DEPRESSION FOLLOWING FRACTURE IN ADULT WOMEN: A CASE CONTROL STUDY

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DEPRESSION FOLLOWING FRACTURE IN ADULT WOMEN: A CASE CONTROL STUDY

Running title: Depression following fracture in women

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ABSTRACT

Objectives: High levels of disability, functional impairment and mortality are independently associated with both fracture and depression, however the relationship between these is uncertain. The aim of this study was to investigate whether fracture is associated with depressive symptoms in a population-based sample of adult women.

Design: Case control study

Setting: Barwon Statistical Division, South Eastern Australia.

Participants: Two samples of women aged ≥35yr were drawn from the Geelong Osteoporosis Study (GOS). Eligible women with incident fracture identified from radiology reports, and non-fracture controls were randomly selected from the electoral roll during 1994-6.

Outcome measure: Symptoms of depression for both the cases and controls during the 12-month period 2000-1 were identified by self-report questionnaire based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria.

Results: A total of 296 fracture cases (12 hip, 48 vertebral, 91 wrist/forearm, 17 upper arm, 7 pelvis, 11 rib, 62 lower leg and 48 other fractures) and 590 controls were included. Associations between fracture and depression differed between younger (≤65yr) and older (>65yr) women. Age and weight adjusted odds ratio for depression following fracture among younger women was 0.62 (0.35-1.11, p=0.11) and 3.33 (1.24-8.98, p=0.02) for older women. Further adjustment for lifestyle factors did not affect the results.

Conclusions: These findings indicate that differences in mood status exist between older and younger women following fracture and that depression is a persistent health burden, likely to be affecting long-term recovery in the elderly. Assessment of mood status in both the short and long term following fracture in the elderly seems justified, with early detection and treatment likely to result in improved outcomes.

Key Words: Fracture; Depression; Psychiatric illness; Quality of Life; Osteoporosis

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, there are no published studies investigating post fracture depression among the younger, fracture sites other than the hip, or studies with longer follow up periods; these are all strengths of the current study.
- The time lag between fracture and depression measurement, an inability to provide pre-event psychiatric status and the use of a self-report instrument to determine depression are limitations.

BACKGROUND

Independently, depression and fracture are both increasingly prevalent public health concerns, associated with high levels of disability, functional impairment and mortality. Depression is common and often persistent following a medical event, adversely affecting outcomes and prognosis by hindering adherence to treatment regimes and diminishing quality of life [1]. It is estimated that up to 20% of adults are affected by depression [2, 3], regardless of co-morbid medical conditions, with over $644 million per annum spent on health system costs in Australia alone [4].

As a result of an interaction between an ageing population and environmental and medical factors, fracture rates and the associated burden are projected to rise substantially [5, 6]. It has been estimated that the lifetime risk of fracture lies within the range of 40% to 50% in women and 13% to 22% in men [7]. In 2000, the estimated number of fragility fractures worldwide was 9.0 million of which 1.6 million were hip, 1.7 million forearm and 1.4 million clinical vertebral fractures, with 61.0% occurring in women [8].

Declines in quality of life are typical following a fracture and impose substantial medical and social costs [9]. Furthermore, poorer psychological health has also been observed, with the associated declines in physical functioning, physical disability, and a loss of independence associated with fracture [10-12]. A review investigating outcomes following hip fracture concluded that post injury depressive symptoms are common and a strong predictor of poor recovery [11].

It is likely that a bi-directional relationship between depression and fracture exists. Recently, depression has been shown to precede fracture, possibly influenced by medication use and biological and lifestyle factors dysregulated in depression [13]. Given that depression has been shown to be a likely response to chronic medical conditions, as well as the previously reported associations showing depression to precede fracture, the aim of this case-control study was to investigate whether fracture is associated with depressive symptoms.

METHODS

Participants

This study included women participating in the Geelong Osteoporosis Study (GOS), who were recruited from the Barwon Statistical Division (BSD) situated in south-eastern Australia to investigate the epidemiology of osteoporosis and fracture [14]. All participants gave written, informed consent, and the study was approved by the Human Research Ethics Committee at Barwon Health.

Fracture cases

Women identified from radiological reports as having sustained an incident fracture between February 1994 to February 1996 (n = 1397), living in the BSD at the time of recruitment and aged 35 years and older were invited to participate in the fracture cohort of the GOS [15]. The process of fracture ascertainment from radiological reports has previously been validated [16]. A total of 1082 women were eligible for participation, with 77.4% accepting initial involvement (n=832). Those who participated in the 6-year follow up (n=439) were sent a depression questionnaire, with a total of 296 returned (67%) and thus included in this study (median age 63.0yr, range 35-87yr).

Non-Fracture controls

Between 1994 and 1997 an age-stratified, random sample of women residing in the BSD was recruited from the Commonwealth electoral rolls. The initial group totalled 1494 women (median age 54yr, range 20-94yr), with a participation rate of 77.1% [17]. Those eligible to participate in the 6-year follow up (n=1275) were sent a depression questionnaire, with a total of 758 returned (60%). For this current study, 590 women aged 35 years and older (median age 59.3yr, range 35-91yr) were included.

Measurements

Outcome variable

Symptoms of depression during the 12-month period 2000-1 were identified using a self-report questionnaire based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [18]. An episode of major depression was defined as a depressed mood state and a loss of interest and pleasure in usual activity lasting for at least a two-week period. In addition, the presence of at least four symptoms including weight change, sleep disturbance, psychomotor changes, fatigue, feelings of worthlessness, poor concentration, and suicidal ideation had to be evident, accompanied by diminished physical performance determined to be causing distress or impairment in at least one domain of work, social or personal

functioning. The Cronbach's alpha co-efficient for determining internal reliability of the questionnaire was 0.895 [19].

Exposure variables

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Information on lifestyle and other health factors was obtained via self-report questionnaire. Women were classed as physically active if they participated in light to vigorous activity on a regular basis. Tobacco smoking was recognised if practised currently, and alcohol use recognised if average consumption exceeded two standard drinks per day.

Statistical Analyses

Statistical analyses were completed using Minitab (Version 15; Minitab, State College PA). Associations between fracture and depression differed for younger and older women, thus all analyses were stratified by age (≤65yr and >65 years). Differences in characteristics between the fracture cases and controls according to age group were compared using t-tests for continuous parametric data, Mann-Whitney for continuous non-parametric and chi-square analyses for categorical data. Logistic regression was used to determine the association between fracture and the likelihood of depressive symptoms among the younger (≤65yr) and older (>65) women. Age, anthropometry, physical activity, smoking and alcohol use were tested

in the models as potential confounders and/or effect modifiers. Values of $p<0{\cdot}05$ were considered as significant.

RESULTS

A total of 296 fracture cases (12 hip, 48 vertebral, 92 wrist/forearm, 17 upper arm, 7 pelvis, 12 rib, 64 lower leg and 48 other fractures) and 590 controls were included in the analyses. Characteristics of the fracture cases and controls according to age are shown in Table 1.

Younger women (≤65 years)

Among the younger women (n=552), there were no differences in weight, height, physical activity or alcohol consumption between the fracture cases and the controls, however the fracture cases were older, more likely to smoke and less likely to have depression (Table 1).

The unadjusted odds of having depression following fracture was 0.60 (95% CI 0.34-1.06, p=0.08) compared to controls. The relationship was attenuated after adjusting for age and weight (OR=0.62, 95% CI 0.35-1.11, p=0.12). Further adjustment for height, physical activity, smoking and alcohol consumption did not affect the relationships.

Older women (>65 years)

Among the older women (n=334), no differences in weight, height, physical activity, alcohol or smoking status were evident between the cases and controls; however the fracture cases were younger and more likely to have depression (Table 1).

The odds of having depression following fracture was three times greater (OR 3.02, 95% CI 1.16-7.89, p=0.02) for the fracture cases compared to controls. Adjusting for age and weight did not affect the relationship (OR=3.33, 95% CI 1.24-8.98, p=0.02), which was also sustained after further adjustment for height, physical activity, smoking and alcohol consumption.

DISCUSSION

The findings from this case-control study indicate an association between fracture and depression, although only among older women. Those aged >65 years were up to three-times more likely to have depression post fracture, while this relationship was not evident for younger women (≤65 years). These associations were independent of age, anthropometry, and lifestyle factors.

Our findings suggesting the risk of depression post fracture is increased among older women are consistent with findings from previous studies. Recently, several publications have explored health outcomes following hip fracture surgery and found depression to be common and to impact negatively on recovery up to two years post fracture [20-22]. A systematic review that investigated the prevalence of psychiatric illness in hip fracture patients found that the prevalence of depression following fracture ranged from 9% to 47% [23]; those rates being somewhat higher than community rates. Similarly, the prevalence of depressive symptoms in postmenopausal women with osteoporosis was reported to be greater for women who also had prevalent vertebral fractures compared to those without [24]. Both depressive symptoms following fracture and pre-injury mood state have been shown to be predictive of recovery in the elderly, while a failure to regain pre-injury functional and ability levels increases the possibility of persistent depressive symptomatology [10, 25]. In a prospective cohort study of 240 older participants, those who experienced high levels of depressive symptoms prior to a medical event (hip fracture, stroke and heart attack), had a poorer likelihood of recovery in

activities of daily living [26]. Lastly, a recent study using a cultural models approach to understand how older women viewed osteoporosis reported that experiencing a fracture coincided with the acknowledgement of 'getting older' [27], thus we may expect a fracture to increase the likelihood of depression for some older women. It is plausible that stigma may be associated with a fracture in older age [27], and thus impact negatively on an older woman's self-identity. Taken in context, although a lower prevalence of depression overall has been reported among older women [3], the occurrence of a fracture may enhance the susceptibility to depression for a variety of reasons.

Our findings suggest no relationship between fracture and later depression among younger women. It is plausible that the causal pathway to fracture may differ across age groups, resulting in differing effects on psychological and physical outcomes. For instance, an internal locus of control (the belief one can control one's own life), high self-esteem, hope, acceptance, optimism, and a sense of mastery have all been associated with resilience or the ability to maintain or regain mental health following adversity [28]. Furthermore, differences in pre-morbid emotional and cognitive state may have existed between the younger and older women prior to fracture. This is an important factor, as high positive affect and motivation has been observed as increasing the chances of returning to pre-morbid levels of functioning after a major health event [26]. Lastly, compared to older women, younger women may have more access to social networks on which they can draw on for support, be less likely to remain homebound post-fracture, and be able to fulfil ongoing work and social commitments during recovery.

Some methodological issues should be considered when interpreting the study findings. The time lag between fracture and depression measurement and an inability to provide pre-event psychiatric status is a limitation; however it has to be taken into consideration that depression is a long-term, recurrent disorder in most individuals [29]. The use of a self-report instrument, rather than a clinical diagnostic interview must also be acknowledged. Response bias may also have influenced the findings, with higher rates of psychopathology and other co-morbid conditions being present in the population declining participation. To our knowledge, there are no published studies investigating post fracture depression among the younger, fracture sites other than the hip, or studies with longer follow up periods; these are all strengths of the current study.

CONCLUSION

In conclusion, this study demonstrated that differences in mood status exist between older and younger women following fracture and that depression is a persistent health burden, likely to affect long-term recovery in the elderly. Assessment of mood status in both the short- and long-term following fracture in the elderly seems justified, with early detection and treatment of elevated levels of depression likely to result in improved outcomes. Further research investigating a causal link between fracture and depression is warranted and is currently underway.

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Lana Williams has received Grant/Research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and the NHMRC.

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Margaret Henry and Amanda Stuart have no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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AUTHORS' CONTRIBUTIONS

LJW took part in the conception and design of the study, data cleaning, statistical analysis, interpretation of the data and took primary responsibility for writing the manuscript. MB and SLB took part in the interpretation of data and critically revised the manuscript. MH and ALS took part in the conception and design of the study, statistical analysis, interpretation of the data and critically revised the manuscript.

