Title: Familial resemblance of bone health in maternal lineage pairs and triads: A scoping review protocol

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PCC

Population: Maternal Pairs or Triads

Concept: Familial Resemblance

Context: Bone Health

Primary Question: What is the familial resemblance of bone health in pairs or triads within maternal biological lineage?

Secondary Question: What is the correlation between bone health and bone health affecting behaviours of triads and pair within familial lineages?

Introduction

Osteoporosis is defined as a systemic skeletal disease consisting of low bone mass, deterioration of bone architecture, and increased fracture risk and fragility (Peck et al., 1993). Women, have an approximately 3 times greater occurrence of major osteoporosis-related fractures in Canada when compared to men in the age group of 65 and older (Lam et al., 2014). The economic burden associated with osteoporosis was reported to be $4.6 billion (Hopkins et al., 2016), however it will continue to grow as those adults in this age group are projected to increase from 17.2% in 2018, to 21.4 - 29.5% of the overall population in 2068 (Statistics Canada, 2019).

The non-modifiable risk factors associated with osteoporosis are well documented and include sex-specific risks such as menopause, as well as aging, shorter stature, Caucasian or Asian descent, and family history. There are also several modifiable risk factors associated with lifestyle, including smoking, low calcium intake and Vitamin D intake, physical inactivity, and excessive alcohol consumption (NIH Consensus Development Panel on Osteoporosis, 2001; Peck et al., 1993; Peña & Perez, 2012; World Health Organization, 2003). In summary, women are at a higher risk than men of the same age (Peck et al., 1993; World Health Organization, 2003) and subsequently have a higher prevalence of not only low bone mass (Garriguet, 2011; Statistics Canada, 2021), but also osteoporosis-related fractures (Lam et al., 2014). Therefore, investigating these and addition risk factors will improve our understanding of osteoporosis-related fractures and lead to the implementation of evidence-based prevention strategies.

Females achieve peak bone mass (PBM) in their hips between the ages of 16 and 19, and in their lumbar spine between the ages of 33 and 40 (Berger et al., 2010). These numbers, however, may be misleading since some researchers stated that 94% of bone mass is accrued by

16 years of age, (Berger et al., 2010) and others state that 97% of bone mineral content is achieved by 18.8 years of age (Baxter-Jones, Faulkner, Forwood, Mirwald, & Bailey, 2011). Baxter-Jones et al. (2011) also demonstrated that femoral neck bone mineral content (BMC) has already been lost by 18.8 years, and that ~39% of total-body bone mineral content is accrued just in the four peripubertal years (average of 11.8 ± 2 years). Both the NIH Consensus Development Panel on Osteoporosis (2001) and the World Health Organization (2003)have stated that PBM is a predictor of future osteoporosis and osteoporotic fracture risk, since bone mass over a lifetime is equal to an individual's achieved PBM minus what has been lost since puberty.

Longitudinal studies are ideally the best designs to investigate the lifelong impact of genetics, lifestyle, and other factors (i.e., exogenous hormones, age at menses, age at menopause) on achieved peak bone mass, and development of osteoporosis. Such study designs, however, are costly, and require a long-term commitment from participants, which leads to substantial participant loss. To counteract this, several cross-sectional studies have used a multi-generational approach to studying bone health in women, given that roughly 60-80% of bone mass is genetic (Brown et al., 2004; Eisman, 1999; Weaver et al., 2016).

Multi-generational (or intergenerational) studies include both pairs and/or triads and in this scoping review we are interested in investigating both population types of generational studies. The three generational studies contain a daughter, a mother, and a grandmother. We will label and define the pairs or triads groupings as one of the following in the review: daughter-mother-grandmother, elder daughter-mother, or younger daughter-mother (Appendix A). In the triad pair the daughter will be defined as the youngest of a given three generations with the grandmother as the eldest, and the intermediate will be labelled as the mother. For pair studies, reproductive maturity (i.e., years since puberty and menopausal status) will be used in

conjuncture with age to determine whether the study is elder daughter-mother or younger daughter-mother. If the eldest group is peri- and/or post-menopausal, then they will be labelled elder mother and the younger will be labelled elder daughter for that study. If the eldest group in the pair is not peri- or post-menopausal, and between the age of 30-55, they will be labelled younger mother, and the younger will be defined as the younger daughter group. These definitions with specific distinctions will allow the pair studies to be compared with the triad studies.

The objective of this scoping review is to determine the familial resemblance of bone health and to identify bone health behaviours that contribute to enhanced osteoporosis risk within maternal pairs and triads. To be the best of our knowledge no other scoping reviews and protocols exist based on a search was completed (April 20, 2021) of Google Scholar, MEDLINE, PROSPERO, and Open Science Framework (OSF)

Methods

This scoping review protocol, and subsequent scoping review, follow the methodology described in the *JBI Manual for Evidence Synthesis* (2020) and will cover the reporting items outlined in the 2018 PRISMA extension for scoping review (Tricco et al., 2018).

Inclusion/Exclusion

Participants and defining characteristics

- Biologically related females of multiple generations
- If daughter and mom - the youngest generation must be sexually mature (have already begun menstruating)
- If mom and grandmother – the eldest must be post-menopausal
- Screened for conditions/medication affecting bone

Concept:

- Bone health must be quantified
    - Can be DXA, FRAX, fracture history, or other

Types of sources:

- All peer-reviewed studies
- Grey literature such as conference abstracts, dissertations, and theses will be included to minimize publication bias
- Case reports, opinion articles, editorials and non-human studies will be excluded
- No date, country, or language restrictions

Search Strategy

Seed articles (Appendix B) were used in the creation of the search strategy (Table 1). This strategy will be used to search the following databases: MEDLINE (OVID), EMBASE (OVID), SPORTDiscus (Ebsco), CINAHL Plus with Full Text (Ebsco), Cochrane Central Register of Controlled Trials (OVID), and Scopus (Elsevier).

Grey literature searching will include Clinicaltrials.gov for clinical trials, ProQuest Dissertations and Theses Global for dissertations and theses, and foundations such as the International Osteoporosis Foundation and North American Menopause Society for conference abstracts.

Table 1

Search Strategy Compiled from Seed Articles and Tested in Following Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to April 28, 2021

#	Searches	Results
1	Mothers/	46014
2	Nuclear Family/	5642
3	Family/	78050
4	Family Health/	23636
5	(familial adj3 (correlation* or resemblance* or pattern* or characteristic* or similarit* or component* or lineage)).tw,kf.	3023
6	(mother* adj6 daughter*).tw,kf.	5113
7	(mother* adj6 (grand-mother* or grandmother*)).tw,kf.	1069
8	(daughter* adj6 (grand-mother* or grandmother*)).tw,kf.	101

9	((grand-daughter* or granddaughter* or grandaughter*) adj6 (grand-mother* or grandmother*)).tw,kf.	44
10	((two or three or "2" or "3" or triad*) adj2 generation*).tw,kf.	20189
11	((family or familial) adj6 (pair* or triad*)).tw,kf.	2226
12	((mother* or daughter* or grand-mother* or grandmother* or grand-daughter* or granddaughter* or grandaughter*) adj3 (pair* or triad*)).tw,kf.	6999
13	(multi-generation* or multigeneration* or inter-generation* or intergeneration* or bi-generation* or bigeneration* or tri-generation* or trigeneration*).tw,kf.	10486
14	or/1-12	181320
15	Bone Density/	54902
16	osteoporosis/ or osteoporosis, postmenopausal/	57331
17	exp Fractures, Bone/	189320
18	(bone adj3 (densit* or health or mass or mineral* or content* or fracture* or characteristic* or qualit*)).tw,kf.	113620
19	bmd.tw,kf.	30739
20	(osteoporosis or osteopenia).tw,kf.	77727
21	(fracture* adj2 (risk* or history or bone*)).tw,kf.	32720
22	(dual-energy adj2 absorptiometry).tw,kf.	424
23	(DXA or DEXA or FRAX).tw,kf.	17241
24	or/15-23	339242
25	14 and 24	695

Source of Evidence Selection

All studies found during the search will be uploaded to Covidence and de-duplicated. Prior to the first round of screening (title and abstract) the two screening authors will screen 50 studies independently to determine inter-rated reliability and resolve any discrepancies. They will discuss and clarify any found discrepancies in advance of the first round of screening.

Studies will be screened by two of the authors. First, they will screen the titles and abstracts, and secondly, they will screen the studies using their full text. Disagreements will be solved when all screening in the given step is completed by the two screeners. They will discuss the disputed studies until a consensus is reached. If a consensus cannot be reached a third reviewer will be asked to participate in the discussion.

If a reviewer is unsure during the title and abstract screening stage, they will err on the side of caution by voting to include the study. This ensures no studies will be missed in this step without them clearly being irrelevant.

Before full text screening, all full texts of articles that have made it this round will be found and uploaded to Covidence. In the full text screening, the reviewers will indicate the reason for excluding all excluded papers.

All publication types deemed grey literature, such as theses, government publications, and conference proceedings, will be screened in the same 2 step manner. The process will be tracked and split in two separate excel sheets; one per reviewer. Again, at the end of title/abstract review and full text review, the reviewers will meet to compare their excel sheets.

The number of studies will be tracked through each procedure and compiled in a PRISMA flow chart in accordance with the newly released PRISMA Statement (Page et al., 2021).

Data Charting

Information charted in an excel sheet (draft found in Appendix C) for this review will include:

1. Title
2. Author(s)
3. Year of publication
4. Country of origin
5. Sample size (including number of pairs and/or triads)
6. Category of population (i.e., daughter-mother-grandmother, elder-daughter-mother, or younger-daughter-mother)
7. Aims/purposes
8. Method of bone health quantification
9. Site of bone health quantification
10. Health behaviours (if measured)
11. Other risk factors
12. Other measurements
13. Key findings
14. Limitations

The data charting categories have been compiled from a review of the seed articles (see Appendix B). Data charting will be an iterative process.

Final charted data will be presented in the scoping review in a table (or tables). Frequency will also be displayed for categories such as number of studies (including number of pairs/triads) for each category, i.e., daughter-mother-grandmother, elder-daughter-mother,

and younger-daughter-mother. Breadth of knowledge for bone-health related behaviours will likely be displayed in a bubble chart, to visually exhibit to breadth of knowledge in relation to year of publication.

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Peck, W. A., Burckhardt, P., Christiansen, C., Fleisch, H. A., Genant, H. K., Gennari, C., . . . et al. (1993). Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. *AM J MED, 94*(6), 646-650. doi:10.1016/0002-9343(93)90218-E

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Appendix A

Table 1: Table for the definition and comparison of triads, elder pairs, and younger pairs

	Youngest Category		Intermediate Category		Eldest Category	
	Label	**Definition**	**Label**	**Definition**	**Label**	**Definition**
Triad Studies	Daughter	Youngest of the three generations	Mother	Intermediate generation	Grandmother	Eldest of the three generations
Younger Daughter-Mother Studies	Younger Daughter	Youngest of the two	Younger Mother	Eldest of the pair AND Not per- or post-menopausal	—	—
Elder Daughter-Mother Studies	—	—	Elder-Daughter	Younger of the two generations	Elder-Mother	Peri- or post-menopausal AND Eldest of the two generations

Appendix B

Seed Articles

Ulrich, C. M., Georgiou, C. C., Snow-Harter, C. M., & Gillis, D. E. (1996). Bone mineral density in mother-daughter pairs: relations to lifetime exercise, lifetime milk consumption, and calcium supplements. *The American journal of clinical nutrition*, *63*(1), 72-79.

Abstract

This study investigated associations between lifetime milk consumption, calcium intake from supplements, lifetime weight-bearing exercise, and bone mineral density (BMD) among 25 elderly women (mean age 72 y) and their premenopausal daughters (mean age 41 y). The BMD of the total, axial, and peripheral skeleton was measured by dual-energy X-ray absorptiometry. Lifetime milk consumption, supplemental calcium intake, and weight-bearing exercise were estimated retrospectively by questionnaire and interview. In multiple-linear-regression analyses, mothers' total and peripheral BMD were positively associated with supplemental calcium intake after age 60 y, body weight, current estrogen replacement therapy (ERT), and past oral contraceptive (OC) use, and negatively associated with age and height (all $P < 0.05$). Mothers' axial BMD was positively correlated with body weight and past OC use. Among daughters, lifetime weight-bearing exercise was a predictor of total and peripheral BMD, whereas total lean mass was a predictor of axial BMD. Mothers' lifetime milk consumption was positively associated with that of their daughters. Mothers' and daughters' peripheral BMD values were positively correlated after adjustment for daughters' exercise, and mothers' age, body weight, and ERT. These results suggest that calcium supplementation and exogenous estrogen positively influence bone mass in postmenopausal years. Our findings lend support to recommendations for physical activity as a means of osteoporosis prevention. In the age groups studied, the effects of behavioral and hormonal factors on BMD appeared to dominate over familial similarity, which suggests that women may successfully enhance their genetically determined bone mass through weight-bearing exercise, post-menopausal ERT, and adequate calcium intake.

Kuroda, T., Onoe, Y., Miyabara, Y., Yoshikata, R., Orito, S., Ishitani, K., ... & Ohta, H. (2009). Influence of maternal genetic and lifestyle factors on bone mineral density in adolescent daughters: a cohort study in 387 Japanese daughter-mother pairs. *Journal of bone and mineral metabolism*, *27*(3), 379-385.

Abstract

We conducted a cross-sectional study in a cohort of Japanese adolescent schoolgirls (12–18 years of age) and their mothers (387 pairs). Age, lumbar bone mineral density (BMD), birth and menarche-related status, height, body weight and lifestyles were surveyed in the participants. The values of BMD, height and body weight were converted to standard deviation (SD) by age. There were 49 (12.7%) pre-menarche and 338 (87.3%) post-menarche daughters. BMD-SD, height-SD, vitamin D intake and vitamin K intake were significantly correlated between the pre-menarche daughters and mothers ($P < 0.05$), while BMD-SD, birth weight, age at menarche and all lifestyle-related factors were significantly correlated between the post-menarche daughters and mothers ($P < 0.05$). BMD-SD in the pre-menarche daughters was affected by BMD-SD in mothers ($R 2 = 0.069$, $P = 0.033$) and their own height-SD ($R 2 = 0.199$, $P = 0.001$) (model $R 2 = 0.340$), independently. BMD-SD in the post-menarche daughters was affected by BMD-SD in mothers ($R 2 = 0.073$, $P < 0.001$) as well as by their own age at menarche ($R 2 = 0.020$, $P = 0.001$), height-SD ($R 2 = 0.022$, $P < 0.001$), body weight-SD ($R 2 = 0.081$, $P < 0.001$) and intensity of exercise ($R 2 = 0.015$, $P = 0.045$) (model $R 2 = 0.372$), independently. The results suggest that BMD is strongly correlated between daughters and mothers and that a greater age at menarche leads to lower peak bone mass. It was also suggested that maintaining high-intensity physical activity and adequate body weight is important in achieving maximum BMD as factors amenable to intervention in post-menarche daughters.

Sobas, K., Wadolowska, L., Slowinska, M. A., Czlapka-Matyasik, M., Wuenstel, J., & Niedzwiedzka, E. (2015). Like mother, like daughter? Dietary and non-dietary bone fracture risk factors in mothers and their daughters. *Iranian journal of public health*, *44*(7), 939.

