Concept Paper Template

Provisional Conference Abstract Title: Repeated childhood fracture is not related to abnormal bone or body composition in middle age

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Today's Date: 2/6/2018

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

To determine the association between children (<18 years) who suffered multiple fractures (>1) compared to those who did not suffer from multiple fracture on abnormal bone and body composition at age 45y.

Data analysis methods:

The original dataset relating to childhood fracture history was developed by Jones et al. [1] and methods used to determine the fracture history were as follows: At age 5 years (phase 5) the parents were asked to provide information on all injuries requiring medical attention suffered by their children during the first 5 years of the child's life. This covered inpatient, outpatient and general practitioner treatment. Thereafter injury information was collected at each phase and covered the period of time since the last assessment. Information was obtained regarding the nature of the injury and the age of the child when the injury occurred. All fractures were given a separate code and site of fracture was identified. No information concerning the severity of trauma associated with individual fractures was available and no attempt to evaluate the possible contribution of underlying medical conditions or medication use to fracture occurrence was made. Cases were censored on the first occasion they did not attend for assessment or failed to complete the questions about injuries. To be included they had to have completed the questions about injuries sustained since birth at age 5 years. This dataset was combined with preliminary data collected (n-660) on bone and body composition at Phase 45 and two fracture groups were created for the current analyses; children who suffered from more than 1 fracture (Repeat fracture, n=106) and those who suffered from 1 or less (n=554). Regression was used to analyse the association between repeat fracture and body composition and bone density at age 45. Statistical analyses were performed with STATA (release 6, StataCorp, College Station, TX).

Variables needed at which ages:

- Fractures prior to age 18 (childhood): This dataset is already available within the Dunedin School of Medicine's Bone and Body Composition Unit as it was created for the publication titled "How Many Children Remain Fracture-Free During Growth? A Longitudinal Study of Children and Adolescents Participating in the Dunedin Multidisciplinary Health and Development Study. (2002). Jones I.E., Williams S.M., Goulding A.

- Age 45 DXA body composition variables (lean mass, fat mass, % body fat, appendicular lean muscle index) and DXA hip bone density variables (hip BMD, hip BMC, hip T-scores, hip z-scores). This dataset has been developed with the preliminary data and at the time of analyses included a sample of n=660.

- The full publication will aim to control for other variables known to affect fracture history and bone health including birthweight, childhood and adult SES, abuse, maltreatment, Vit D, serum calcium.

Significance of the Study (for theory, research methods or clinical practice):

Personal fracture history is one of the strongest predictors of future fractures,[2] yet current practice guidelines, including commonly used osteoporosis risk scores, ignore fractures that occur during childhood.[3, 4] Several years ago our lab investigated the incidence of childhood fractures in the Dunedin Study cohort and demonstrated that although about half of the sample remained fracture-free during childhood almost a quarter of boys and 15% of girls suffered from multiple fractures.[1] The reasons some children fracture repeatedly are unclear. These children may have especially fragile skeletons or they may be accident-prone or conversely these fractures may be the price of risk-taking behaviors that could optimize bone strength during growth.[1] While the majority of adult fracture research has focused on determinants of fractures with aging, [5, 6] fracture risk has two peaks with an earlier peak during puberty. [7, 8] Thus, it remains unclear whether childhood fractures are related, in part, to transient reductions in bone strength during rapid growth or to skeletal deficits that will track into adulthood. Because achieving optimal bone strength early in life likely predicts lower fracture risk later in life,[9] it is critical to identify events during childhood that foreshadow suboptimal peak bone strength in adulthood.

If poor adult bone health has its antecedents in childhood so to could abnormal body composition such as low muscle mass and strength (sarcopenia) or low muscle and low bone (osteosarcopenia) and high fat mass. Recent research has demonstrated a close relationship between skeletal muscle mass and bone mass that exists throughout the lifecourse.[10] Children who fracture have lower muscle mass and higher fat mass[11, 12] and during growth bones mineralize in response to changes in lean mas.[13] In adults, age-related loss of muscle mass (sarcopenia) is

intricately linked with changes in bone mass.[14] Osteoporotic fracture accelerates the onset of sarcopenia in older adults and sarcopenia increases the risk of falls and fractures;[15] thus, these two conditions feed perpetually into each other. Obesity, once believed to be protective of bone and muscle mass, is increasingly linked to deterioration in bone and muscle, especially with aging.[16]

Thus, identifying children who fracture repeatedly could have important clinical ramifications to identifying those at risk of future fracture and abnormal body composition if the skeletal deficits track into adulthood and predict changes in muscle and fat mass. Although some observational studies have demonstrated that bone size and shape tend to track throughout life[17, 18] and cross-sectional studies have found that volumetric bone mineral density (vBMD) and bone structure are worse in young adults,[19, 20] with prior fracture, no longitudinal study has tested whether individuals who repeatedly fracture in childhood have altered bone and/or body composition in adulthood. If skeletal deficits in children and adolescents with repeat fracture persist into adult life and predict abnormal body composition, then individuals with a history of such fractures may need to be more aggressively monitored for subsequent skeletal and body composition complications.