FNJ took part in the conception and design of the study, acquisition of the data and critically revised the manuscript. JAP took part in the conception and design of the study, interpretation of the analysis and critically revised the manuscript. All authors read and approved the final manuscript.

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Table 1: Characteristics of the fracture cases and controls according to age (≤65yr and >65 years). Values are given as median (interquartile range), mean (± standard deviation) or n (%).

	Fracture cases	Controls	p-values
≤65 years	**n = 170**	**n = 382**	
Age (yr)	54.0 (45.0-60.2)	50.6 (43.2-58.5)	0.019
Weight (kg)	69.1 (61.4-78.4)	67.6 (60.1-79.0)	0.386
Height (cm)	162.2 ± 6.5	161.9 ± 5.9	0.619
Depression (12-month)	17 (10.0%)	60 (15.7%)	0.074
Physical activity (active)	117 (79.6%)	275 (75.6%)	0.328
Alcohol consumption (current)	77 (52.4%)	198 (54.4%)	0.679
Smoking (current)	20 (26.7%)	40 (11.0%)	<0.001
>65 years	**n = 126**	**n = 208**	
Age (yr)	72.2 (69.2-76.4)	74.1 (70.3-81.0)	0.002
Weight (kg)	64.7 (57.0-70.6)	63.7 (56.0-71.9)	0.736
Height (cm)	157.21 ± 6.3	156.7 ± 6.4	0.502
Depression (12-month)	12 (9.5%)	7 (3.4%)	0.019
Physical activity (active)	48 (45.7%)	78 (50.0%)	0.497
Alcohol consumption (current)	40 (38.1%)	69 (44.2%)	0.324
Smoking (current)	3 (5.3%)	3 (1.9%)	0.192

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y
Methods			
Study design	4	Present key elements of study design early in the paper	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Y
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Y
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Y*
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	Y
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y
		(*b*) Describe any methods used to examine subgroups and interactions	Y
		(*c*) Explain how missing data were addressed	Y
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Y
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y
		(b) Give reasons for non-participation at each stage	Y
		(c) Consider use of a flow diagram	N
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y
		(b) Indicate number of participants with missing data for each variable of interest	Y
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*Y*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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ABSTRACT

Objectives: High levels of disability, functional impairment and mortality are independently associated with both fracture and depression, however the relationship between fracture and depression is uncertain. The aim of this study was to investigate whether fracture is associated with subsequent depressive symptoms in a population-based sample of women.

Design: A study of age-matched fracture vs. non fracture cohorts of women

Setting: Barwon Statistical Division, South Eastern Australia.

Participants: Two samples of women aged ≥35yr were drawn from the Geelong Osteoporosis Study (GOS). The fracture cohort included women with incident fracture identified from radiology reports and the non-fracture cohort were randomly selected from the electoral roll during 1994-6.

Outcome measure: Symptoms of depression for women with and without fracture during the 12-month period 2000-1 were identified by self-report questionnaire based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria.

Results: A total of 296 women with fracture (12 hip, 48 vertebral, 91 wrist/forearm, 17 upper arm, 7 pelvis, 11 rib, 62 lower leg and 48 other fractures) and 590 women without fracture were included. Associations between fracture and depression differed between younger (≤65yr) and older (>65yr) women. Age and weight adjusted odds ratio for depression following fracture among younger women was 0.62 (0.35-1.11, p=0.12) and 3.33 (1.24-8.98, p=0.02) for older women. Further adjustment for lifestyle factors did not affect the results.

Conclusions: This study demonstrated that differences in mood status exist between older and younger women following fracture and that fracture is associated with increased depression in older women. Assessment of mood status in both the short and long term following fracture in the elderly seems justified, with early detection and treatment likely to result in improved outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, there are no published studies investigating post fracture depression among the younger, fracture sites other than the hip, or studies with longer follow up periods; these are all strengths of the current study.
- The time lag between fracture and depression measurement, an inability to provide pre-event psychiatric status and the use of a self-report instrument to determine depression are limitations.

BACKGROUND

Independently, depression and fracture are both increasingly prevalent public health concerns, particularly in women, and are associated with high levels of disability, functional impairment and early mortality. Depression is common and often persistent following a medical event, adversely affecting outcomes and prognosis by hindering adherence to treatment regimes and diminishing quality of life [1]. It is estimated that up to 20% of adults are affected by depression [2, 3], with over $644 million per annum spent on health system costs in Australia alone [4].

As a function of an ageing population, fracture rates and the associated burden are projected to rise substantially [5, 6]. It has been estimated that the lifetime risk of fracture lies within the range of 40% to 50% in women and 13% to 22% in men [7]. In 2000, the estimated number of fragility fractures worldwide was 9.0 million, of which 1.6 million were hip, 1.7 million forearm, and 1.4 million clinical vertebral fractures, with 61.0% occurring in women [8].

Declines in quality of life are typical following a fracture, regardless of the site of fracture, and impose substantial medical and social costs [9]. Furthermore, poorer psychological health has also been observed, with the associated declines in physical functioning, physical disability, and a loss of independence associated with fracture [10-12]. A review investigating outcomes following hip fracture concluded that post injury depressive symptoms are common and a strong predictor of poor recovery in the elderly [11].

It is likely that a bi-directional relationship between depression and fracture exists. Recently, depression has been shown to precede fracture, possibly influenced by medication use and biological and lifestyle factors dysregulated in depression [13]. Moreover, depression has been shown to be a common response to chronic medical conditions that can, in turn, impact on symptom burden and treatment adherence and increase the risk of complications [14]. Given the high prevalence of both depression and fracture in women, as well as the previously reported associations showing depression to precede fracture, the aim of this study was to investigate whether fracture is associated with subsequent depressive symptoms in a study of age-matched fracture *vs.* non-fracture cohorts. Understanding such an association is important in providing integrated and effective treatment.

METHODS

Participants

This study included women participating in the Geelong Osteoporosis Study (GOS), who were recruited from the Barwon Statistical Division (BSD) situated in south-eastern Australia to investigate the epidemiology of osteoporosis and fracture [15]. All participants gave written, informed consent, and the study was approved by the Human Research Ethics Committee at Barwon Health.

Fracture cohort

Women identified from radiological reports as having sustained an incident fracture between February 1994 to February 1996 (n = 1397), living in the BSD at the time of recruitment and aged 35 years and older were invited to participate in the fracture cohort of the GOS [16]. The process of fracture ascertainment from radiological reports has previously been validated [17]. A total of 1082 women were eligible for participation, with 77.4% accepting initial involvement (n=832). Those who participated in the 6-year follow up (n=439) were sent a depression questionnaire, with a total of 296 returned (67%) and thus included in this study (median age 63.0yr, range 35-87yr).

Non-Fracture cohort

Between 1994 and 1997 an age-stratified, random sample of women residing in the BSD was recruited from the Commonwealth electoral rolls. The initial group totalled 1494 women (median age 54yr, range 20-94yr), with a participation rate of 77.1% [18]. Those eligible to participate in the 6-year follow up (n=1275) were sent a depression questionnaire, with a total of 758 returned (60%). For this current study, 590 women aged 35 years and older (median age 59.3yr, range 35-91yr) were included.

Measurements

Outcome variable

Symptoms of depression during the 12-month period 2000-1 were identified using a self-report questionnaire based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [19]. An episode of major depression was defined as a depressed mood state and a loss of interest and pleasure in usual activity lasting for at least a two-week period. In addition, the presence of at least four symptoms including weight change, sleep disturbance, psychomotor changes, fatigue, feelings of worthlessness, poor concentration, and suicidal ideation had to be evident, accompanied by diminished physical performance determined to be causing distress or impairment in at least one domain of work, social or personal

functioning. The Cronbach's alpha co-efficient for determining internal reliability of the questionnaire was 0.895 [20].

Exposure variables

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Information on lifestyle and other health factors was obtained via self-report questionnaire. Women were classed as physically active if they participated in light to vigorous activity on a regular basis. Tobacco smoking was recognised if practised currently, and alcohol use recognised if average consumption exceeded two standard drinks per day.

Statistical Analyses

Statistical analyses were completed using Minitab (Version 15; Minitab, State College PA). Associations between fracture and depression differed for younger and older women; thus all analyses were stratified by age (≤65yr and >65 years). Differences in characteristics between those with fracture and those without fracture according to age group were compared using t-tests for continuous parametric data, Mann-Whitney for continuous non-parametric and chi-square analyses for categorical data. Logistic regression was used to determine the association between fracture and the likelihood of depressive symptoms among the younger (≤65yr) and older (>65) women. Age, anthropometry, physical activity, smoking and alcohol use were tested

in the models as potential confounders and/or effect modifiers. Values of $p<0{\cdot}05$ were considered as significant.

RESULTS

A total of 296 women with fracture (12 hip, 48 vertebral, 92 wrist/forearm, 17 upper arm, 7 pelvis, 12 rib, 64 lower leg and 48 other fractures) and 590 women without fracture were included in the analyses. Characteristics of the women with fracture *vs.* those without fracture according to age are shown in Table 1.

Younger women (≤65 years)

Among the younger women (n=552), there were no differences in weight, height, depression, physical activity or alcohol consumption between those with and those without fracture, however women with fracture were older and more likely to smoke (Table 1).

The association between fracture and depression among younger women was not significant. The unadjusted odds of having depression following fracture was 0.60 (95% CI 0.34-1.06, p=0.08) compared to those without fracture. Adjustment for age and weight did not affect the relationship (OR=0.62, 95% CI 0.35-1.11, p=0.12), nor did further adjustment for height, physical activity, smoking and alcohol consumption.

Older women (>65 years)

Among the older women (n=334), no differences in weight, height, physical activity, alcohol or smoking status were evident between those without or without fracture; however women with fracture were younger and more likely to have depression (Table 1).

The odds of having depression following fracture was three times greater (OR 3.02, 95% CI 1.16-7.89, p=0.02) for women with fracture compared to those without. Adjusting for age and weight did not affect the relationship (OR=3.33, 95% CI 1.24-8.98, p=0.02), which was also sustained after further adjustment for height, physical activity, smoking and alcohol consumption.

DISCUSSION

The findings from this study indicate an association between fracture and depression, although only among older women. Those aged >65 years were up to three-times more likely to have depression post fracture, while this relationship was not evident for younger women (≤65 years). These associations were independent of age, anthropometry, and lifestyle factors.

Our findings suggesting the risk of depression post fracture is increased among older women are consistent with findings from previous studies. Recently, several publications have explored health outcomes following hip fracture surgery and found depression to be common and to impact negatively on recovery up to two years post fracture [21-23]. A systematic review that investigated the prevalence of psychiatric illness in hip fracture patients found that the prevalence of depression following fracture ranged from 9% to 47% [24]; those rates being somewhat higher than community rates. Similarly, the prevalence of depressive symptoms in postmenopausal women with osteoporosis was reported to be greater for women who also had prevalent vertebral fractures compared to those without [25]. Both depressive symptoms following fracture and pre-injury mood state have been shown to be predictive of recovery in the elderly, while a failure to regain pre-injury functional and ability levels increases the possibility of persistent depressive symptomatology [10, 26]. In a prospective cohort study of 240 older participants, those who experienced high levels of depressive symptoms prior to a medical event (hip fracture, stroke and heart attack), had a poorer likelihood of recovery in

activities of daily living [27]. Lastly, a recent study using a cultural models approach to understand how older women viewed osteoporosis reported that experiencing a fracture coincided with the acknowledgement of 'getting older' [28], thus we may expect a fracture to increase the likelihood of depression for some older women. It is plausible that stigma may be associated with a fracture in older age [28], and thus impact negatively on an older woman's self-identity. Taken in context, although a lower prevalence of depression overall has been reported among older women [3], the occurrence of a fracture may enhance the susceptibility to depression for a variety of reasons.

Our findings suggest no relationship between fracture and later depression among younger women. It is plausible that the causal pathway to fracture may differ across age groups, resulting in differing effects on psychological and physical outcomes. For instance, an internal locus of control (the belief one can control one's own life), high self-esteem, hope, acceptance, optimism, and a sense of mastery have all been associated with resilience or the ability to maintain or regain mental health following adversity [29]. Furthermore, differences in pre-morbid emotional and cognitive state may have existed between the younger and older women prior to fracture. This is an important factor, as high positive affect and motivation has been observed as increasing the chances of returning to pre-morbid levels of functioning after a major health event [27]. Lastly, compared to older women, younger women may have more access to social networks on which they can draw on for support, be less likely to remain homebound post-fracture, and be able to fulfil ongoing work and social commitments during recovery [30-32].

Some methodological issues should be considered when interpreting the study findings. The time lag between fracture and depression measurement and an inability to provide pre-event psychiatric status is a limitation and it has to be taken into consideration that depression is a long-term, recurrent disorder in most individuals [33]. Thus, it is likely that depression preceded fracture in at least some of the women. The use of a self-report instrument, rather than a clinical diagnostic interview must also be acknowledged, also sensitivity and specificity of this scale was not determined. Response bias may also have influenced the findings, with higher rates of psychopathology and other co-morbid conditions possibly present in the population declining participation. Last, as with all observational studies, our results could be biased by unrecognised confounders and may not be generalizable to other populations of women, men, or those with other medical conditions. To our knowledge, there are no published studies investigating post fracture depression among the younger, fracture sites other than the hip, or studies with longer follow up periods; these are all strengths of the current study.

CONCLUSION

In conclusion, this study demonstrated that differences in mood status exist between older and younger women following fracture and that fracture is associated with increased depression in older women. Assessment of mood status in both the short- and long-term following fracture in the elderly seems justified, with early detection and treatment of elevated levels of depression likely to result in improved outcomes.

Further research investigating a causal link between fracture and depression is warranted and is currently underway.

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AUTHORS' CONTRIBUTIONS

LJW took part in the conception and design of the study, data cleaning, statistical analysis, interpretation of the data and took primary responsibility for writing the manuscript. MB and SLB took part in the interpretation of data and critically revised the manuscript. MH and ALS took part in the conception and design of the study, statistical analysis, interpretation of the data and critically revised the manuscript. FNJ took part in the conception and design of the study, acquisition of the data and critically revised the manuscript. JAP took part in the conception and design of the study, interpretation of the analysis and critically revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

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Margaret Henry and Amanda Stuart have no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Data Sharing Statement

No additional data

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Table 1: Characteristics of the fracture vs. non-fracture cohorts according to age (≤65yr and >65 years). Values are given as median (interquartile range), mean (± standard deviation) or n (%).

	Women with fracture	Women with no fracture	p-values
≤65 years	**n = 170**	**n = 382**	
Age (yr)	54.0 (45.0-60.2)	50.6 (43.2-58.5)	0.019
Weight (kg)	69.1 (61.4-78.4)	67.6 (60.1-79.0)	0.386
Height (cm)	162.2 ± 6.5	161.9 ± 5.9	0.619
Depression (12-month)	17 (10.0%)	60 (15.7%)	0.074
Physical activity (active)	117 (79.6%)	275 (75.6%)	0.328
Alcohol consumption (current)	77 (52.4%)	198 (54.4%)	0.679
Smoking (current)	20 (26.7%)	40 (11.0%)	<0.001
>65 years	**n = 126**	**n = 208**	
Age (yr)	72.2 (69.2-76.4)	74.1 (70.3-81.0)	0.002
Weight (kg)	64.7 (57.0-70.6)	63.7 (56.0-71.9)	0.736
Height (cm)	157.21 ± 6.3	156.7 ± 6.4	0.502
Depression (12-month)	12 (9.5%)	7 (3.4%)	0.019
Physical activity (active)	48 (45.7%)	78 (50.0%)	0.497
Alcohol consumption (current)	40 (38.1%)	69 (44.2%)	0.324
Smoking (current)	3 (5.3%)	3 (1.9%)	0.192