Abstract

The aim of this study was to demonstrate similarities and differences between mothers and daughters regarding dietary and non-dietary risk factors for bone fractures and osteoporosis. The study was carried out in 2007-2010 on 712 mothers (29-59 years) and daughters (12-21 years) family pairs. In the sub-sample (170 family pairs) bone mineral density (BMD) was measured for the forearm by dual-energy x-ray absorptiometry (DXA). The consumption of dairy products was determined with a semi-quantitative food frequency questionnaire (ADOS-Ca) and calcium intake from the daily diet was calculated. The presence of risk factors for bone fractures in mothers and daughters was significantly correlated. The Spearman rank coefficient for dietary factors of fracture risk was 0.87 ($P<0.05$) in whole sub-sample, 0.94 ($P<0.05$) in bottom tercile of BMD, 0.82 ($P<0.05$) in middle tercile of BMD, 0.54 ($P>0.05$) in upper tercile of BMD and for non-dietary factors of fracture risk was 0.83 ($P<0.05$) in whole sub-sample, 0.86 ($P<0.05$) in bottom tercile of BMD, 0.93 ($P<0.05$) in middle tercile of BMD, 0.65 ($P<0.05$) in upper tercile of BMD. Our results confirm the role of the family environment for bone health and document the stronger effect of negative factors of the family environment as compared to other positive factors on bone fracture risk.

Runyan, S. M., Stadler, D. D., Bainbridge, C. N., Miller, S. C., & Moyer-Mileur, L. J. (2003). Familial resemblance of bone mineralization, calcium intake, and physical activity in early-adolescent daughters, their mothers, and maternal grandmothers. *Journal of the American Dietetic Association*, *103*(10), 1320-1325.

Abstract

OBJECTIVE: To describe familial relationships among bone mineral density (BMD), calcium intake, and physical activity in early-adolescent daughters, their premenopausal mothers, and postmenopausal maternal grandmothers., SUBJECTS: Healthy, early adolescent daughter and premenopausal mother pairs (n=72) were enrolled in the study. In addition, a cohort of 22 postmenopausal maternal grandmothers were measured for comparison of related triads (n=22)., DESIGN: Cross-sectional measurements of hip (three sites) and lumbar spine BMD by dual energy x-ray absorptiometry (DXA), body height and weight, menstrual function, current calcium intake, and current and past physical activity patterns were assessed using recalls and questionnaires., STATISTICAL ANALYSIS: Correlational analysis was used to establish relationships between bone characteristics and body size, menstrual function, calcium intake, and physical activity. Multiple regression analyses with backward elimination were used to examine heritability of bone characteristics in daughter-mother and mother-grandmother pairs and daughter-mother-grandmother triads. Quick cluster analysis and cross-tabulation with Pearson's chi (2) were used to evaluate familial patterns for bone characteristics and lifestyle practices., RESULTS: Height, weight, and lumbar spine BMD were significantly correlated within mother-daughter pairs. Current and past calcium intakes were not related within pairs or triads or to BMD in the daughters or the grandmothers. A weak inverse relationship between calcium intake and the hip trochanter and lumbar spine BMD was observed in the mothers (R (2) =-0.25; P=.05). Physical activity, independent of calcium intake, was strong predictor of BMD for daughters and mothers. Among the daughters, the heritability estimates for trochanter and lumbar spine BMD were 0.56 and 0.70, respectively (P<.01). The heritability estimate for premenopausal mothers were significant for lumbar spine BMD (h (2) =0.66; P<.01). Daughter-mother-grandmother triads with low physical activity had low femoral neck BMD whereas those with high physical activity had high femoral neck BMD (P<.001)., APPLICATIONS: Making physical activity a part of the daily routine, in addition to an adequate intake of calcium and bone-related nutrients, is an important goal for maintaining or improving bone health for women of all ages.