Therefore, we aim to examine whether study members who sustained more than one fracture during childhood (at age <18 years) have alterations in bone density, and/or body composition compared to those who did not repeatedly fracture during childhood. In the full publication, we also plan to conduct sensitivity analyses to determine whether there were any differences between those with no history of fracture, <2 fractures or 2 or more fractures, while controlling for other measures known to affect bone and body composition including demographics including birthweight, childhood and adult SES, maltreatment and child abuse.

The abstract to submit to the Australia and New Zealand Bone Mineral Society Annual General Meeting, Queenstown, New Zealand is below. The meeting is in Sept 2018. **The abstract deadline is 8th June.**

Repeated childhood fracture is not related to abnormal bone or body composition in middle age.

Meredith-Jones K, Vlietstra L, Waters D, Haszard J.

Although personal fracture history is one of the strongest predictors of future fractures, current guidelines ignore fractures that occur during childhood. However, it is not clear if multiple childhood fractures are related to transient reductions in bone during growth or skeletal deficits that will track into adulthood. Furthermore because of the close relationship between skeletal muscle mass and bone mass throughout the lifecourse skeletal deficits in childhood may be able to predict abnormal adult body composition. We studied 660 men and women from a birth cohort, of which 39 females and 67 males suffered from two or more childhood (age <18 years) fractures. Dual x-ray absorptiometry was used to examine body composition (fat mass, lean mass, % body fat), total bone mineral content, total

bone mineral density, hip bone mineral content and hip bone mineral density at age 45. Compared to those who did not repeatedly fracture as children, those with multiple childhood fractures did not differ in terms of body composition, total body bone mineral density, or bone mineral content ($p>0.05$). However, there were small differences in hip bone density in those that repeatedly fractured compared to those that did not. Total hip BMD was 3% (95%CI: -6%, -1%; $p=0.041$) lower, T-scores were 0.24 standard deviations (95% CI: -0.47, -0.01; $p=0.036$) lower and Z-scores were 0.22 standard deviations (95% CI: -0.43, -0.02; $p=0.034$) lower than those without repeat fractures. These associations were not moderated by sex. Further investigation is required to determine other early childhood factors that predict abnormal adult bone and body composition.

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Data Security Agreement

Provisional paper title	*Repeated childhood fracture is not related to abnormal bone or body composition in middle age*
Proposing authors	Dr. Kim Meredith-Jones, Assoc Prof Debra Waters, Lara Vlietstra, Dr. Jill Haszard
Today's date	10th April, 2018

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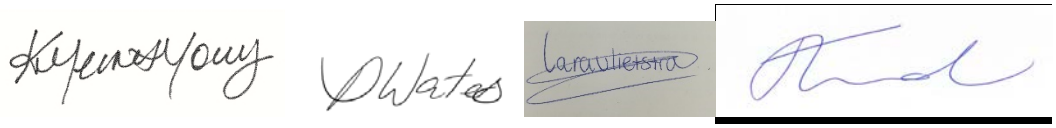
Signature: 

CONCEPT PAPER RESPONSE FORM

A

Repeated childhood fracture is not related to abnormal bone or body composition in middle age	
Proposing Authors: Dr. Kim Meredith-Jones, Assoc Prof Debra Waters, Lara Vlietstra, Dr Jill Haszard	
Other Contributors: **we have not contacted anyone formally yet, but we will contact the PI's responsible for all of the other data included in the model.	
Potential Journals: TBD Abstract to be submitted to Australia and New Zealand Bone Mineral Society Annual General Meeting, Queenstown, NZ, Sept 2018	
Intended Submission Date: **Abstract deadline June 8th, 2018** Full manuscript to be developed when Phase 45 is complete.	

Please keep one copy for your records and return one to the proposing author

B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
KMJ	Conceptualizing and collecting one or more variables
KMJ	Data collection
KMJ	Conceptualizing and designing this specific paper project
LV, JH	Statistical analyses
KMJ, LV, DW, JH	Writing
KMJ, LV, DW, JH	Reviewing manuscript drafts
KMJ, LV, DW, JH	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature: