the work has focused on benign paroxysmal positional vertigo (BPPV) as the most prevalent form of PVD, and has observed a greater prevalence of osteoporosis amongst those with BPPV than healthy adults (Byun et al., 2019; Chan et al., 2017). As 70% of our PVD group were diagnosed with BPPV, the absence of a statistically significant between-group difference in BMD was at odds with previous reports.

Whilst there have been numerous theories to explain the association between BPPV and osteoporosis, a study involving surgical excision of human otoconia was the first to demonstrate a potential biological link between the conditions (Walther et al., 2014). Older human otoconia specimens obtained via surgical labyrinthectomy, were found to exhibit degenerative morphologies. Otoconial degeneration was characterised by increased porosity, loss of mass and fractures, akin to some of the age-associated changes exhibited by the skeleton. Additionally, the degenerative features were likely to predispose otoconia to detachment from the otolithic membrane, supporting the proposed pathogenesis of BPPV. Given otoconia are comprised of calcium carbonate, it is

reasonable to hypothesise, that their morphology might be influenced by calcium bioavailability. As such, the association between BPPV and osteoporosis may be explained by aberrant systemic calcium homeostasis (Walther et al., 2014).

Support for this concept may be obtained from recent studies investigating the association between BPPV and vitamin D – a regulator of calcium homeostasis and biomarker of bone metabolism (Ding et al., 2019). Several studies have observed lower serum vitamin D levels amongst adults with BPPV, which has fostered the notion that vitamin D deficiency may be associated with the development and recurrence of BPPV (Dhameliya et al., 2020; Ding et al., 2019; S. H. Jeong, J. S. Kim, et al., 2013 et al., 2013). Conversely, vitamin D supplementation has been shown to reduce BPPV recurrence, potentially through vitamin D receptor expression within the peripheral vestibular end organ (Jeong et al., 2020; Yang et al., 2020). Other biomarkers of bone metabolism including procollagen type 1 N propeptide and β-isomerised carboxy-terminal telopeptide of type 1 collagen (markers of bone formation and bone resorption, respectively) have not been found to differ between adults with or without BPPV (Yunqin Wu et al., 2018). Nevertheless, the association between BPPV and osteoporosis may be coincidental, as both conditions increase in prevalence with advancing age (Karataş et al., 2017). It is clear from the literature, that further research on calcium homeostasis in BPPV is required to clarify this association.

Another explanation for our findings, or lack thereof, may relate to the fact that BPPV is quite distinct from other peripheral vestibular disorders. Dysfunction in BPPV arises from hyperexcitability of the canal, rather than a loss of function as in VN or VH (Baloh et al., 2010; Herdman et al., 2014). In addition, BPPV symptoms generally last < 60 seconds and may be prevented by avoidance of gravity-dependent head movements (Herdman et al., 2014). Although BPPV can persist for weeks or months, it is typically episodic in nature and therefore, may not provide the most appropriate human model of chronic PVD (Herdman et al., 2014). Therefore, it is possible that BPPV might not affect an individual in the same way, or to the same extent as chronic vestibular loss. Moreover, it is possible that our BPPV participants (who predominated the PVD group) reported PA levels that were comparable to our healthy participants, because positional symptoms are usually not worsened by PA (Herdman et al., 2014). This may have accounted for the comparable current BPAQ scores seen in our groups. As such, BPPV predominance within the current study may have contributed to the lack of between-group differences across most bone-related and fall-related indices of fracture risk.

It is also possible that our sample of BPPV participants was not representative of the typical BPPV participants examined in other studies. Approximately 41% of the participants with BPPV were diagnosed with the condition during the vestibular screening stage of the study activities, after having entered the study as a healthy participant. Whilst the proportion of undiagnosed BPPV within our study, closely reflects what has been reported in previous literature (53%), no study has investigated the association between osteoporosis and BPPV in asymptomatic individuals (Hawke et al., 2021). Therefore, it remains to be elucidated whether those with worse BPPV symptoms exhibit worse decrement in bone strength. A recent study investigating BMD in MD has found greater decrement in BMD to be associated with greater percentage vestibular loss on vestibular function testing (Shupak & Faranesh, 2020). However, objective vestibular loss does not necessarily correspond to subjective symptoms or perceived handicap. This is certainly true in the case of chronic PVD, where well-compensated patients may report that they are asymptomatic and have achieved full functional recovery, despite having a measurable vestibular deficit (Yip & Strupp, 2018).

Temporal incongruity between central compensation and bone loss may have also contributed to our lack of findings. In most cases, compensation for vestibular impairment can be achieved within 3 months (Han et al., 2011). Therefore, it was likely that most of our "chronic" PVD participants would have achieved some degree of compensation by the time they entered the study. A complete bone remodelling cycle, however, takes almost twice as long to complete (4-6 months) (Clarke, 2008; Kenkre & Bassett, 2018). Thus, it is possible that we may have missed the window of opportunity to observe a difference BMD, as compensation would have likely been achieved prior to the completion of a full bone remodelling cycle. Should there be a true association between bone loss and PVD, it is likely that the association is not directly causal, as these two events (central compensation and bone remodelling) appear to be taking place independently of each other. Further investigation into markers of bone metabolism throughout the acute and chronic phases of vestibular dysfunction, may provide an earlier indication of dynamic changes in bone health. Notwithstanding, these potential reasons for a lack of differences between the PVD and healthy groups in bone-related outcomes, it is possible the lack of between-group differences is merely a reflection of insufficient study power (See Appendix G).

Although we did not find a difference between the groups in the overall analysis, our female sub-group analysis revealed women with PVD had markedly lower FN BMD than healthy women. Whilst males with PVD also appeared to have lower BMD at the FN, our male sample was insufficient to power a valid sub-group analysis. Our sub-group findings were consistent with much

of the literature surrounding the association between BPPV and osteoporosis, as females with BPPV were found to have lower FN BMD than those without the condition (Byun et al., 2019; Choi et al., 2019; Jang & Kang, 2009). Importantly, our female PVD group were found to have a greater proportion of participants with FN T-scores that were suggestive of osteopenia or osteoporosis. As such, the degree of bone loss exhibited by women in the PVD group, appeared to be of clinical relevance.

Our sex-specific findings may be explained in part, by sex-related differences in bone health between men and women. Whilst ageing is associated with bone loss in both sexes, post-menopausal women experience accelerated bone loss, secondary to oestrogen withdrawal (De Martinis et al., 2021; Hannan et al., 2000). As such, post-menopausal women may be more susceptible than men, to the negative changes in bone health that may be associated with PVD. Support for this notion may be obtained from a recent study of males with and without BPPV, which failed to find any differences between the groups in FN or spine BMD (Yunqin Wu et al., 2018). Sex-related differences in bone size may also account for the conflicting results. Two-dimensional DXA may overestimate BMD in males, owing to their larger bone size relative to females (Choksi et al., 2018). Potentially, between-group differences in the overall analysis, may have been masked by overestimated BMD, even though there were no differences in proportion of males within each group. Whilst this finding suggests that PVD may be negatively related to bone health, the cross-sectional study design cannot establish causality.

Paradoxical to the notion that vestibular dysfunction may be associated with disturbances in systemic calcium homeostasis, was our finding of a possible site-specific reduction in FN BMD in our female sub-group analysis. Whilst we had expected to see a reduction in BMD irrespective of skeletal scan site, there were no between-group differences in BMD at the L1-4 site. As such, these findings suggested that the association between reduced BMD and PVD may be limited to the lower limb weight-bearing bones. Indeed, similar site-specific findings have been reported in a prospective cohort study, examining BMD in healthy older adults with age-associated saccular dysfunction (otolith organ impairment). Whilst vestibular impairment was associated with reduced BMD at the hip, there were no differences in spine BMD between those with or without vestibular dysfunction (Bigelow et al., 2016). Notably, this study population comprised of healthy older adults, who were inadvertently found to have age-associated saccular dysfunction on vestibular function testing. When compared to healthy controls, Meniere's disease and BPPV patient populations have also demonstrated a reduction in BMD at femoral scan sites but not lumbar spine sites.

(Shupak & Faranesh, 2020; Yunqin Wu et al., 2018). It may be possible however, that the limitations of DXA may account for the lack of findings at the lumbar spine. Specifically, DXA may overestimate BMD at the lumbar spine in those with aortic calcification or osteophytes which may conceal BMD losses (Watts, 2004; Yoon & Kim, 2021). Overall, these findings suggest that a site-specific reduction in BMD at the weight-bearing lower limbs may be associated with PVD, irrespective of type of peripheral vestibular impairment.

Whilst the mechanism underlying this association remains to be elucidated in humans, rodent models of bilateral vestibular loss may provide some insight. Indeed, chronic bilateral vestibular ablation appears to induce bone loss exclusively in the load-bearing femur, without impacting upon whole body or vertebral BMD (Vignaux et al., 2013; Vignaux et al., 2015). Greater bone loss at lumbar spine would be expected because of the increased trabecular content of the lumbar spine which predisposes it to higher turnover than the hip which is largely cortical bone (Seeman, 2013). The authors speculated that weight bearing bone loss may arise from interactions between skeletal and vestibular systems. More specifically, the vestibular system, which is capable of sensing gravity and verticality, may indirectly influence bone remodelling in response to gravity or weight-bearing. Investigations into potential mechanisms of vestibular induced bone loss have revealed a potential role for the sympathetic nervous system (SNS). Administration of a beta blocker was shown to attenuate the bone loss induced by vestibular ablation in rats, suggesting a role for the sympathetic nervous system in mediating the link between skeletal and vestibular systems. We did not find any between-group differences in beta blocker use, suggesting it was unlikely to be a confounding factor in the current study. However, some human studies have observed a reduction in bone loss with beta blocker usage, whilst others have found equivocal evidence for their effectiveness in the treatment of osteoporosis and prevention of MTF (Langerhuizen et al., 2022; Lary et al., 2020). Ultimately, further research in this area is required to better understand the relationship between SNS and bone health.

Regarding geometric indices of bone strength, we found that older adults with PVD had a lower tibial endocortical circumference than healthy older adults. There was a concomitant trend for increased cortical thickness, aligned with the finding of reduced endocortical circumference. Although these findings are not necessarily suggestive of improved bone strength (especially as there were no differences in BSI or SSI_p), we were not expecting to find less cortical bone loss in the PVD group compared to the healthy group. In fact, we had expected the opposite based on their DXA results. Advancing age and oestrogen deficiency typically foster cortical thinning and endosteal circumference expansion, reflecting disproportionate endosteal resorption and periosteal

apposition (Seeman, 2013; Shanbhogue et al., 2016). Given the older age of participants and the female predominance within the PVD group, our findings of increased endocortical thickness and reduced endocortical circumference were unexpected.

Fall-related outcomes

Another unexpected finding was that our PVD group performed similarly to our healthy group across many of the fall-related outcomes. Poor grip strength and longer FTSTS and TUG times are widely recognised as being associated with adverse health outcomes such as fracture, hospital admission and all-cause mortality (Cooper et al., 2010; A. J. Cruz-Jentoft et al., 2019; Jeong et al., 2019; Sim et al., 2019; Sobestiansky et al., 2019). Contrary to the literature, our PVD group demonstrated mean grip strength, TUG and FTSTS times that were not only comparable to our healthy group, but also reflective of normative values for community-dwelling older adults (A. J. Cruz-Jentoft et al., 2019; Shumway-Cook et al., 2000; Whitney et al., 2005). Furthermore, although the PVD group exhibited worse performance on the DGI, their mean score was not low enough to translate to a clinically relevant, increased risk of falling (< 19/24) (Herman et al., 2009). Thus, it may be possible that our PVD group represented a "healthier" sub-population of older people with vestibular impairment. Alternatively, group performance may have been skewed by the inclusion of asymptomatic participants or those who had achieved central compensation.

Support for the notion that our PVD group might not have been representative of a typical PVD population may be obtained from the minimal fall and fracture history reported by our PVD group. Most literature suggests that that vestibular impairment greatly increases the risk of both adverse outcomes (Agrawal et al., 2009; Liao et al., 2015). Furthermore, literature suggests that fear of falling and maladaptive behaviour (PA avoidance) is highly prevalent in PVD populations and that these issues are directly related to symptom severity or disability (Morimoto et al., 2019; Song & Lee, 2020). Since our PVD group reported mostly mild disbaility associated with their vestibular symptoms (DHI score ≤ 30), it was unsurpsing to find no difference between our groups in terms of current BPAQ scores or FES-I scores. Current BPAQ scores reflect exercise-related bone loading over the previous 12 months. As our PVD participants reported that they did not feel disabled by their disorder (possibly as a result of central compensation during this time or transient pathology), it is likely that they would engage in physical activity comparable to healthy participants'. In addition, they would likely report comparable levels of fear of falling. Whilst underreporting of handicap can be an issue when using the DHI in older populations, central compensation is a more

likely explanation for the reports of mild handicap within our PVD group (Hansson et al., 2005; Yip & Strupp, 2018).

Health-related Quality of Life

Despite reports of mild handicap, our PVD group reported consistently lower HR-QoL across the SF-36 sub-domains of emotional role limitations, vitality, general health and social functioning compared to healthy participants. Female sub-group analysis revealed consistent results, in addition to, lower scores in the mental health sub-domain for women with PVD. Since between-group differences were mostly found in mental and social aspects of the SF-36, this finding suggests that HR-QoL in PVD may be influenced to a greater extent by psychosocial factors, as opposed to physical impairment (Weidt et al., 2014). Whilst other studies have found all 8 sub-domains of SF-36 to be negatively impacted by vestibular disorders in both chronic and acute phases, chronic disorders are associated with greater emotional impact (Bayat et al., 2020; Petri et al., 2017).

Associations between outcomes

Both groups exhibited positive associations between FES-I and TUG, FTSTS and TUG and L1-4 BMD and FN BMD. The association between slower TUG times and slower performance on FTSTS was not surprising, given that both measures involve a STS task and are used in the evaluation of sarcopenia (A. J. Cruz-Jentoft et al., 2019). Although adopted as a test of lower extremity muscle strength, the FTSTS does not appear to be as strongly related to other clinical measures of strength (i.e. grip strength), as TUG performance. We also found a negative correlation between FTSTS and DGI as well as TUG and DGI. These findings may relate to the fact that FTSTS and TUG both involve dynamic tasks which may present as a challenge to those with poor dynamic balance (i.e. low scores on DGI) (Yee et al., 2021). In the clinical setting, fear of falling negatively impacts upon performance on most outcome measures of balance and strength, mostly by virtue of slower gait speed and physical deconditioning. Previous research has also confirmed this to be the case, as TUG times were found to be related to fear of falling, irrespective of falls history (Park et al., 2014). Finally, the association between FN BMD and spine BMD was expected given calcium homeostasis is regulated at a systemic level.

Limitations

Several limitations must be acknowledged. Firstly, we were unable to achieve the target sample size, due to difficulty recruiting participants with PVD (27 participants, for 80% power). Post-hoc power analyses revealed that the project was under powered to detect between-group

differences in most outcome measurements, which would contribute to an increased likelihood of type II error (Appendix G). Although we had attempted to recruit our PVD participants from multiple sites in South-East Queensland, COVID-19 presented a major barrier to recruitment. PVD participants were mostly drawn from public hospital ENT clinics and private physiotherapy practices, which were subject to closure or restricted practice at times during the pandemic. As such, flyers were unable to be delivered to potential participants. In addition, multiple lockdowns delayed the data collection process and contributed to participant withdrawal from the project. Recruitment to the PVD group was also hindered by the fact that patients with PVD, had often been investigated for central causes of dizziness/balance problems (i.e. stroke, tumour), with imaging modalities that are associated with large radiation doses (i.e. head Computed Tomography). Similarly, X-rays were frequently used to rule out fracture following a fall. As such, some PVD participants were excluded from the study based on excessive radiation exposure within the last 12 months. A larger sample size would have enabled the use of more comprehensive statistical analyses (i.e. MANOVA), so that confounding factors could be appropriately adjusted for.

Secondly, the outcomes of this study may not be generalisable to all peripheral vestibular disorders. Future studies should include a larger sample size of PVD participants, which may capture other relatively common, chronic vestibular disorders such as unilateral vestibular hypofunction or Meniere's disease (Parker et al., 2019). BPPV accounted for the over 70% of the PVD population within this study. Whilst BPPV is known to make up the largest proportion of peripheral vestibular diagnoses in ENT and physiotherapy clinics, it is usually diagnosed in approximately 30% of presenting cases (Parker et al., 2019). Therefore, overrepresentation of BPPV prevalence in our study, may impact generalisability to typical clinical populations. Implementation of a vestibular screening process may have contributed to this overrepresentation as BPPV was the only disorder which was screened in this process. Its purpose was to capture healthy participants with incidental BPPV to reduce the likelihood of including a participant with underlying PVD within the healthy group. Whilst the Dix-Hallpike test is the gold standard for the diagnosis of the most common type of vestibular disorder (BPPV), we cannot be certain that we excluded other underlying vestibular disorders in our healthy participants without using formal vestibular function testing. However, other vestibular disorders are far less common than BPPV and our healthy participants did not report any symptoms of vestibular dysfunction. Formal vestibular testing is able to accurately diagnose and quantify vestibular dysfunction, however, it is also expensive, time-consuming and must be performed by a trained Audiologist. As such, this type of testing was not feasible for this project.

Thirdly, some biases require addressing. Recall bias may have been introduced by AusCal and BPAQ questionnaires. Although not assessed in the study, it was likely that some of our older participants would have experienced an age-associated decline in their cognition. Given the AusCal requires detailed information on dietary intake and BPAQ requires participants to recall childhood PA participation, difficulty with recall could contribute to an inaccurate estimate of physical activity participation and dietary calcium intake. Similarly, response bias may have resulted from participants inadvertently overestimating their dietary intake of calcium-rich foods and participation in physical activity to please the researcher.

Finally, there are some limitations with the use of DXA and pQCT. Whilst DXA is the clinical standard for fracture risk prediction and osteoporosis diagnosis, two-dimensional imaging can lead to overestimation of BMD in people with larger bones and underestimation in smaller people. In addition, aBMD is an imperfect surrogate of bone strength as other determinants including bone geometry, size, and microarchitecture are unable to be evaluated by two-dimensional imaging (Choksi et al., 2018; Clarke, 2008). By incorporating pQCT, it was hoped that a more accurate measure of the determinants of bone strength could be achieved. However, optimal participant positioning within the pQCT scanner was limited at times, by age-related musculoskeletal changes such as osteoarthritis or reduced flexibility. Use of the pQCT scanner required participants to sit with their leg outstretched at approximately 90 degrees hip flexion. Many found this position uncomfortable and made slight adjustments to their positioning throughout the scan despite verbal instruction from the researcher to avoid movement. As pQCT is sensitive to movement artefact, scan quality was reduced. Although, scan quality was reviewed before inclusion in the data set, this process further reduced the number of scans that could be analysed, resulting in a smaller sample size for this analysis (13 PVD, 32 healthy).

Future research

Future research in this area is indicated. Collaborative partnerships with other Queensland Health sites and private vestibular physiotherapy clinics may help to overcome challenges with recruitment. Furthermore, exclusion of PVD participants based on excessive radiation exposure (i.e. post-fall investigations) may be avoided by employing an alternative imaging modality, such as Echolight ®. Echolight ® is a novel, radiation free modality that uses quantitative ultrasound to estimate BMD (Cortet et al., 2021; Di Paola et al., 2019).

It would be beneficial to investigate bone health in PVD populations in a longitudinal study, from initial diagnosis to final treatment and beyond. Tracking the evolution of PVD using caloric

testing, Vestibular Evoked Myogenic Potentials (VEMPs), and video head impulse testing (VHIT) to quantify vestibular deficit, may help to unravel the nature of the relationship (whether dynamic or static) between PVD and indices of bone-strength (Jeong et al., 2017). Similarly, the possible existence of a dose-response relationship between severity of vestibular deficit and bone-strength could also be investigated. Monitoring the degree of compensation throughout the rehabilitation process may be important, as VRT may offer a therapeutic target for prevention of osteoporosis and MTF.

Further investigation of sympathetic nervous system activity in PVD populations may shed light on its role as a potential mediator in the complex association between osteoporosis and PVD in humans. Whilst autonomic outflow cannot be directly measured at the bone, systemic autonomic activity may be assessed indirectly by measuring blood pressure and heart rate variability as well as respiratory rate (Valensi, 2021). Direct SNS activity may be measured via invasive means such as plasma noradrenaline or peroneal nerve microneurography (Squair et al., 2021). Similarly, accounting for beta blocker use may demonstrate a potential therapeutic target as some studies have suggested possible attenuation of bone loss (Vignaux et al., 2013; Vignaux et al., 2015). Alternatively, galvanic vestibular stimulation, which uses a safe binaural electrical current, could be used to temporarily and non-invasively induce vestibular dysfunction whilst monitoring the autonomic response in healthy adults (McGeoch, 2019).

Conclusion

PVD and osteoporosis are prevalent amongst older populations, particularly post-menopausal women. Since PVD greatly increases the propensity to fall, it is considered a fall-related risk factor for fracture. However, fracture risk is also determined by bone-related risk factors. Hence, the current study primarily aimed to examine bone- and fall-related determinants of fracture risk concurrently, in an older population with PVD. Secondary aims of this project were to examine HR-QOL and explore associations between the indices of fracture risk.

Contrary to other reports, our study did not find generalised differences in BMD or other indices of bone strength between older men and women with and without PVD. An observed BMD difference in the female subgroup, however, suggests post-menopausal women with PVD may constitute a sub-population of patients who are prone to osteoporosis and MTF. Screening for osteoporosis may therefore, be an especially important adjunct to the clinical management of PVD in this demographic. As there have been reports of increased prevalence of PVD amongst those with osteoporosis, in light of the high treatability of PVD, screening osteoporotic populations for PVD may be judicious.

Overall, older people represent a particularly complex group of patients, having accumulated multiple comorbidities across the lifespan. Although PVD can have a negative impact on falls risk and HR-QoL, it is likely to represent a small part of the overall clinical picture. Whilst PVD should not be overlooked in fracture prevention, other factors or conditions that elevate fall or fracture risk must also be addressed. Given the complex nature of geriatric health, further research is required to understand the association between fracture risk and PVD.

Bibliography

Afrin, N., Sund, R., Honkanen, R., Koivumaa-Honkanen, H., Rikkonen, T., Williams, L., & Kröger, H. (2020). A fall in the previous 12 months predicts fracture in the subsequent 5 years in postmenopausal women. *Osteoporosis international*, *31*(5), 839-847. https://doi.org/10.1007/s00198-019-05255-5

Agrawal, Y., Carey, J. P., Della Santina, C. C., Schubert, M. C., & Minor, L. B. (2009). Disorders of Balance and Vestibular Function in US Adults: Data From the National Health and Nutrition Examination Survey, 2001-2004. *Archives of Internal Medicine*, *169*(10), 938-944. https://doi.org/10.1001/archinternmed.2009.66

Agrawal, Y., Carey, J. P., Hoffman, H. J., Sklare, D. A., & Schubert, M. C. (2011). The modified Romberg Balance Test: normative data in U.S. adults. *Otology & neurotology, 32*(8), 1309-1311. https://doi.org/10.1097/MAO.0b013e31822e5bee

Alessandrini, M., Viziano, A., Pistillo, R., Granito, I., Basso, L., Preziosi, N., & Micarelli, A. (2021). Changes in daily energy expenditure and movement behavior in unilateral vestibular hypofunction: Relationships with neuro-otological parameters. *Journal of Clinical Neuroscience*, *91*, 200-208. https://doi.org/10.1016/j.jocn.2021.07.012

Allen, D., Ribeiro, L., Arshad, Q., & Seemungal, B. M. (2017). Age-Related Vestibular Loss: Current Understanding and Future Research Directions [Mini Review]. *Frontiers in neurology*, *7*. https://doi.org/10.3389/fneur.2016.00231

Baloh, F. R. W., Honrubia, D. V., & Kerber, K. A. (2010). *Baloh and Honrubia's Clinical Neurophysiology of the Vestibular System, Fourth Edition*. Oxford University Press, Incorporated. http://ebookcentral.proquest.com/lib/griffith/detail.action?docID=1036306

Bayat, A., Hoseinabadi, R., Saki, N., & Sanayi, R. (2020). Disability and Anxiety in Vestibular Diseases: A Cross-Sectional Study. *Cureus*, *12*(11), e11813-e11813. https://doi.org/10.7759/cureus.11813

Beck, B., Weeks, B., & Norling, T. (2011). A novel Australian calcium-specific diet questionnaire: validity and reliability. *Osteoporosis international*,22:S626–S27

Bigelow, R. T., Semenov, Y. R., Anson, E., du Lac, S., Ferrucci, L., & Agrawal, Y. (2016). Impaired Vestibular Function and Low Bone Mineral Density: Data from the Baltimore Longitudinal Study of Aging. *Journal of the Association for Research in Otolaryngology*, *17*(5), 433-440. https://doi.org/10.1007/s10162-016-0577-5

Blew, R. M., Lee, V. R., Farr, J. N., Schiferl, D. J., & Going, S. B. (2014). Standardizing evaluation of pQCT image quality in the presence of subject movement: qualitative versus quantitative assessment. *Calcif Tissue Int*, *94*(2), 202-211. https://doi.org/10.1007/s00223-013-9803-x

Boskey, A. L., & Coleman, R. (2010). Aging and bone. *Journal of dental research*, *89*(12), 1333-1348. https://doi.org/10.1177/0022034510377791

Bouxsein, M. L. P., & Karasik, D. P. (2006). Bone geometry and skeletal fragility. *Current Osteoporosis Reports*, *4*(2), 49-56. https://doi.org/10.1007/s11914-006-0002-9

Byun, H., Chung, J. H., Lee, S. H., Park, C. W., Kim, E. M., & Kim, I. (2019). Increased risk of benign paroxysmal positional vertigo in osteoporosis: a nationwide population-based cohort study. *Scientific reports*, *9*(1), 3469-3469. https://doi.org/10.1038/s41598-019-39830-x

Cesari, M., Leeuwenburgh, C., Lauretani, F., Onder, G., Bandinelli, S., Maraldi, C., Guralnik, J. M., Pahor, M., & Ferrucci, L. (2006). Frailty syndrome and skeletal muscle: Results from the Invecchiare in Chianti study. *The American journal of clinical nutrition*, *83*(5), 1142-1148. https://doi.org/10.1093/ajcn/83.5.1142

Chalhoub, D., Orwoll, E. S., Cawthon, P. M., Ensrud, K. E., Boudreau, R., Greenspan, S., Newman, A. B., Zmuda, J., Bauer, D., Cummings, S., Cauley, J. A., & Osteoporotic Fractures in Men Study Research, G. (2016). Areal and volumetric bone mineral density and risk of multiple types of fracture in older men. *Bone*, *92*, 100-106. https://doi.org/10.1016/j.bone.2016.08.014

Chan, K.-C., Tsai, Y.-T., Yang, Y.-H., Chen, P.-C., & Chang, P.-H. (2017). Osteoporosis is associated with increased risk for benign paroxysmal positional vertigo: a nationwide population-based study. *Archives of Osteoporosis*, *12*(1), 106. https://doi.org/10.1007/s11657-017-0403-7

Chen, J., Zhao, W., Yue, X., & Zhang, P. (2020). Risk Factors for the Occurrence of Benign Paroxysmal Positional Vertigo: A Systematic Review and Meta-Analysis [Systematic Review]. *Frontiers in neurology*, *11*. https://doi.org/10.3389/fneur.2020.00506

Choi, H. G., Lee, J. K., Kong, I. G., Lim, H., & Kim, S. Y. (2019). Osteoporosis increases the risk of benign paroxysmal positional vertigo: a nested case–control study using a national sample cohort. *European archives of oto-rhino-laryngology*, *276*(2), 335-342. https://doi.org/10.1007/s00405-018-5230-y

Choi, K. H., Lee, J. H., & Lee, D. G. (2021). Sex-related differences in bone metabolism in osteoporosis observational study. *Medicine*, *100*(21), e26153-e26153. https://doi.org/10.1097/MD.0000000000026153

Choksi, P., Jepsen, K. J., & Clines, G. A. (2018). The challenges of diagnosing osteoporosis and the limitations of currently available tools. *Clinical Diabetes and Endocrinology*, *4*(1), 12. https://doi.org/10.1186/s40842-018-0062-7

Clarke, B. (2008). Normal bone anatomy and physiology. *Clinical Journal of American Society of Nephrology*, *3 Suppl 3*(Suppl 3), S131-139. https://doi.org/10.2215/cjn.04151206

Conley, R. B., Adib, G., Adler, R. A., Åkesson, K. E., Alexander, I. M., Amenta, K. C., Blank, R. D., Brox, W. T., Carmody, E. E., Chapman-Novakofski, K., Clarke, B. L., Cody, K. M., Cooper, C., Crandall, C. J., Dirschl, D. R., Eagen, T. J., Elderkin, A. L., Fujita, M., Greenspan, S. L., Halbout, P., Hochberg, M. C., Javaid, M., Jeray, K. J., Kearns, A. E., King, T., Koinis, T. F., Koontz, J. S., Kužma, M., Lindsey, C., Lorentzon, M., Lyritis, G. P., Michaud, L. B., Miciano, A., Morin, S. N., Mujahid, N., Napoli, N., Olenginski, T. P., Puzas, J. E., Rizou, S., Rosen, C. J., Saag, K., Thompson, E., Tosi, L. L., Tracer, H., Khosla, S., & Kiel, D. P. (2020). Secondary Fracture Prevention: Consensus Clinical Recommendations from a Multistakeholder Coalition. *Journal of bone and mineral research*, *35*(1), 36-52. https://doi.org/https://doi.org/10.1002/jbmr.3877

Cooper, R., Kuh, D., Hardy, R., Mortality Review, G., Falcon, & Teams, H. A. S. (2010). Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *British Medical Journal (Clinical research ed.)*, *341*, c4467-c4467. https://doi.org/10.1136/bmj.c4467

Cortet, B., Dennison, E., Diez-Perez, A., Locquet, M., Muratore, M., Nogués, X., Ovejero Crespo, D., Quarta, E., & Brandi, M. L. (2021). Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context. *Bone*, *143*, 115786. https://doi.org/10.1016/j.bone.2020.115786

Cosman, F., de Beur, S. J., LeBoff, M. S., Lewiecki, E. M., Tanner, B., Randall, S., & Lindsay, R. (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis international*, *25*(10), 2359-2381. https://doi.org/10.1007/s00198-014-2794-2

Cozadd, A. J., Schroder, L. K., & Switzer, J. A. (2021). Fracture Risk Assessment: An Update. *Journal of bone and joint surgery. American volume*, *103*(13), 1238-1246. https://doi.org/10.2106/JBJS.20.01071

Cruz-Jentoft, A., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., & Sayer, A. A. (2019). Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*, *48*(1), 16-31.

Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A. A., Schneider, S. M., Sieber, C. C., Topinkova, E., Vandewoude,

M., Visser, M., & Zamboni, M. (2019). Sarcopenia: revised European consensus on definition and diagnosis. *Age and ageing*, *48*(1), 16-31. https://doi.org/10.1093/ageing/afy169

Daly, R. M., Rosengren, B. E., Alwis, G., Ahlborg, H. G., Sernbo, I., & Karlsson, M. K. (2013). Gender specific age-related changes in bone density, muscle strength and functional performance in the elderly: a-10 year prospective population-based study. *BioMed Central geriatrics*, *13*(1), 71. https://doi.org/10.1186/1471-2318-13-71

Dancey, C. P., & Reidy, J. (2007). *Statistics without maths for psychology*. Pearson education.

De Martinis, M., Sirufo, M. M., Polsinelli, M., Placidi, G., Di Silvestre, D., & Ginaldi, L. (2021). Gender Differences in Osteoporosis: A Single-Center Observational Study. *The world journal of men's health*, *39*(4), 750-759. https://doi.org/10.5534/wjmh.200099

Değer, T. B., Saraç, Z. F., Savaş, E. S., & Akçiçek, S. F. (2019). The Relationship of Balance Disorders with Falling, the Effect of Health Problems, and Social Life on Postural Balance in the Elderly Living in a District in Turkey. *Geriatrics (Basel, Switzerland)*, *4*(2), 37. https://doi.org/10.3390/geriatrics4020037

Delbaere, K., Close, J. C. T., Mikolaizak, A. S., Sachdev, P. S., Brodaty, H., & Lord, S. R. (2010). The Falls Efficacy Scale International (FES-I). A comprehensive longitudinal validation study. *Age and ageing*, *39*(2), 210-216. https://doi.org/10.1093/ageing/afp225

Dhalwani, N. N., Fahami, R., Sathanapally, H., Seidu, S., Davies, M. J., & Khunti, K. (2017). Association between polypharmacy and falls in older adults: a longitudinal study from England. *BMJ Open*, *7*(10), e016358. https://doi.org/10.1136/bmjopen-2017-016358

Dhameliya, J. D., Chandra, U. K., Vishwakarma, S. K., Ganganpalli, D., & Verma, A. (2020). Investigating the Association Between Serum Vitamin D Deficiency and Idiopathic Benign Paroxysmal Positional Vertigo. *International Clinical Neuroscience Journal*, *7*(3), 122-126. https://doi.org/10.34172/icnj.2020.12

Di Paola, M., Gatti, D., Viapiana, O., Cianferotti, L., Cavalli, L., Caffarelli, C., Conversano, F., Quarta, E., Pisani, P., Girasole, G., Giusti, A., Manfredini, M., Arioli, G., Matucci-Cerinic, M., Bianchi, G., Nuti, R., Gonnelli, S., Brandi, M. L., Muratore, M., & Rossini, M. (2019). Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *30*(2), 391-402. https://doi.org/10.1007/s00198-018-4686-3

Ding, J., Liu, L., Kong, W.-K., Chen, X.-B., & Liu, X. (2019). Serum levels of 25-hydroxy vitamin D correlate with idiopathic benign paroxysmal positional vertigo. *Bioscience Reports*, *39*(4). https://doi.org/10.1042/bsr20190142

Duan, Y., Beck, T. J., Wang, X. F., & Seeman, E. (2003). Structural and biomechanical basis of sexual dimorphism in femoral neck fragility has its origins in growth and aging. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, *18*(10), 1766-1774. https://doi.org/10.1359/jbmr.2003.18.10.1766

Dyer, S. M., Crotty, M., Fairhall, N., Magaziner, J., Beaupre, L. A., Cameron, I. D., Sherrington, C., & Fragility Fracture Network Rehabilitation Research Special Interest, G. (2016). A critical review of the long-term disability outcomes following hip fracture. *BioMed Central geriatrics*, *16*(1), 158-158. https://doi.org/10.1186/s12877-016-0332-0

Edwards, M. H., Gregson, C. L., Patel, H. P., Jameson, K. A., Harvey, N. C., Sayer, A. A., Dennison, E. M., & Cooper, C. (2013). Muscle size, strength, and physical performance and their associations with bone structure in the Hertfordshire Cohort Study. *Journal of bone and mineral research*, *28*(11), 2295-2304. https://doi.org/10.1002/jbmr.1972

Eller-Vainicher, C., Falchetti, A., Gennari, L., Cairoli, E., Bertoldo, F., Vescini, F., Scillitani, A., & Chiodini, I. (2019). DIAGNOSIS OF ENDOCRINE DISEASE: Evaluation of bone fragility

in endocrine disorders. *European Journal of Endocrinology*, *180*(6), R213-R232. https://doi.org/10.1530/eje-18-0991
Fetter, M. (2016). Chapter 15 - Acute unilateral loss of vestibular function. In J. M. Furman & T. Lempert (Eds.), *Handbook of Clinical Neurology* (Vol. 137, pp. 219-229). Elsevier. https://doi.org/https://doi.org/10.1016/B978-0-444-63437-5.00015-7
Florencio-Silva, R., Sasso, G. R. d. S., Sasso-Cerri, E., Simões, M. J., & Cerri, P. S. (2015). Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. *BioMed research international*, *2015*, 421746-421746. https://doi.org/10.1155/2015/421746
Gadelha, A. B., Vainshelboim, B., Ferreira, A. P., Neri, S. G. R., Bottaro, M., & Lima, R. M. (2018). Stages of sarcopenia and the incidence of falls in older women: A prospective study. *Archives of Gerontology and Geriatrics*, *79*, 151-157. https://doi.org/https://doi.org/10.1016/j.archger.2018.07.014
Ganança, F. F., Gazzola, J. M., Ganança, C. F., Caovilla, H. H., Ganança, M. M., & Cruz, O. L. (2010). Elderly falls associated with benign paroxysmal positional vertigo. *Braz J Otorhinolaryngol*, *76*(1), 113-120. https://doi.org/10.1590/s1808-86942010000100019
Goldschagg, N., Teupser, D., Feil, K., & Strupp, M. (2021). No evidence for a specific vitamin D deficit in benign paroxysmal positional vertigo. *European Journal of Neurology*, *28*(9), 3182-3186. https://doi.org/https://doi.org/10.1111/ene.14980
Hallen, J. F., Stewart; Close, Jacqueline & Harris, Ian. (2021). *ANZHFR Annual Report of Hip Fracture Care 2021*. A. a. N. Z. H. F. Registry.
Han, B. I., Song, H. S., & Kim, J. S. (2011). Vestibular rehabilitation therapy: Review of indications, mechanisms, and key exercises. *Journal of clinical neurology (Seoul, Korea)*, *7*(4), 184-196. https://doi.org/10.3988/jcn.2011.7.4.184
Hanley, K., & T, O. D. (2002). Symptoms of vertigo in general practice: a prospective study of diagnosis. *Br J Gen Pract*, *52*(483), 809-812.
Hannan, M. T., Felson, D. T., Dawson-Hughes, B., Tucker, K. L., Cupples, L. A., Wilson, P. W., & Kiel, D. P. (2000). Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *Journal of bone and mineral research*, *15*(4), 710-720.
Hansson, E. E., Månsson, N.-O., & Håkansson, A. (2005). Balance performance and self-perceived handicap among dizzy patients in primary health care. *Scandinavian Journal of Primary Health Care*, *23*(4), 215-220. https://doi.org/10.1080/02813430500287299
Hawke, L. J., Barr, C. J., & McLoughlin, J. V. (2021). The frequency and impact of undiagnosed benign paroxysmal positional vertigo in outpatients with high falls risk. *Age Ageing*, *50*(6), 2025-2030. https://doi.org/10.1093/ageing/afab122
Hays, R. D., Sherbourne, C. D., & Mazel, R. (1995). *User's Manual for the Medical Outcomes Study (MOS) Core Measures of Health-Related Quality of Life*. RAND Corporation. https://www.rand.org/pubs/monograph_reports/MR162.html
Health & Welfare. (2018). *Hip Fracture Incidence and Hospitalisations in Australia 2015-16*. Canberra.
Health & Welfare. (2020). *Osteoporosis*. https://www.aihw.gov.au/reports/chronic-musculoskeletal-conditions/osteoporosis
Health & Welfare. (2021). *Falls*. https://www.aihw.gov.au/reports/injury/falls
Health & Welfare. (2022). *Falls in older Australians 2019–20: hospitalisations and deaths among people aged 65 and over*. https://www.aihw.gov.au/reports/injury/falls-in-older-australians-2019-20-hospitalisation
Herdman, S., Clendaniel, R. A., & ProQuest, E. (2014). *Vestibular rehabilitation* (4th ed.). F. A. Davis Company. https://go.exlibris.link/Gs8SD1bH
Herman, T., Inbar-Borovsky, N., Brozgol, M., Giladi, N., & Hausdorff, J. M. (2009). The Dynamic Gait Index in healthy older adults: The role of stair climbing, fear of falling and gender. *Gait & Posture*, *29*(2), 237-241. https://doi.org/https://doi.org/10.1016/j.gaitpost.2008.08.013

Hülse, R., Biesdorf, A., Hörmann, K., Stuck, B., Erhart, M., Hülse, M., & Wenzel, A. (2019). Peripheral Vestibular Disorders: An Epidemiologic Survey in 70 Million Individuals. *Otology & neurotology*, *40*(1), 88-95. https://doi.org/10.1097/MAO.0000000000002013

Jacobson, G. P., & Newman, C. W. (1990). The Development of the Dizziness Handicap Inventory. *Archives of Otolaryngology–Head & Neck Surgery*, *116*(4), 424-427. https://doi.org/10.1001/archotol.1990.01870040046011

Jang, Y. S., & Kang, M.-K. (2009). Relationship between bone mineral density and clinical features in women with idiopathic benign paroxysmal positional vertigo. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology*, *30*(1), 95-100. https://doi.org/10.1097/MAO.0b013e31818f5777

Jeong, J., Jung, J., Lee, J. M., Suh, M. J., Kwak, S. H., & Kim, S. H. (2017). Effects of Saccular Function on Recovery of Subjective Dizziness After Vestibular Rehabilitation. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology*, *38*(7), 1017-1023. https://doi.org/10.1097/MAO.0000000000001467

Jeong, S.-H., Kim, J.-S., Shin, J. W., Kim, S., Lee, H., Lee, A. Y., Kim, J.-M., Jo, H., Song, J., & Ghim, Y. (2013). Decreased serum vitamin D in idiopathic benign paroxysmal positional vertigo. *Journal of Neurology*, *260*(3), 832-838. https://doi.org/10.1007/s00415-012-6712-2

Jeong, S.-M., Shin, D. W., Han, K., Jung, J. H., Chun, S., Jung, H.-W., & Son, K. Y. (2019). Timed up-and-go test is a useful predictor of fracture incidence. *Bone (New York, N.Y.)*, *127*, 474-481. https://doi.org/10.1016/j.bone.2019.07.018

Jeong, S. H., Choi, S. H., Kim, J. Y., Koo, J. W., Kim, H. J., & Kim, J. S. (2009). Osteopenia and osteoporosis in idiopathic benign positional vertigo. *Neurology*, *72*(12), 1069-1076. https://doi.org/10.1212/01.wnl.0000345016.33983.e0

Jeong, S. H., Kim, H. J., & Kim, J. S. (2013). Vestibular neuritis. *Seminars in Neurology*, *33*(3), 185-194. https://doi.org/10.1055/s-0033-1354598

Jeong, S. H., Kim, J. S., Kim, H. J., Choi, J. Y., Koo, J. W., Choi, K. D., Park, J. Y., Lee, S. H., Choi, S. Y., Oh, S. Y., Yang, T. H., Park, J. H., Jung, I., Ahn, S., & Kim, S. (2020). Prevention of benign paroxysmal positional vertigo with vitamin D supplementation: A randomized trial. *Neurology*, *95*(9), e1117-e1125. https://doi.org/10.1212/wnl.0000000000010343

Jeong, S. H., Kim, J. S., Shin, J. W., Kim, S., Lee, H., Lee, A. Y., Kim, J. M., Jo, H., Song, J., & Ghim, Y. (2013). Decreased serum vitamin D in idiopathic benign paroxysmal positional vertigo. *J Neurol*, *260*(3), 832-838. https://doi.org/10.1007/s00415-012-6712-2

Ji, L., & Zhai, S. (2018). Aging and the peripheral vestibular system. *Journal of otology (Beijing)*, *13*(4), 138-140. https://doi.org/10.1016/j.joto.2018.11.006

Kanis, J. A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. *Osteoporosis international*, *4*(6), 368-381.

Kanis, J. A., McCloskey, E. V., Johansson, H., Oden, A., Melton, L. J., & Khaltaev, N. (2008). A reference standard for the description of osteoporosis. *Bone*, *42*(3), 467-475. https://doi.org/10.1016/j.bone.2007.11.001

Karataş, A., Acar Yüceant, G., Yüce, T., Hacı, C., Taylan Cebi, I., & Salviz, M. (2017). Association of benign paroxysmal positional vertigo with osteoporosis and vitamin D deficiency: A case controlled study. *The journal of international advanced otology*, *13*(2), 259-265. https://doi.org/10.5152/iao.2016.2640

Kenkre, J. S., & Bassett, J. (2018). The bone remodelling cycle. *Annals of Clinical Biochemistry*, *55*(3), 308-327. https://doi.org/10.1177/0004563218759371

Kim, A. Y., Lee, J. K., Kim, S. H., Choi, J., Song, J. J., & Chae, S. W. (2020). Is postural dysfunction related to sarcopenia? A population-based study. *PloS one*, *15*(5), e0232135-e0232135. https://doi.org/10.1371/journal.pone.0232135

Kim, H.-J., Lee, J.-O., Choi, J.-Y., & Kim, J.-S. (2020). Etiologic distribution of dizziness and vertigo in a referral-based dizziness clinic in South Korea. *Journal of Neurology*, *267*(8), 2252-2259. https://doi.org/10.1007/s00415-020-09831-2

Kim, S. Y., Cho, Y.-S., Kim, J.-S., & Koo, J.-W. (2020). Association between Bone Metabolism and Vestibular Problems in the Modified Romberg Test: Data from the 2009-2010 Korean National Health and Nutrition Examination Survey. *Journal of clinical medicine*, *9*(8), 2415. https://doi.org/10.3390/jcm9082415

Kistler-Fischbacher, M., Weeks, B. K., & Beck, B. R. (2021). The effect of exercise intensity on bone in postmenopausal women (part 1): A systematic review. *Bone*, *143*, 115696. https://doi.org/https://doi.org/10.1016/j.bone.2020.115696

Langerhuizen, D. W. G., Verweij, L. P. E., van der Wouden, J. C., Kerkhoffs, G., & Janssen, S. J. (2022). Antihypertensive drugs demonstrate varying levels of hip fracture risk: A systematic review and meta-analysis. *Injury*, *53*(3), 1098-1107. https://doi.org/10.1016/j.injury.2021.09.036

Lary, C. W., Hinton, A. C., Nevola, K. T., Shireman, T. I., Motyl, K. J., Houseknecht, K. L., Lucas, F. L., Hallen, S., Zullo, A. R., Berry, S. D., & Kiel, D. P. (2020). Association of Beta Blocker Use With Bone Mineral Density in the Framingham Osteoporosis Study: A Cross-Sectional Study. *JBMR Plus*, *4*(9), e10388. https://doi.org/10.1002/jbm4.10388

Liao, W.-L., Chang, T.-P., Chen, H.-J., & Kao, C.-H. (2015). Benign Paroxysmal Positional Vertigo Is Associated With an Increased Risk of Fracture: A Population-Based Cohort Study. *Journal of Orthopaedic & Sports Physical Therapy*, *45*(5), 406-412. https://doi.org/10.2519/jospt.2015.5707

Lindell, E., Karlsson, T., Kollén, L., Johansson, M., Finizia, C., Institutionen för kliniska, v., Göteborgs, u., Gothenburg, U., Sahlgrenska, A., Institutionen för kliniska vetenskaper, A. f. ö.-n.-o. h., Sahlgrenska, a., Institute of Clinical, S., & Institute of Clinical Sciences, D. o. O. (2021). Benign paroxysmal positional vertigo and vestibular impairment among older adults with dizziness. *Laryngoscope investigative otolaryngology*, *6*(3), 488-495. https://doi.org/10.1002/lio2.566

Liu, D.-H., Kuo, C.-H., Wang, C.-T., Chiu, C.-C., Chen, T.-J., Hwang, D.-K., & Kao, C.-L. (2017). Age-Related Increases in Benign Paroxysmal Positional Vertigo Are Reversed in Women Taking Estrogen Replacement Therapy: A Population-Based Study in Taiwan. *Frontiers in aging neuroscience*, *9*, 404-404. https://doi.org/10.3389/fnagi.2017.00404

Marchetti, G. F. P. P. T., Whitney, S. L. P. P. T. N. C. S. A. T. C., Redfern, M. S. P., & Furman, J. M. M. D. P. (2011). Factors Associated With Balance Confidence in Older Adults With Health Conditions Affecting the Balance and Vestibular System. *Archives of physical medicine and rehabilitation*, *92*(11), 1884-1891. https://doi.org/10.1016/j.apmr.2011.06.015

McGeoch, P. D. (2019). Can Vestibular Stimulation be Used to Treat Obesity?: Vestibular stimulation targeting the otoliths could rebalance energy homeostasis to trigger a leaner body habitus and thus treat metabolic syndrome. *BioEssays*, *41*(2), e1800197-e1800197. https://doi.org/10.1002/bies.201800197

Meyer, F., König, H.-H., & Hajek, A. (2019). Osteoporosis, Fear of Falling, and Restrictions in Daily Living. Evidence From a Nationally Representative Sample of Community-Dwelling Older Adults [Original Research]. *Frontiers in Endocrinology*, *10*. https://doi.org/10.3389/fendo.2019.00646

Montero-Odasso, M. M. (2016). Falls as a Geriatric Syndrome: Mechanisms and Risk Identification. In G. Duque & D. P. Kiel (Eds.), *Osteoporosis in Older Persons: Advances in*

Pathophysiology and Therapeutic Approaches (pp. 171-186). Springer International Publishing. https://doi.org/10.1007/978-3-319-25976-5_10

Morimoto, H., Asai, Y., Johnson, E. G., Koide, Y., Niki, J., Sakai, S., Nakayama, M., Kabaya, K., Fukui, A., Mizutani, Y., Mizutani, T., Ueki, Y., Mizutani, J., Ueki, T., & Wada, I. (2019). Objective measures of physical activity in patients with chronic unilateral vestibular hypofunction, and its relationship to handicap, anxiety and postural stability. *Auris, nasus, larynx*, *46*(1), 70-77. https://doi.org/10.1016/j.anl.2018.06.010

Osterhoff, G., Morgan, E. F., Shefelbine, S. J., Karim, L., McNamara, L. M., & Augat, P. (2016). Bone mechanical properties and changes with osteoporosis. *Injury*, *47 Suppl 2*(Suppl 2), S11-S20. https://doi.org/10.1016/S0020-1383(16)47003-8

Panula, J., Pihlajamäki, H., Mattila, V. M., Jaatinen, P., Vahlberg, T., Aarnio, P., & Kivelä, S.-L. (2011). Mortality and cause of death in hip fracture patients aged 65 or older: a population-based study. *BMC Musculoskeletal Disorders*, *12*, 105-105. https://doi.org/10.1186/1471-2474-12-105

Park, J. H., Cho, H., Shin, J.-H., Kim, T., Park, S.-B., Choi, B.-Y., & Kim, M. J. (2014). Relationship Among Fear of Falling, Physical Performance, and Physical Characteristics of the Rural Elderly. *American journal of physical medicine & rehabilitation*, *93*(5), 379-386. https://doi.org/10.1097/PHM.0000000000000009

Park, R. J., & Kim, Y. H. (2016). Association Between Osteoporosis/Osteopenia and Vestibular Dysfunction in South Korean Adults. *Ear and hearing*, *37*(5), 615-619. https://doi.org/10.1097/AUD.0000000000000320

Parker, I. G., Hartel, G., Paratz, J., Choy, N. L., & Rahmann, A. (2019). A Systematic Review of the Reported Proportions of Diagnoses for Dizziness and Vertigo. *Otology & neurotology*, *40*(1), 6-15. https://doi.org/10.1097/MAO.0000000000002044

Patel, H. P., Dawson, A., Westbury, L. D., Hasnaoui, G., Syddall, H. E., Shaw, S., Sayer, A. A., Cooper, C., & Dennison, E. M. (2018). Muscle Mass, Muscle Morphology and Bone Health Among Community-Dwelling Older Men: Findings from the Hertfordshire Sarcopenia Study (HSS). *Calcified tissue international*, *103*(1), 35-43. https://doi.org/10.1007/s00223-018-0388-2

Petri, M., Chirilă, M., Bolboacă, S. D., & Cosgarea, M. (2017). Health-related quality of life and disability in patients with acute unilateral peripheral vestibular disorders. *Brazilian journal of otorhinolaryngology*, *83*(6), 611-618. https://doi.org/10.1016/j.bjorl.2016.08.004

Pouresmaeili, F., Kamalidehghan, B., Kamarehei, M., & Goh, Y. M. (2018). A comprehensive overview on osteoporosis and its risk factors. *Therapeutics and clinical risk management*, *14*, 2029-2049. https://doi.org/10.2147/TCRM.S138000

RACGP. (2010). *Clinical Guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men*. The Royal Australian College of General Practitioners.https://www.racgp.org.au/download/documents/Guidelines/Musculoskeletal/racgp_osteo_guideline.pdf

Ralston, S. H., & Uitterlinden, A. G. (2010). Genetics of Osteoporosis. *Endocrine Reviews*, *31*(5), 629-662. https://doi.org/10.1210/er.2009-0044

Rasman, B. G., Forbes, P. A., Tisserand, R., & Blouin, J.-S. (2018). Sensorimotor Manipulations of the Balance Control Loop–Beyond Imposed External Perturbations [Review]. *Frontiers in neurology*, *9*. https://doi.org/10.3389/fneur.2018.00899

Santos, L., Elliott-Sale, K. J., & Sale, C. (2017). Exercise and bone health across the lifespan. *Biogerontology*, *18*(6), 931-946. https://doi.org/10.1007/s10522-017-9732-6

Santy-Tomlinson, J., Speerin, R., Hertz, K., Tochon-Laruaz, A. C., & Oostwaard, M. v. (2018). Falls and secondary fracture prevention. *Fragility Fracture Nursing*, 27-40.

Seeman, E. (2013). Age- and Menopause-Related Bone Loss Compromise Cortical and Trabecular Microstructure. *The Journals of Gerontology: Series A*, *68*(10), 1218-1225. https://doi.org/10.1093/gerona/glt071

Sepúlveda-Loyola, W., Phu, S., Bani Hassan, E., Brennan-Olsen, S. L., Zanker, J., Vogrin, S., Conzade, R., Kirk, B., Al Saedi, A., Probst, V., & Duque, G. (2020). The Joint Occurrence of Osteoporosis and Sarcopenia (Osteosarcopenia): Definitions and Characteristics. *Journal of the American Medical Directors Association*, *21*(2), 220-225. https://doi.org/https://doi.org/10.1016/j.jamda.2019.09.005

Shanbhogue, V. V., Brixen, K., & Hansen, S. (2016). Age-and sex-related changes in bone microarchitecture and estimated strength: a three-year prospective study using HRpQCT. *Journal of bone and mineral research*, *31*(8), 1541-1549.

Sheu, Y., Zmuda, J. M., Boudreau, R. M., Petit, M. A., Ensrud, K. E., Bauer, D. C., Gordon, C. L., Orwoll, E. S., Cauley, J. A., & Osteoporotic Fractures in Men Mr, O. S. R. G. (2011). Bone strength measured by peripheral quantitative computed tomography and the risk of nonvertebral fractures: the osteoporotic fractures in men (MrOS) study. *Journal of bone and mineral research, 26*(1), 63-71. https://doi.org/10.1002/jbmr.172

Shiozaki, T., Ito, T., Wada, Y., Yamanaka, T., & Kitahara, T. (2021). Effects of Vestibular Rehabilitation on Physical Activity and Subjective Dizziness in Patients With Chronic Peripheral Vestibular Disorders: A Six-Month Randomized Trial. *Frontiers in neurology*, *12*, 656157-656157. https://doi.org/10.3389/fneur.2021.656157

Shumway-Cook, A., Brauer, S., & Woollacott, M. (2000). Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther*, *80*(9), 896-903.

Shupak, A., & Faranesh, N. (2020). Bone Mineral Density in Patients Suffering from Ménière's Disease. *Audiology and Neurotology*, *25*(3), 158-163. https://doi.org/10.1159/000506039

Sim, M., Prince, R. L., Scott, D., Daly, R. M., Duque, G., Inderjeeth, C. A., Zhu, K., Woodman, R. J., Hodgson, J. M., & Lewis, J. R. (2019). Sarcopenia Definitions and Their Associations With Mortality in Older Australian Women. *Journal of the American Medical Directors Association*, *20*(1), 76-82.e72. https://doi.org/https://doi.org/10.1016/j.jamda.2018.10.016

Sobestiansky, S., Michaelsson, K., & Cederholm, T. (2019). Sarcopenia prevalence and associations with mortality and hospitalisation by various sarcopenia definitions in 85-89 year old community-dwelling men: A report from the ULSAM study. *BioMed Central geriatrics*, *19*(1), 318-318. https://doi.org/10.1186/s12877-019-1338-1

Song, H. S., & Lee, H. J. (2020). Fear of falling and associated factors among patients with peripheral vestibular hypofunction. *Journal of exercise rehabilitation*, *16*(2), 162-167. https://doi.org/10.12965/jer.2040094.047

Squair, J. W., Gautier, M., Mahe, L., Soriano, J. E., Rowald, A., Bichat, A., Cho, N., Anderson, M. A., James, N. D., Gandar, J., Incognito, A. V., Schiavone, G., Sarafis, Z. K., Laskaratos, A., Bartholdi, K., Demesmaeker, R., Komi, S., Moerman, C., Vaseghi, B., Scott, B., Rosentreter, R., Kathe, C., Ravier, J., McCracken, L., Kang, X., Vachicouras, N., Fallegger, F., Jelescu, I., Cheng, Y., Li, Q., Buschman, R., Buse, N., Denison, T., Dukelow, S., Charbonneau, R., Rigby, I., Boyd, S. K., Millar, P. J., Moraud, E. M., Capogrosso, M., Wagner, F. B., Barraud, Q., Bezard, E., Lacour, S. P., Bloch, J., Courtine, G., & Phillips, A. A. (2021). Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury. *Nature (London)*, *590*(7845), 308-314. https://doi.org/10.1038/s41586-020-03180-w

Swenson, R. S. (2017). Chapter 8 - The Vestibular System. In P. M. Conn (Ed.), *Conn's Translational Neuroscience* (pp. 167-183). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-802381-5.00014-2

Talaat, H. S., Abuhadied, G., Talaat, A. S., & Abdelaal, M. S. (2015). Low bone mineral density and vitamin D deficiency in patients with benign positional paroxysmal vertigo. *Eur Arch Otorhinolaryngol*, *272*(9), 2249-2253. https://doi.org/10.1007/s00405-014-3175-3

Tatangelo, G., Watts, J., Lim, K., Connaughton, C., Abimanyi-Ochom, J., Borgström, F., Nicholson, G. C., Shore-Lorenti, C., Stuart, A. L., Iuliano-Burns, S., Seeman, E., Prince, R., March, L., Cross, M., Winzenberg, T., Laslett, L. L., Duque, G., Ebeling, P. R., & Sanders, K. M. (2019). The Cost of Osteoporosis, Osteopenia, and Associated Fractures in Australia in 2017. *Journal of bone and mineral research*, *34*(4), 616-625. https://doi.org/10.1002/jbmr.3640

Valensi, P. (2021). Autonomic nervous system activity changes in patients with hypertension and overweight: role and therapeutic implications. *Cardiovascular Diabetology*, *20*(1), 170. https://doi.org/10.1186/s12933-021-01356-w

Vignaux, G., Besnard, S., Ndong, J., Philoxène, B., Denise, P., & Elefteriou, F. (2013). Bone remodeling is regulated by inner ear vestibular signals. *Journal of bone and mineral research*, *28*(10), 2136-2144. https://doi.org/10.1002/jbmr.1940

Vignaux, G., Ndong, J. D. L. C., Perrien, D. S., & Elefteriou, F. (2015). Inner Ear Vestibular Signals Regulate Bone Remodeling via the Sympathetic Nervous System. *Journal of bone and mineral research*, *30*(6), 1103-1111. https://doi.org/10.1002/jbmr.2426

von Brevern, M., Radtke, A., Lezius, F., Feldmann, M., Ziese, T., Lempert, T., & Neuhauser, H. (2007). Epidemiology of benign paroxysmal positional vertigo: a population based study. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(7), 710. https://doi.org/10.1136/jnnp.2006.100420

Walther, L. E., Wenzel, A., Buder, J., Bloching, M. B., Kniep, R., & Blödow, A. (2014). Detection of human utricular otoconia degeneration in vital specimen and implications for benign paroxysmal positional vertigo. *European archives of oto-rhino-laryngology*, *271*(12), 3133-3138. https://doi.org/10.1007/s00405-013-2784-6

Watts, J. J., Abimanyi-Ochom, J., & Sanders, K. M. (2013). Osteoporosis costing all Australian: a new burden of disease analysis-2012 to 2022.