Picard, D., Imbach, A., Couturier, M., Lepage, R., & Picard, M. (2001). Familial resemblance of bone mineral density between females 18 years and older and their mothers. *Canadian journal of public health*, *92*(5), 353-358.

Abstract

Potential determinants of bone mass were investigated in a group of 70 young females (mean age 26.6 years), daughters of women studied in premenopause. Nutritional data, leisure physical activity level, lifestyle habits as well as familial similarities were assessed. The daughters' bone mineral density (BMD), measured by dual-energy absorptiometry, was significantly correlated with their body mass index (BMI) ($r = 0.22$), dietary vitamin D intake ($r = 0.19$) and their mothers' BMD ($r = 0.44$). Multiple regression analysis indicated that only the mothers' BMD remained an independent predictor of bone mass. Mother-daughter correlations were also observed for body weight ($r = 0.24$), height ($r = 0.39$), BMI ($r = 0.29$), dietary calcium intake ($r = 0.20$), and calcium ($r = 0.20$) or vitamin D ($r = 0.25$) intakes from dairy products. Hence, these observations support the evidence that mothers' BMD is the strongest predictor of bone mass of young women in their third decade.

Ohta, H., Kuroda, T., Onoe, Y., Nakano, C., Yoshikata, R., Ishitani, K., ... & Kume, M. (2010). Familial correlation of bone mineral density, birth data and lifestyle factors among adolescent daughters, mothers, and grandmothers. *Journal of bone and mineral metabolism*, *28*(6), 690-695.

Abstract

This study aimed to clarify the relationship between skeletal or lifestyle factors among Japanese daughter-mother, mother-grandmother, and daughter-grandmother pairs. We performed a cross-sectional study in a cohort of Japanese adolescent daughters (12-18 years of age), their mothers (339 pairs) and grandmothers on their mothers' side (34 pairs). Gestational age, birth weight, age at menarche and presence of menarche or menopause were surveyed in the participants. Height, body weight and lumbar 2-4 bone mineral density (BMD) were measured. Dietary intake and current physical activity were assessed by using questionnaires. Gestational age and age at menarche were significantly correlated among daughters, mothers, and grandmothers ($P < 0.001$). BMD was significantly correlated between daughters and mothers ($P < 0.001$), while it was not significantly correlated between daughters and grandmothers or between mothers and grandmothers. Dietary intake of calcium and vitamin D, and the frequency, duration and intensity of current physical activity were significantly correlated between daughters and mothers ($P < 0.05$), although no significant correlation was found between daughters and grandmothers, or between mothers and grandmothers. The parameters for exercise indicated a positive correlation for BMD in the daughters and the mothers, but not in the grandmothers. The results suggested that estrogen deficiency decreases familial correlation for BMD after menopause. Achieving high BMD through exercise may be important for prevention of postmenopausal osteoporosis in premenopausal low-height mothers.

Kahn, S. A., Pace, J. E., Cox, M. L., Gau, D. W., Cox, S. A., & Hodkinson, H. M. (1994). Osteoporosis and genetic influence: a three-generation study. *Postgraduate medical journal*, *70*(829), 798-800.

Abstract

We have studied 27 triads of mother, daughter, and grandmother for possible genetic influence on distal and proximal forearm bone density, measured by single photon absorptiometry. We found a significant correlation of bone density at the proximal forearm between the mothers and grandmothers ($r = 0.499$, $P < 0.01$). There was also a weak correlation between proximal forearm bone densities of mothers and daughters ($r = 0.327$, $P < 0.1$). Significant correlations were found between the three generations for grip strength, pedometry, height and triceps skinfold thickness. There was also significant correlation between mother and grandmother for alcohol intake. There was no correlation for contraceptive pill use, smoking, dietary calcium intake, body weight or body mass index. The study concludes that, although there are similarities in bone mineral content between the three generations, genetic factors cannot be conclusively proven to be the major determinant of bone density. Lifestyle and environmental factors may have a bearing on achieving the peak bone mass and subsequent development of osteoporosis.