Watts, N. B. (2004). Fundamentals and pitfalls of bone densitometry using dual-energy X-ray absorptiometry (DXA). *Osteoporosis international*, *15*(11), 847-854. https://doi.org/10.1007/s00198-004-1681-7

Weaver, C. M., Gordon, C. M., Janz, K. F., Kalkwarf, H. J., Lappe, J. M., Lewis, R., O'Karma, M., Wallace, T. C., & Zemel, B. S. (2016). The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *27*(4), 1281-1386. https://doi.org/10.1007/s00198-015-3440-3

Weeks, B. K., & Beck, B. R. (2008). The BPAQ: a bone-specific physical activity assessment instrument. *Osteoporosis international*, *19*(11), 1567-1577. https://doi.org/10.1007/s00198-008-0606-2

Weeks, B. K., & Beck, B. R. (2020). Exercise and Physical Activity Recommendations for Optimizing Musculoskeletal Health in Older Adults. In S. I. S. Rattan (Ed.), *Encyclopedia of Biomedical Gerontology* (pp. 68-77). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-801238-3.11413-8

Weidt, S., Bruehl, A. B., Straumann, D., Hegemann, S. C. A., Krautstrunk, G., & Rufer, M. (2014). Health-related quality of life and emotional distress in patients with dizziness: a cross-sectional approach to disentangle their relationship. *BioMed Central health services research*, *14*(1), 317. https://doi.org/10.1186/1472-6963-14-317

Whitney, S. L., Hudak, M. T., & Marchetti, G. F. (2000). The dynamic gait index relates to self-reported fall history in individuals with vestibular dysfunction. *Journal of vestibular research : equilibrium & orientation*, *10*(2), 99-105.

Whitney, S. L., Wrisley, D. M., Brown, K. E., & Furman, J. M. (2004). Is Perception of Handicap Related to Functional Performance in Persons with Vestibular Dysfunction? *Otology & neurotology*, *25*(2), 139-143. https://journals.lww.com/otology-neurotology/Fulltext/2004/03000/Is_Perception_of_Handicap_Related_to_Functional.10.aspx

Whitney, S. L., Wrisley, D. M., Marchetti, G. F., Gee, M. A., Redfern, M. S., & Furman, J. M. (2005). Clinical measurement of sit-to-stand performance in people with balance disorders: validity of data for the Five-Times-Sit-to-Stand Test. *Phys Ther*, *85*(10), 1034-1045.

WHO. (1994). *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group* (0512-3054 (Print)
0512-3054).

WHO. (2007). *WHO Global Report on Falls Prevention in Older Age : Prevention in Older Age*. World Health Organization. https://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=349983

Wu, Y., Fan, Z., Jin, H., Guan, Q., Zhou, M., Lu, X., Li, L., Yan, W., Gu, C., Chen, C., & Han, W. (2018). Assessment of Bone Metabolism in Male Patients With Benign Paroxysmal Positional Vertigo [Original Research]. *Frontiers in neurology*, *9*. https://doi.org/10.3389/fneur.2018.00742

Wu, Y., Gu, C., Han, W., Lu, X., Chen, C., & Fan, Z. (2018). Reduction of bone mineral density in native Chinese female idiopathic benign paroxysmal positional vertigo patients. *Am J Otolaryngol*, *39*(1), 31-33. https://doi.org/10.1016/j.amjoto.2017.09.004

Wu, Y., Hu, Z., Cai, M., Fan, Z., Han, W., Guan, Q., Zhou, M., Li, L., Yan, W., & Lu, X. (2019). Decreased 25-Hydroxyvitamin D Levels in Patients With Vestibular Neuritis. *Front Neurol*, *10*, 863. https://doi.org/10.3389/fneur.2019.00863

Yang, B., Lu, Y., Xing, D., Zhong, W., Tang, Q., Liu, J., & Yang, X. (2020). Association between serum vitamin D levels and benign paroxysmal positional vertigo: a systematic review and meta-analysis of observational studies. *European archives of oto-rhino-laryngology*, *277*(1), 169-177. https://doi.org/10.1007/s00405-019-05694-0

Yee, X. S., Ng, Y. S., Allen, J. C., Latib, A., Tay, E. L., Abu Bakar, H. M., Ho, C. Y. J., Koh, W. C. C., Kwek, H. H. T., & Tay, L. (2021). Performance on sit-to-stand tests in relation to measures of functional fitness and sarcopenia diagnosis in community-dwelling older adults. *European Review of Aging and Physical Activity*, *18*(1), 1. https://doi.org/10.1186/s11556-020-00255-5

Yip, C. W., & Strupp, M. (2018). The Dizziness Handicap Inventory does not correlate with vestibular function tests: a prospective study. *Journal of Neurology*, *265*(5), 1210-1218. https://doi.org/10.1007/s00415-018-8834-7

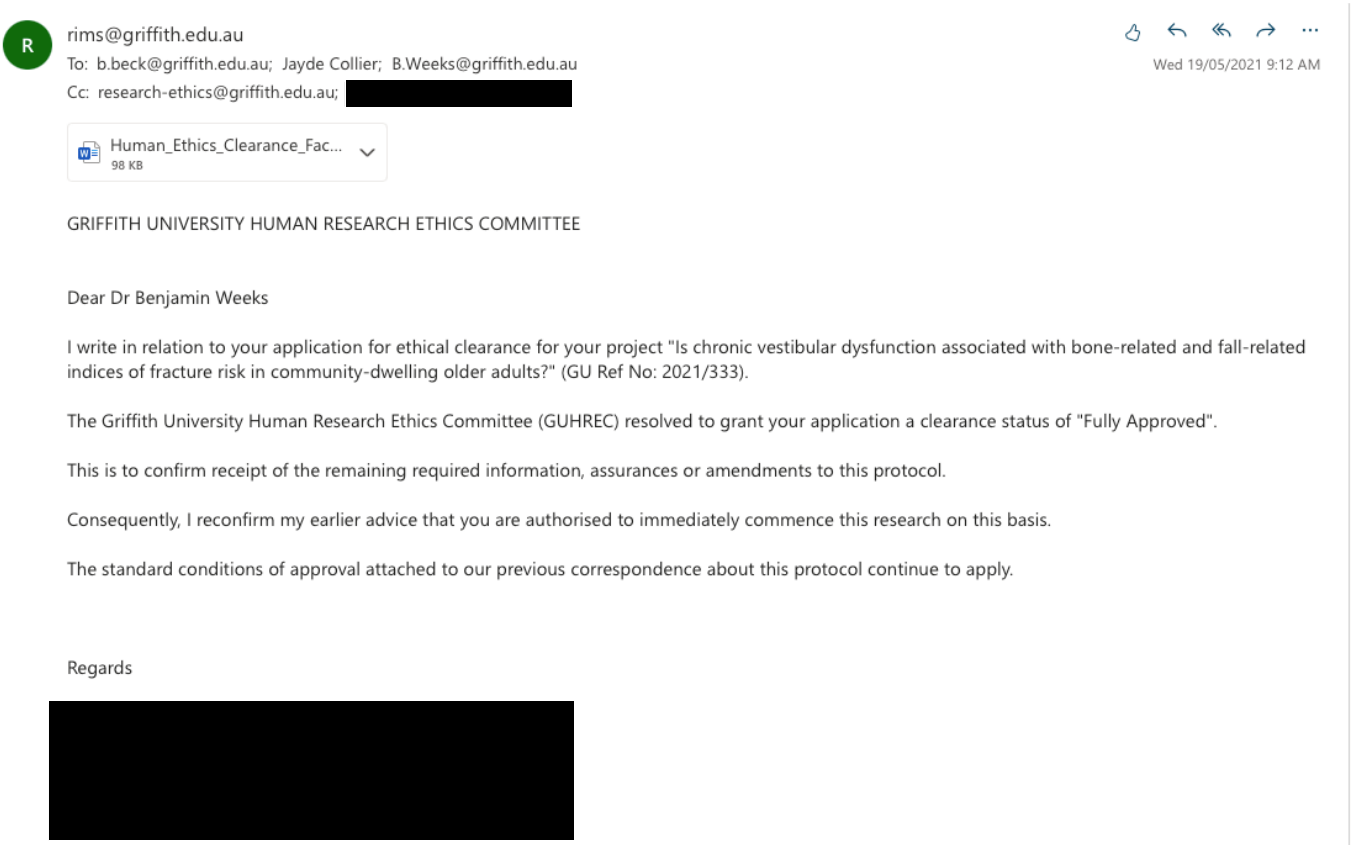
Yoon, B. H., & Kim, D. Y. (2021). Discordance between Hip and Spine Bone Mineral Density: A Point of Care. *J Bone Metab*, *28*(4), 249-251. https://doi.org/10.11005/jbm.2021.28.4.249

Zhang, S., Xing, J., Gong, Y., Li, P., Wang, B., & Xu, L. (2021). Downregulation of VDR in benign paroxysmal positional vertigo patients inhibits otolith-associated protein expression levels. *Mol Med Rep*, *24*(2), 591. https://doi.org/10.3892/mmr.2021.12230

Appendices

Appendix A: ethics, consent, and recruitment

i) Ethics approval GUHREC



R

rims@griffith.edu.au

To: b.beck@griffith.edu.au; Jayde Collier; B.Weeks@griffith.edu.au

Cc: research-ethics@griffith.edu.au; [redacted]

Wed 19/05/2021 9:12 AM

Human_Ethics_Clearance_Fac...
98 KB

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

Dear Dr Benjamin Weeks

I write in relation to your application for ethical clearance for your project "Is chronic vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?" (GU Ref No: 2021/333).

The Griffith University Human Research Ethics Committee (GUHREC) resolved to grant your application a clearance status of "Fully Approved".

This is to confirm receipt of the remaining required information, assurances or amendments to this protocol.

Consequently, I reconfirm my earlier advice that you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.

Regards

[redacted]

ii) Approval to advertise from Metro South HREC

M MSH-Ethics <MSH-Ethics@health.qld.gov.au>
To: Jayde Collier
Fri 11/06/2021 2:00 PM

Good afternoon Jayde,

I have spoken with the team here and we all agreed you do not need to submit an ethics application to put up the flyer in the Vestibular Physiotherapy clinic at LGH.

The University approval and support from the LGH staff as supplied will be sufficient; no further action is required

All the best,

[redacted]

Metro South Health | ICARE² values

Metro South Health acknowledges the traditional custodians of whose land and waters we provide health services and pays respect to Elders past, present and emerging.

iii) Approval to advertise from GCUH HREC

G GCHResearch <GCHResearch@health.qld.gov.au>
To: Jayde Collier
Wed 19/05/2021 4:15 PM

Hi Jayde,

Thank you, that is sufficient.

We are happy to authorise the use of the flyer, to be placed in the physiotherapy vestibular clinic at GCHHS, noting the head of department support from Dean Blond, Director of Physiotherapy.

If there are any amendments made to the flyer, or if you would like to advertise in any other areas within GCHHS in the future, then please notify us via email for further authorisation prior to doing so.

If you have any questions, please don't hesitate to contact our office.

Many thanks,

[redacted]

Gold Coast Health always care

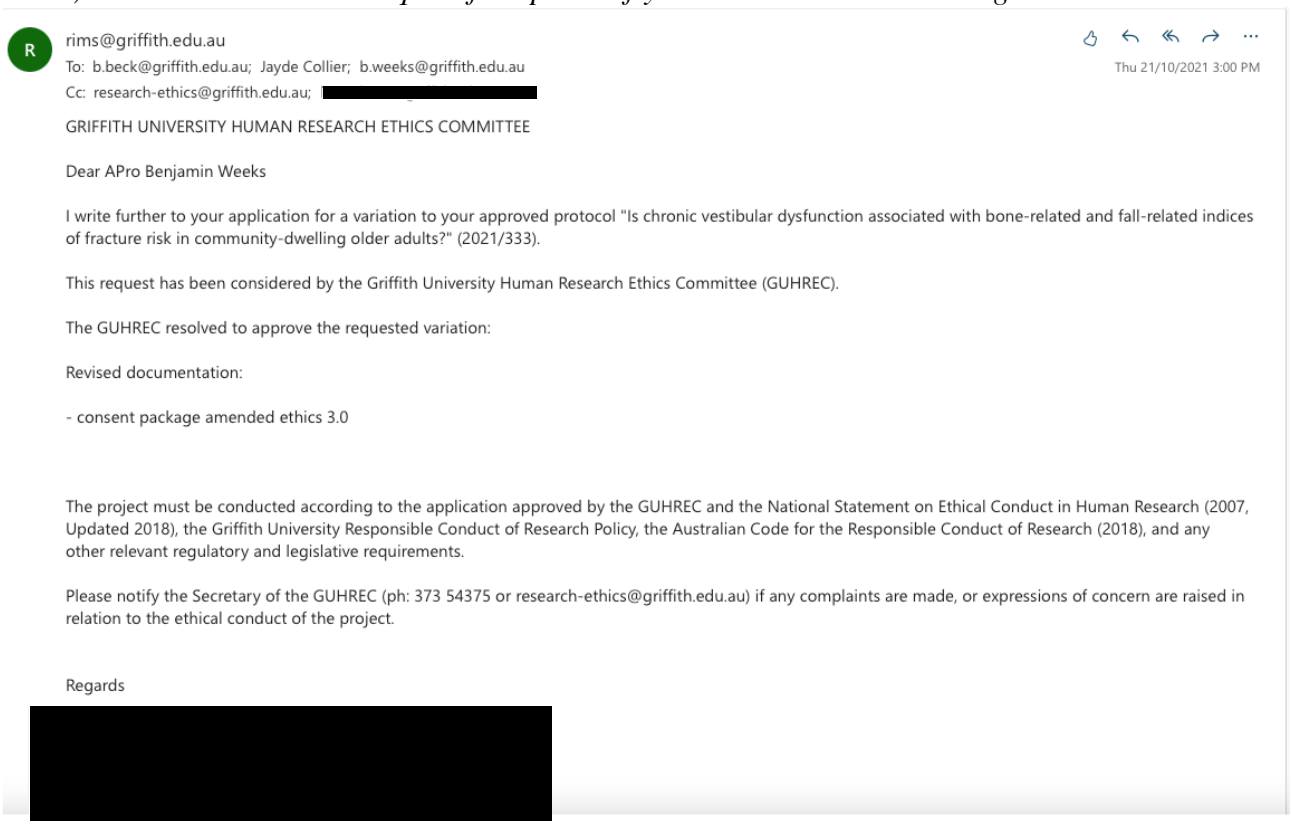
Queensland Government

Our values: Integrity | Community first | Excellence | Respect | Compassion | Empower

Jingeri. We acknowledge the Traditional Custodians of the land in which we work, live and grow, the Kombumerri, Wangerriburra, Bullongin, Minjungbal and Birinburra peoples, of the Yugambeh Language speaking nation. We also pay our respects to Elders past, present and emerging.

Research at GCHHS

iv) Ethics variation request for updated flyer and vestibular screening



R rims@griffith.edu.au

To: b.beck@griffith.edu.au; Jayde Collier; b.weeks@griffith.edu.au

Cc: research-ethics@griffith.edu.au; [redacted]

Thu 21/10/2021 3:00 PM

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

Dear APro Benjamin Weeks

I write further to your application for a variation to your approved protocol "Is chronic vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?" (2021/333).

This request has been considered by the Griffith University Human Research Ethics Committee (GUHREC).

The GUHREC resolved to approve the requested variation:

Revised documentation:

- consent package amended ethics 3.0

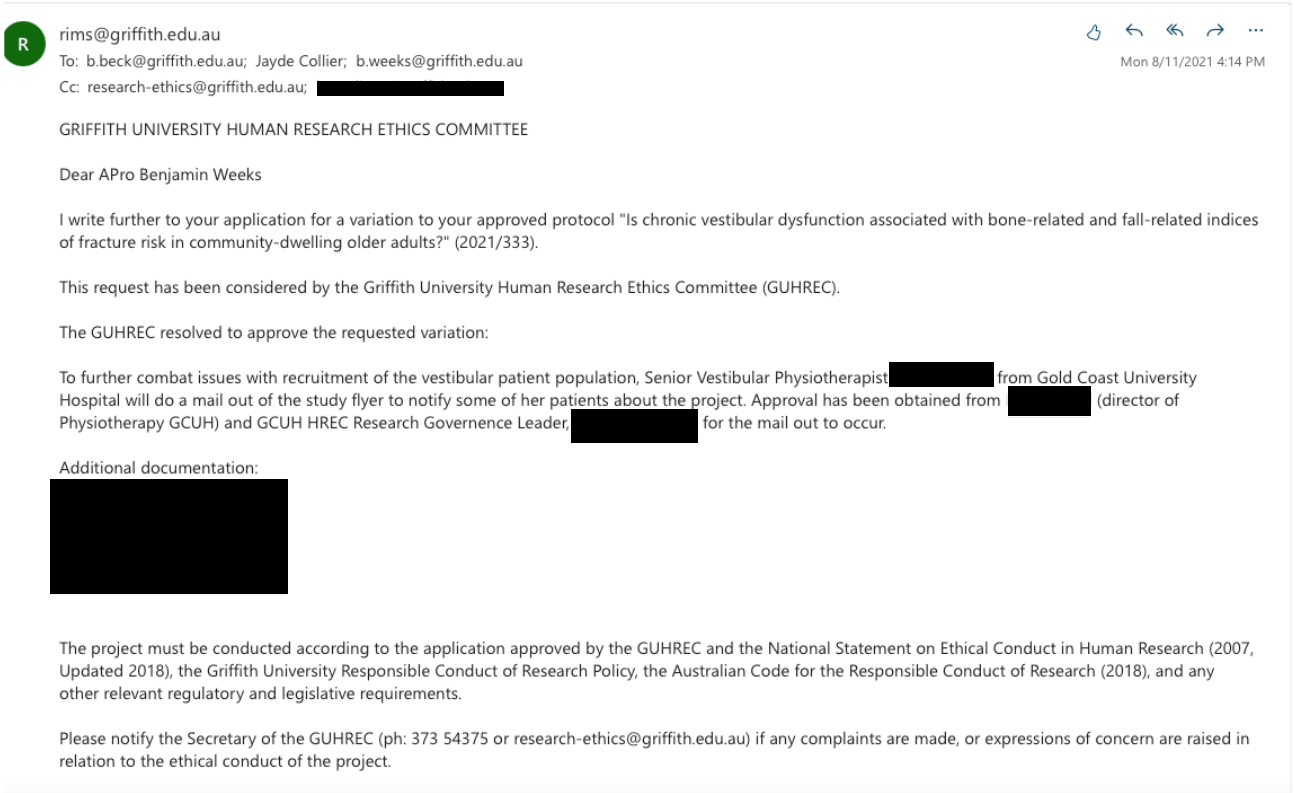
The project must be conducted according to the application approved by the GUHREC and the National Statement on Ethical Conduct in Human Research (2007, Updated 2018), the Griffith University Responsible Conduct of Research Policy, the Australian Code for the Responsible Conduct of Research (2018), and any other relevant regulatory and legislative requirements.

Please notify the Secretary of the GUHREC (ph: 373 54375 or research-ethics@griffith.edu.au) if any complaints are made, or expressions of concern are raised in relation to the ethical conduct of the project.

Regards

[redacted]

v) *Ethics variation request for Facebook page and flyer mail-out (GCUH*



R rims@griffith.edu.au

To: b.beck@griffith.edu.au; Jayde Collier; b.weeks@griffith.edu.au

Cc: research-ethics@griffith.edu.au; [redacted]

Mon 8/11/2021 4:14 PM

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

Dear APro Benjamin Weeks

I write further to your application for a variation to your approved protocol "Is chronic vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?" (2021/333).

This request has been considered by the Griffith University Human Research Ethics Committee (GUHREC).

The GUHREC resolved to approve the requested variation:

To further combat issues with recruitment of the vestibular patient population, Senior Vestibular Physiotherapist [redacted] from Gold Coast University Hospital will do a mail out of the study flyer to notify some of her patients about the project. Approval has been obtained from [redacted] (director of Physiotherapy GCUH) and GCUH HREC Research Governence Leader, [redacted] for the mail out to occur.

Additional documentation:

[redacted]

The project must be conducted according to the application approved by the GUHREC and the National Statement on Ethical Conduct in Human Research (2007, Updated 2018), the Griffith University Responsible Conduct of Research Policy, the Australian Code for the Responsible Conduct of Research (2018), and any other relevant regulatory and legislative requirements.

Please notify the Secretary of the GUHREC (ph: 373 54375 or research-ethics@griffith.edu.au) if any complaints are made, or expressions of concern are raised in relation to the ethical conduct of the project.

vi) *Original flyer*

Griffith UNIVERSITY

Want to know how strong your muscles and bones are?

Free bone density and muscle strength tests!

What is this study about?

Vestibular dysfunction (inner-ear balance system problems) is a major contributor to falls in older populations. Using measures of bone and muscle health, this study will determine whether there are differences between healthy older adults and those with inner-ear balance problems. These measures will provide information about risk of fall and fracture.

Who can participate?

- Adults **over 65 years** of age with diagnosed **vestibular dysfunction** (condition that causes dizziness)
- Healthy adults **over 65 years** of age who are not dizzy

What's involved?

Attend Griffith University, Gold Coast campus for approximately 2 hours (one-off visit) for:

- Simple tests of strength, balance and walking
- Diet and exercise surveys
- Free bone density scans

Why participate?

- You will receive free bone density scans and muscle strength tests
- You will help us better understand the bone and muscle health of people with inner-ear balance problems

If you are interested in participating or would like further information, please contact:

Miss Jayde Collier
jayde.collier@griffithuni.edu.au
[redacted]

GU Ref No: 2021/333

vii) Updated flyer and consent package

Want to know how strong your muscles and bones are?

Free bone density and muscle strength tests!

GU Ref No: 2021/333

What is this study about?

Vestibular dysfunction (problem with inner ear balance system) is a major contributor to falls in older populations. Using measures of bone and muscle health, this study will determine whether there are differences between healthy older adults and those with inner-ear balance problems, in terms of fall and fracture risk.

Who can participate?

- Adults **over 65 years** of age with diagnosed **vestibular dysfunction** (condition that causes dizziness)

OR

- Healthy adults **over 65 years** of age who are not dizzy

What's involved?

Attend Griffith University, Gold Coast campus for approximately 2 hours (one-off visit) for:

- Free bone density scans
- Simple tests of strength, balance and walking
- Diet and exercise surveys

Why participate?

- You will receive free bone density scans and muscle strength tests
- You will help us better understand the bone and muscle health of people with inner-ear balance problems

If you are interested in participating or would like further information, please contact:

Miss Jayde Collier (BExSc, MPthy)
jayde.collier@griffithuni.edu.au
[redacted]

INFORMATION SHEET

Project Title:
Is chronic vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?

Griffith University Ethics Reference Number: 2021/333

Investigators

Jayde Collier
MPhty, BExSc
Master of Medical Research Student
School of Health Sciences and Social Work
Griffith University, Gold Coast
Ph: [redacted]
Email: jayde.collier@griffithuni.edu.au

Dr Benjamin Weeks
BPhty(Hons), BExSc, GCertHigherEd, PhD
Senior Lecturer
School of Health Sciences and Social Work
Griffith University, Gold Coast
Ph: (07) 5552 9336
Email: b.weeks@griffith.edu.au

Prof Belinda Beck
BHMS(Ed), MS, PhD
Professor
School of Health Sciences and Social Work
Griffith University, Gold Coast
Ph: (07) 5552 8793
Email: b.beck@griffith.edu.au

Background
Fracture in the elderly population is a major public health challenge. It is associated with significant economic burden, morbidity and mortality. Prevention is necessary although it requires a thorough understanding of risk factors (bone-related and fall-related) and early identification of high-risk groups. Vestibular dysfunction (inner-ear balance system problems) is a major contributor to falls in older populations. Therefore, this sub-population is at increased risk of fracture. This project will explore indices of fracture risk in older populations with vestibular dysfunction. This study is being undertaken as part of a Master of Medical Research degree.

Method
Who: Healthy participants and participants with chronic vestibular dysfunction
What:

- One-off testing session of approximately 2 hours in duration
- Testing will include the following:
  - we will assess your height, weight and your ability to do some simple physical tasks such as standing from sitting, walking and balance tasks.
  - We will screen your inner-ear function through a series of basic tests that involve gentle neck movements.
  - you will be asked to complete questionnaires regarding your diet, the amount of exercise you undertake, your past medical history, your fear of falling and quality of life.
  - we will conduct a number of scans using a dual-energy x-ray absorptiometer (DXA) and peripheral quantitative computed tomography (pQCT). Those tests are painless and non-invasive but involve either sitting beside or lying still on special scanners for between 3-10 minutes per scan.

Where:

- Testing and training will take place at Griffith University's Gold Coast campus (Southport)

Inclusion Criteria
You may be eligible to participate in this study if you are at least 50 years of age and haven't experienced dizziness recently. You may also be eligible to participate if you are at least 50 years of age and have a formal diagnosis of vestibular dysfunction (inner-ear problem), or initial phone screening indicates likely vestibular disorder.

Exclusion Criteria
You may be excluded if any of the following apply to you:

- Less than five years post menopause
- Need assistance from somebody to walk
- Recent fracture, musculoskeletal condition/s (e.g. low back pain or osteoarthritis) or joint surgery preventing physical activity
- Metallic implants (e.g. staples, joint replacement) or foreign bodies (e.g. shrapnel)
- More than two x-ray examinations in the past year or radiation treatment

- Cancer
- Cognitive impairment
- Medications and/or conditions know to influence bone health (e.g. Paget's Disease)

Risks
The risks associated with the project are relatively minor. We require you to complete some physical tasks that involve light physical activity, no more than what is involved in everyday tasks. For those unaccustomed to physical activity, some muscle soreness may be experienced following any change in exercise habits. We also require you to complete some basic inner-ear function testing that will involve gentle neck movements. Neck range of movement will be assessed at baseline and positioning will be facilitated by the investigator to ensure movement is safe and comfortable. There is also a small risk of injury during the testing. Such injuries are uncommon but may include low back pain, joint sprains, or muscle strains. All physical testing sessions at Griffith will be closely supervised by the investigators to minimise those risks. Should a study-related injury occur, consultations are available at discounted concession rates at the Griffith Allied Health Clinic.

There are also slight risks associated with some of our tests. DXA and pQCT scans are non-invasive and painless, but they do involve exposure to small quantities of ionising radiation. The amount of radiation exposure during a chest x-ray is 8 times greater than that for either pQCT or DXA tests. The radiation exposure for DXA and pQCT scans is less than 0.01 mSv. For comparison, natural background radiation to which individuals living in developed countries are exposed is estimated to be around 2.4 mSv per year. The exposure to radiation during plane travel is approximately 0.005 mSv per hour, thus a 14 hour international flight from Australia to Los Angeles would expose an individual to approximately 0.07 mSv, or 28 times the radiation from a single DXA scan.

Benefits
- Each participant will receive free bone, muscle and fat scans, an estimate of daily calcium consumption in relation to the recommended amount and the results of their physical tests in relation to normative values.
- Your involvement in this study will help contribute to the understanding of risk factors for fracture in those with chronic vestibular dysfunction.

Confidentiality
The conduct of this research involves the collection, access, storage and/or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. Data will de-identified and retained in a password protected Microsoft Excel spreadsheet that is stored securely in the Griffith University Research Space. Data will be stored for a period of five years from the date of the final publication before being destroyed. A de-identified copy of this data may be used for other research purposes, including publishing openly (eg. in an open access repository). However, your anonymity will at all times be safeguarded. For further information consult the University's Privacy Plan at http://www.griffith.edu.au/about-griffith/plans-publications/griffith-university-privacy-plan or telephone (07) 3735 4375.

Contacting the Investigators
We are happy to answer any questions you may have. For general inquiries please contact Jayde Collier (Master of Medical Research student), at jayde.collier@griffithuni.edu.au or on 0466 463 533 You may also contact the other study investigators (details above).

Feedback
Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if you're interested, the overall study findings.

Voluntary Participation
Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you decide to participate, you are free to withdraw your consent and discontinue your involvement at any time.

Complaints Mechanism
Griffith University conducts research in accordance with the *National Statement on Ethical Conduct in Human Research*. If you have any concerns or complaints about the ethical conduct of the research project, please contact the Manager, Research Ethics on 3735 4375 or **research-ethics@griffith.edu.au**.

Please retain this document for your information

CONSENT FORM

Project Title:
Is chronic vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?

Griffith University Ethics Reference Number: 2021/333

Investigators

Jayde Collier
MPhty, BExSc
Master of Medical Research Student
School of Health Sciences and Social Work
Griffith University, Gold Coast
Ph: [redacted]
Email: jayde.collier@griffithuni.edu.au

Dr Benjamin Weeks
BPhty(Hons), BExSc, GCertHigherEd, PhD
Senior Lecturer
School of Health Sciences and Social Work
Griffith University, Gold Coast
Ph: (07) 5552 9336
Email: b.weeks@griffith.edu.au

Prof Belinda Beck
BHMS(Ed), MS, PhD
Professor
School of Health Sciences and Social Work
Griffith University, Gold Coast
Ph: (07) 5552 8793
Email: b.beck@griffith.edu.au

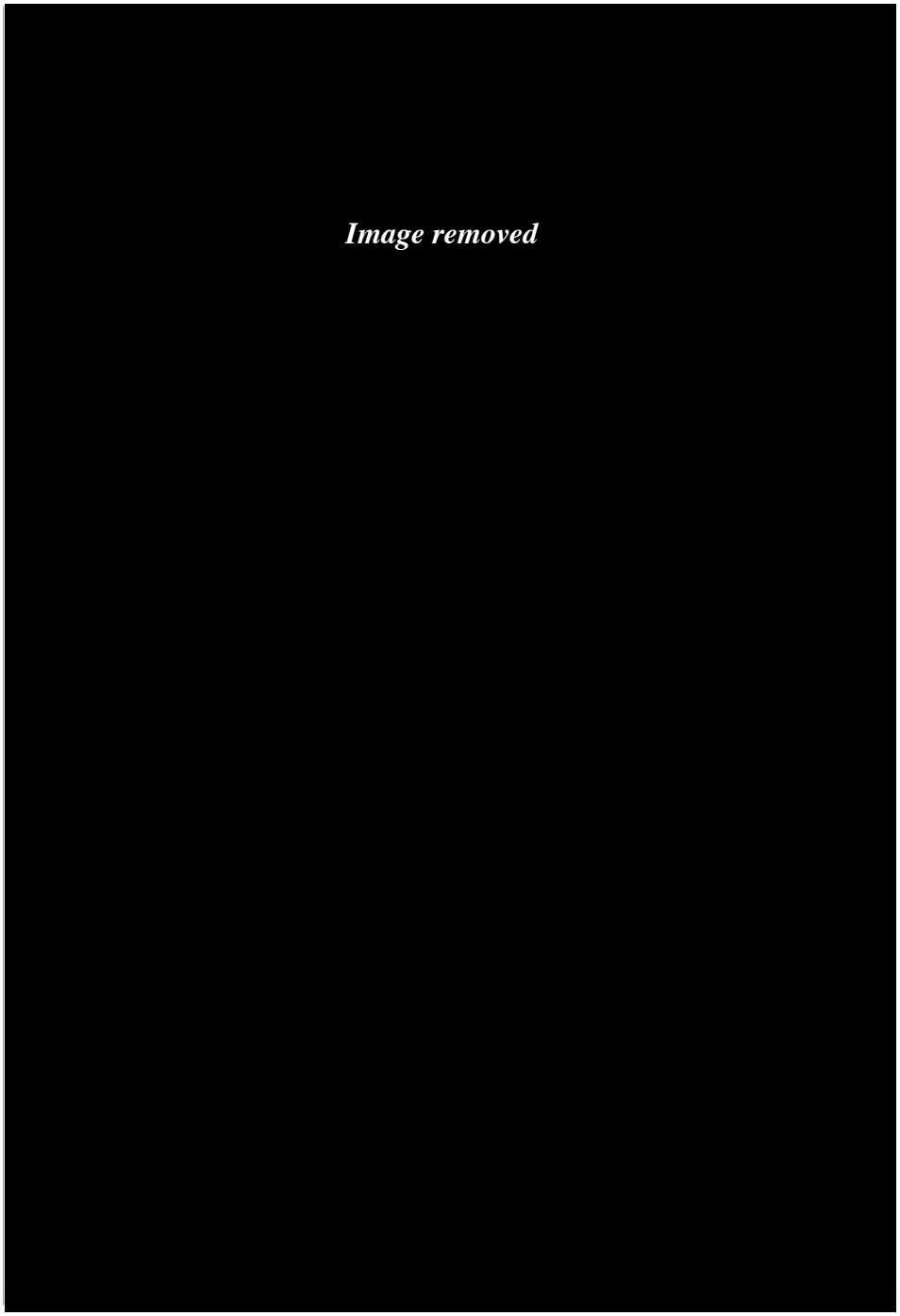
Consent Statement
By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that I will undergo dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) scans and measurements of weight and height;
- I understand that I will be asked to complete several questionnaires relating to physical activity, diet, past medical history, quality of life and fear of falling;
- I understand that I will be asked to perform a series of physical tasks such as standing from sitting, walking and balance tasks, as well as, basic inner-ear function tests (head turning, lying down);
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand the benefits of my participation in this research;
- I understand that my participation in this research is voluntary;
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without comment or penalty;
- I understand that I can contact the Manager, Research Ethics, on 373 54375 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

Participant name	Participant signature	Date

Normal

Appendix B: AusCal questionnaire



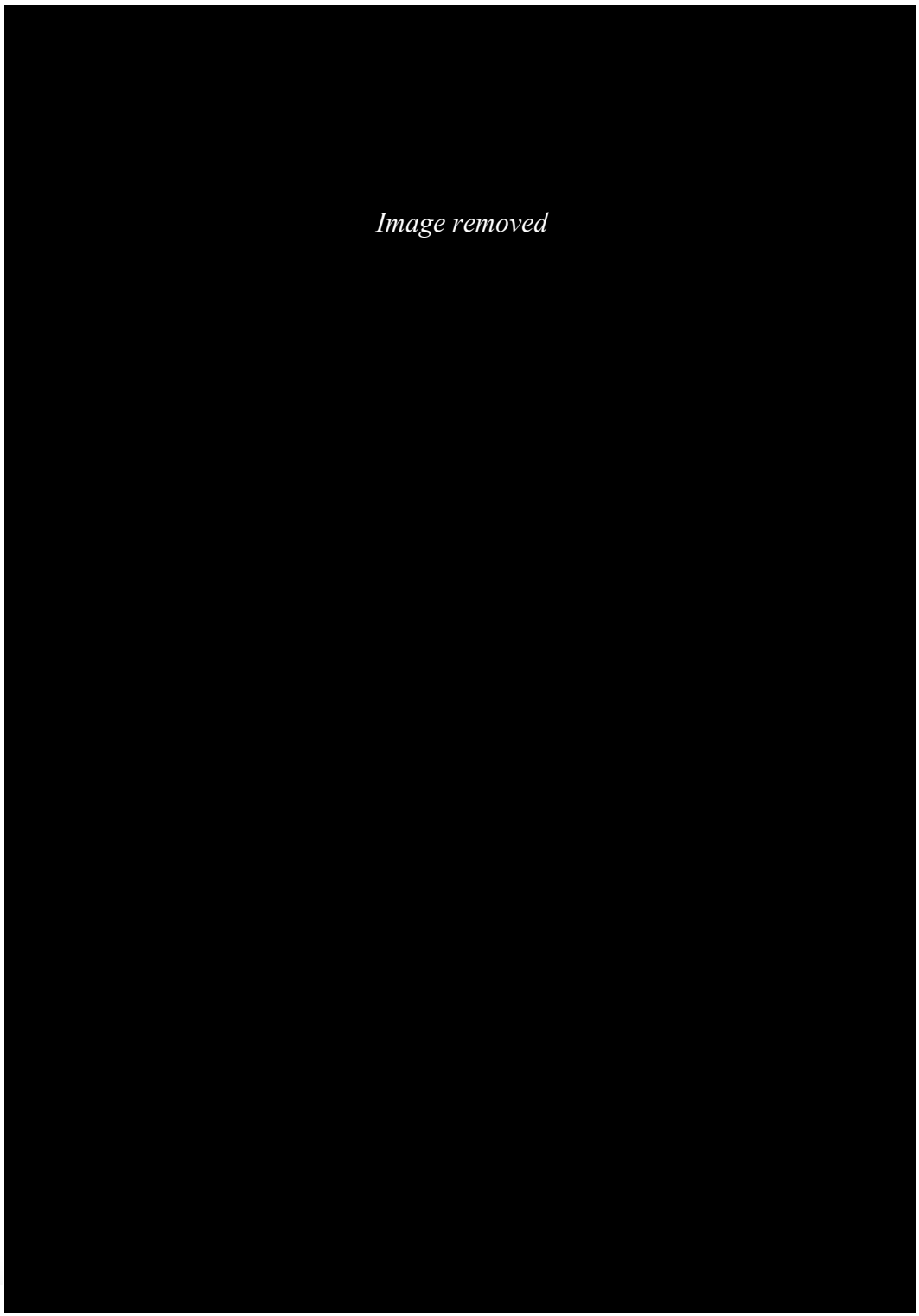


Image removed

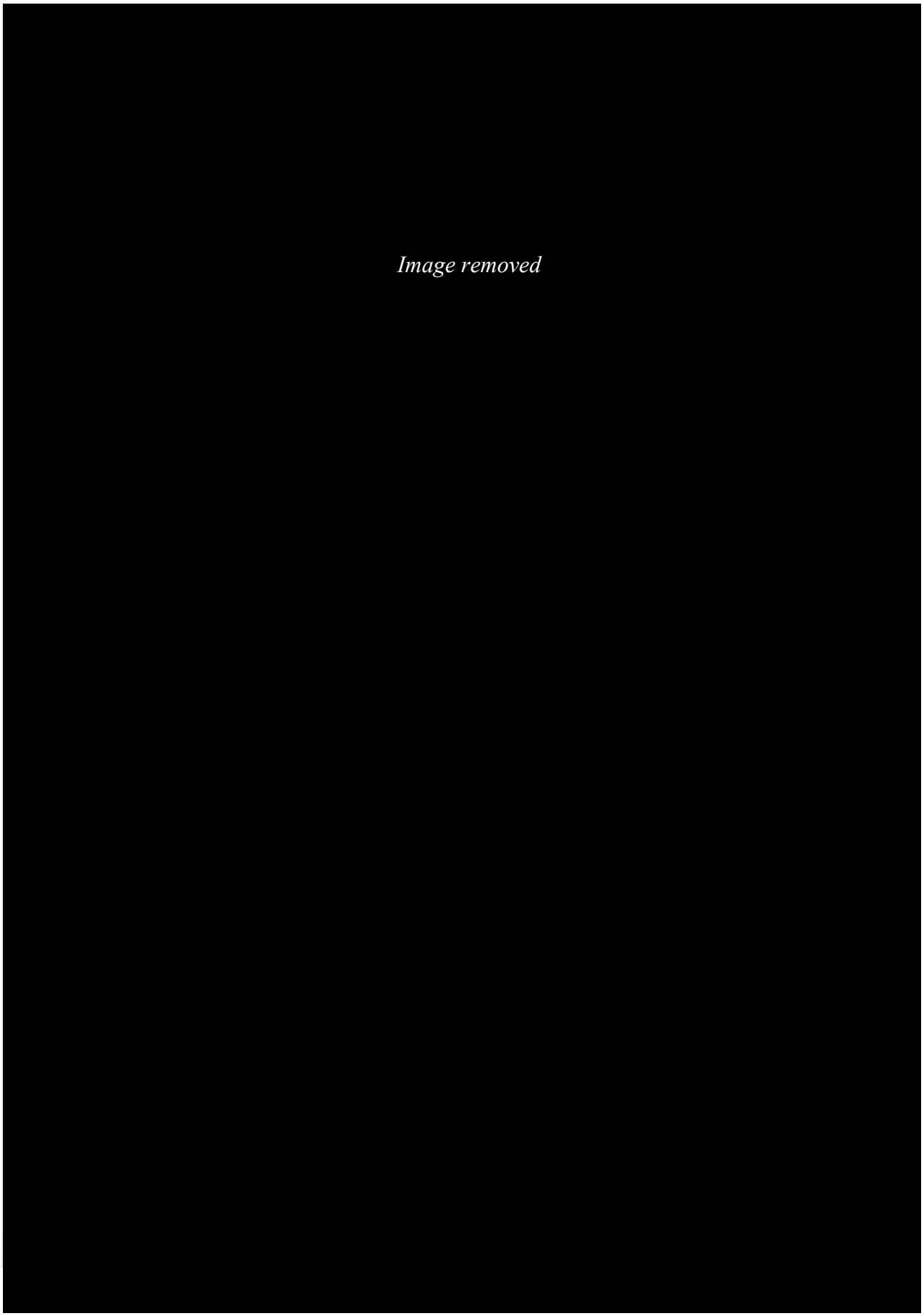


Image removed

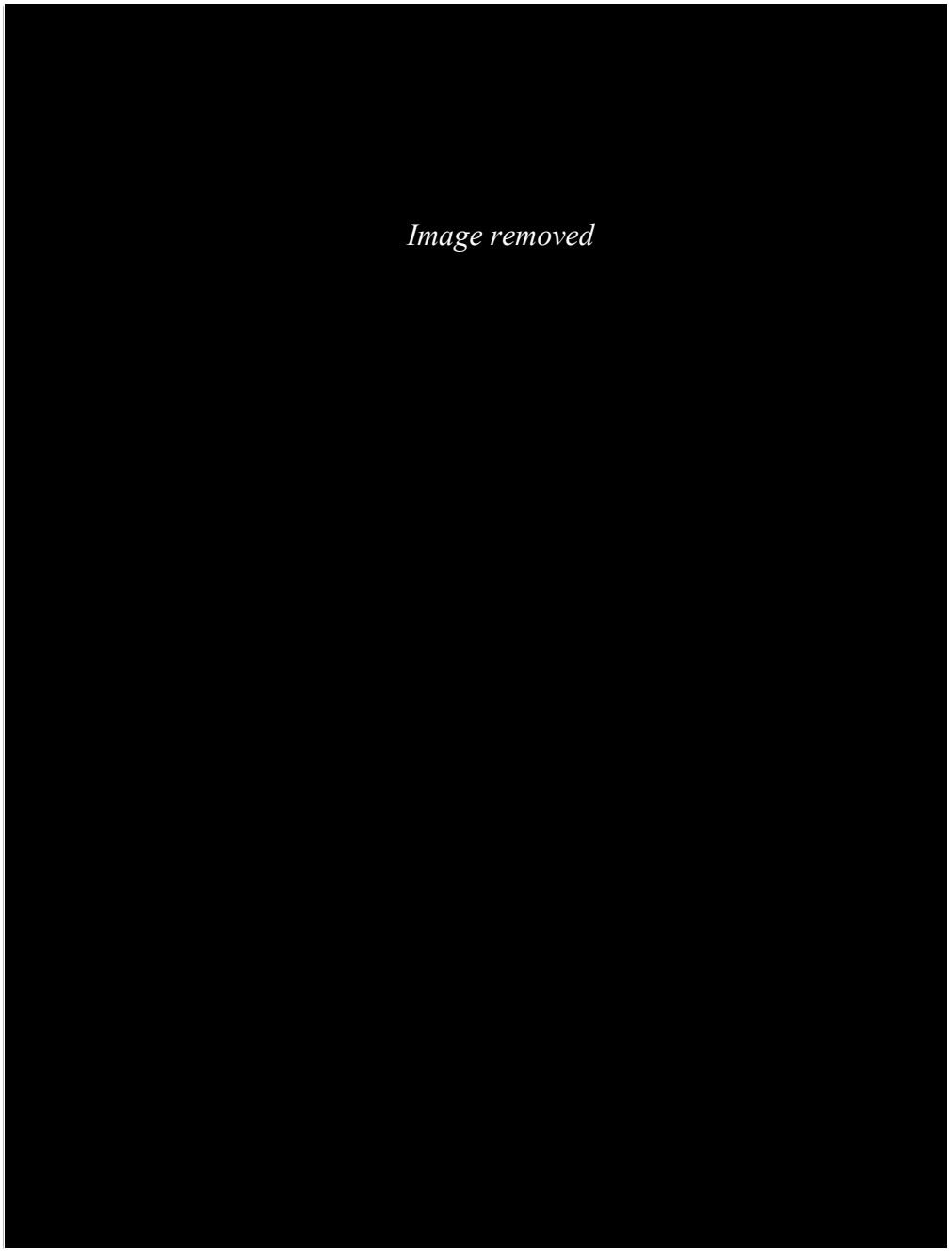
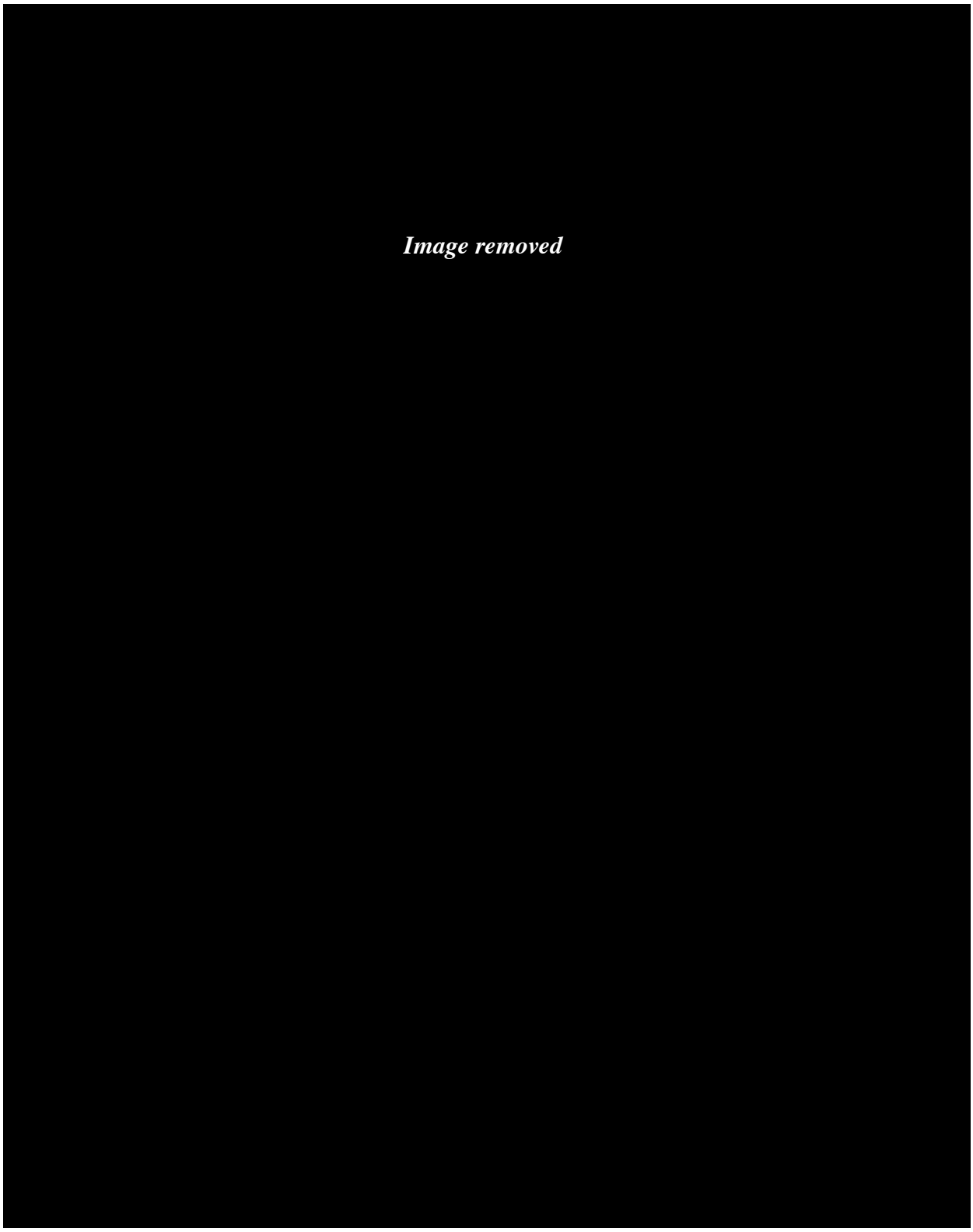
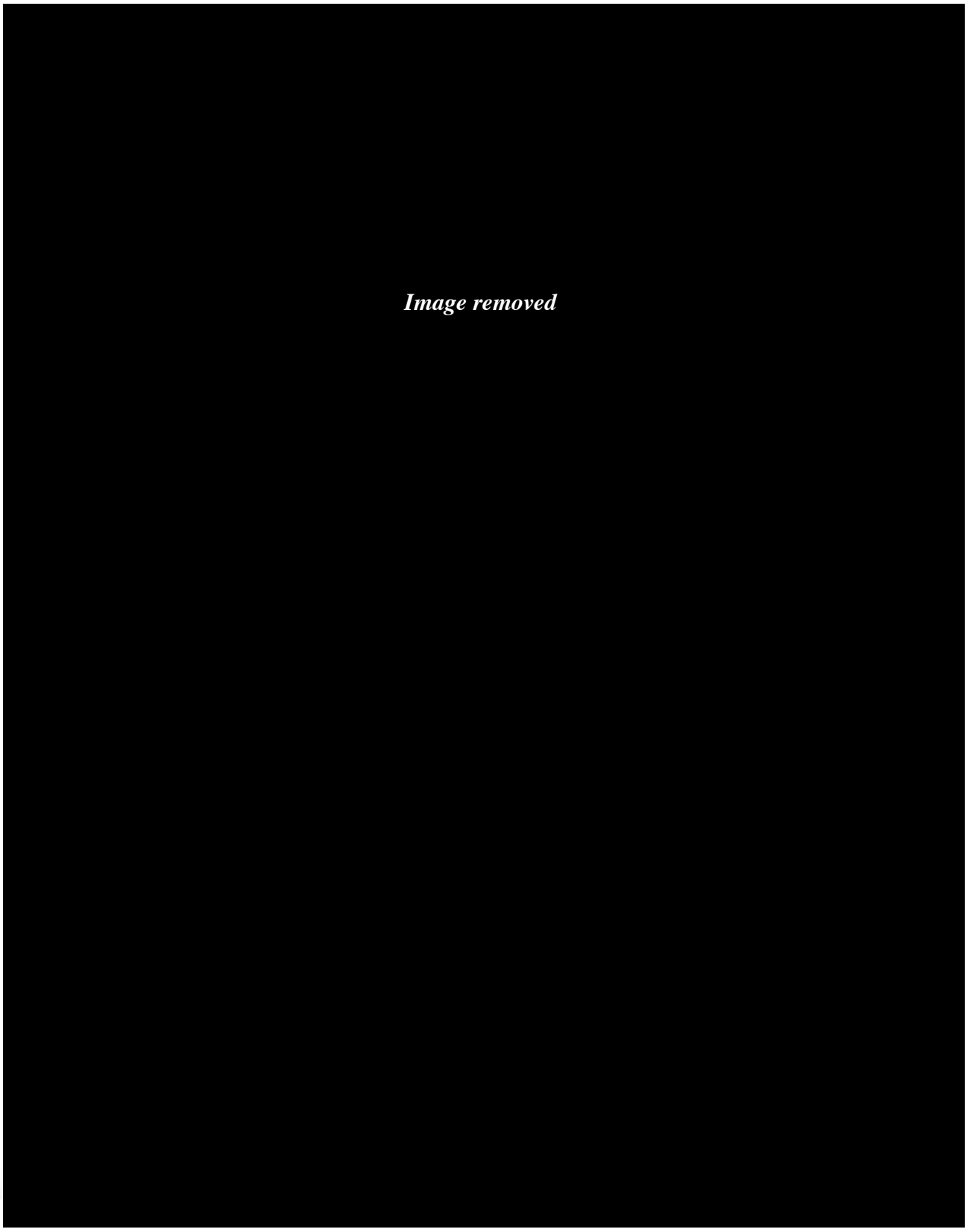


Image removed

Appendix C: BPAQ – Bone-specific Physical Activity Questionnaire



Appendix D*: *Dizziness Handicap Inventory (DHI)



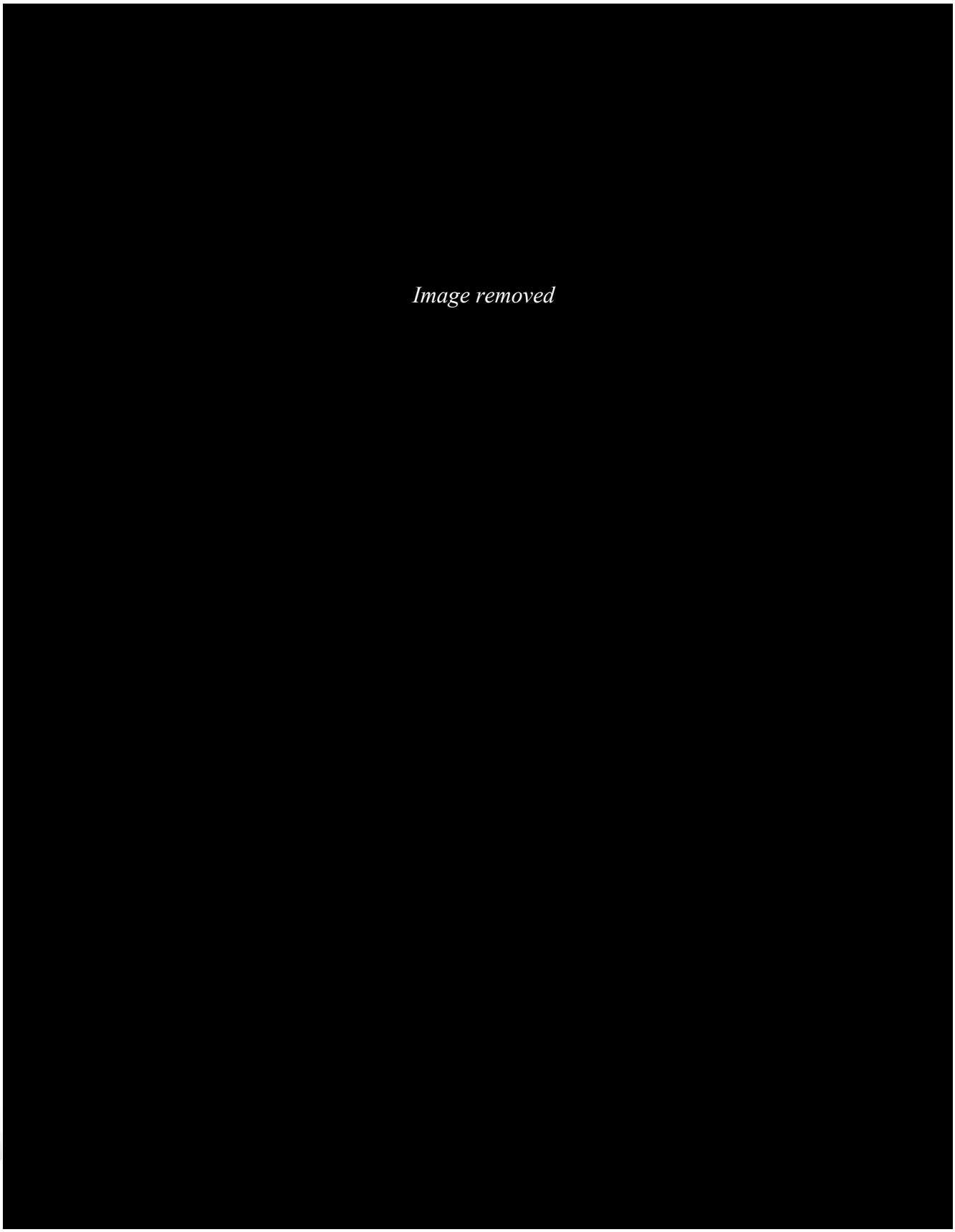


Image removed

Appendix E: Record of scans removed from analysis due to poor quality

Participant ID	Group (PVD or healthy)	Scan type (pQCT or DXA)	Site
[redacted]	healthy	DXA	spine
[redacted]	healthy	DXA pQCT	Spine Tibia
[redacted]	healthy	DXA	Spine
[redacted]	healthy	DXA	FN
[redacted]	healthy	pQCT	Tibia
[redacted]	healthy	DXA	Spine
[redacted]	healthy	pQCT	Tibia
[redacted]	healthy	pQCT	Tibia
[redacted]	healthy	pQCT	Tibia
[redacted]	healthy	pQCT	Tibia
[redacted]	healthy	pQCT	Tibia
[redacted]	PVD	pQCT	Tibia
[redacted]	PVD	pQCT	Tibia
[redacted]	PVD	pQCT	Tibia
[redacted]	PVD	pQCT	Tibia
[redacted]	PVD	pQCT	Tibia
[redacted]	PVD	pQCT	Tibia
[redacted]	PVD	pQCT DXA	Tibia Spine

Appendix F: Example participant letter of results

Griffith UNIVERSITY
Queensland Australia

Participant DOB:
Participant ID:
Date:

Dear.....,

Thank you for volunteering to participate in the study titled "Is chronic vestibular dysfunction associated with bone-related and fall-related indices of fracture risk in community-dwelling older adults?". Your results will help us to determine whether or not older adults that suffer from inner-ear balance problems are at increased risk of fracture.

Please find the results of your testing session below. Your scans will be attached to this letter should you wish to show them to your GP. Should you have any concerns with the results of your testing, please discuss with your GP.

BONE DENSITY SCAN AND FUNCTIONAL TESTING RESULTS:

Test	Your values	Normal range	Other
Dual Energy X-ray Absorptiometry (DXA) – measure of bone mineral density (BMD)	T-score Femoral Neck BMD: -1.92		*
	T-score Lumbar Spine BMD: -2.99		*
Falls Efficacy Scale – measure of fear of falling	19/64= low fear of falling	*	
Dynamic Gait Index – measure of walking balance	21/24	*	
Timed up and go test – measure of physical performance	5.26 seconds	*	
5 times sit to stand test – measure of lower limb strength	10.18 seconds	*	
Grip strength – measure of upper limb strength	27.3 Kg	*	

INNER-EAR FUNCTION TESTING RESULTS:

Test	Your outcomes	Normal outcomes
Positional testing – posterior canal Dix-Hallpike test	Left- nil abnormality Right- nil abnormality	Nil abnormal eye movement
Positional testing – horizontal canal - head roll test	Left- nil abnormality Right- nil abnormality	Nil abnormal eye movement
Modified Rhomberg balance test (foam)	Passed 3 conditions	Passed all 4 conditions

Should you have any questions regarding your participation in this study or if you would like to know any further information, please do not hesitate to contact Jayde Collier.

If you are interested in learning more about how to reduce your risk of falls and keep active, please see the following free resources:

https://www.health.qld.gov.au/__data/assets/pdf_file/0028/429814/33381_full.pdf
https://www.health.qld.gov.au/__data/assets/pdf_file/0026/844181/ageing-vitality-guide.pdf

Kind Regards,

Jayde Collier (BExSc, MPhty)
Master of Medical Research Student
School of Health Sciences and Social Work
Griffith University, Gold Coast
Email: Jayde.collier@griffithuni.edu.au
Phone: [redacted]

Appendix G: Post-hoc power analysis for t-tests

Outcome variable	Total or sub-group analysis	Post-hoc power
BMD FN	Total	28.1%
BMD FN	Female sub-group	73.4%
BMD L1-4	Total	46.4%
BMD L1-4	Female sub-group	55%
Calf CSA	Total	8.1%
Calf CSA	Female sub-group	16.1%
Calf Density	Total	25.8%
Calf Density	Female subgroup	51.2%
ASM/h2	Total	15.1%
ASM/h2	Female subgroup	13.2%
Tibia SSI	Total	4.1%
Tibia SSI	Female sub-group	3.6%
Tibia polar modulus	Total	7%
Tibia polar modulus	Female sub-group	3.1%