DEPRESSION FOLLOWING FRACTURE IN WOMEN: A STUDY OF AGE-MATCHED COHORTS

Running title: Depression following fracture in women

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functioning. The Cronbach's alpha co-efficient for determining internal reliability of the questionnaire was 0.895 [20].

Exposure variables

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Information on lifestyle and other health factors was obtained via self-report questionnaire. Women were classed as physically active if they participated in light to vigorous activity on a regular basis. Tobacco smoking was recognised if practised currently, and alcohol use recognised if average consumption exceeded two standard drinks per day.

Statistical Analyses

Statistical analyses were completed using Minitab (Version 15; Minitab, State College PA). Associations between fracture and depression differed for younger and older women; thus all analyses were stratified by age (≤65yr and >65 years). Differences in characteristics between those with fracture and those without fracture according to age group were compared using t-tests for continuous parametric data, Mann-Whitney for continuous non-parametric and chi-square analyses for categorical data. Logistic regression was used to determine the association between fracture and the likelihood of depressive symptoms among the younger (≤65yr) and older (>65) women. Age, anthropometry, physical activity, smoking and alcohol use were tested

in the models as potential confounders and/or effect modifiers. Values of $p<0{\cdot}05$ were considered as significant.

RESULTS

A total of 296 women with fracture (12 hip, 48 vertebral, 92 wrist/forearm, 17 upper arm, 7 pelvis, 12 rib, 64 lower leg and 48 other fractures) and 590 women without fracture were included in the analyses. Characteristics of the women with fracture *vs.* those without fracture according to age are shown in Table 1.

Younger women (≤65 years)

Among the younger women (n=552), there were no differences in weight, height, depression, physical activity or alcohol consumption between those with and those without fracture, however women with fracture were older and more likely to smoke (Table 1).

The association between fracture and depression among younger women was not significant. The unadjusted odds of having depression following fracture was 0.60 (95% CI 0.34-1.06, p=0.08) compared to those without fracture. Adjustment for age and weight did not affect the relationship (OR=0.62, 95% CI 0.35-1.11, p=0.12), nor did further adjustment for height, physical activity, smoking and alcohol consumption.

Older women (>65 years)

Among the older women (n=334), no differences in weight, height, physical activity, alcohol or smoking status were evident between those without or without fracture; however women with fracture were younger and more likely to have depression (Table 1).

The odds of having depression following fracture was three times greater (OR 3.02, 95% CI 1.16-7.89, p=0.02) for women with fracture compared to those without. Adjusting for age and weight did not affect the relationship (OR=3.33, 95% CI 1.24-8.98, p=0.02), which was also sustained after further adjustment for height, physical activity, smoking and alcohol consumption.

DISCUSSION

The findings from this study indicate an association between fracture and depression, although only among older women. Those aged >65 years were up to three-times more likely to have depression post fracture, while this relationship was not evident for younger women (≤65 years). These associations were independent of age, anthropometry, and lifestyle factors.

Our findings suggesting the risk of depression post fracture is increased among older women are consistent with findings from previous studies. Recently, several publications have explored health outcomes following hip fracture surgery and found depression to be common and to impact negatively on recovery up to two years post fracture [21-23]. A systematic review that investigated the prevalence of psychiatric illness in hip fracture patients found that the prevalence of depression following fracture ranged from 9% to 47% [24]; those rates being somewhat higher than community rates. Similarly, the prevalence of depressive symptoms in postmenopausal women with osteoporosis was reported to be greater for women who also had prevalent vertebral fractures compared to those without [25]. Both depressive symptoms following fracture and pre-injury mood state have been shown to be predictive of recovery in the elderly, while a failure to regain pre-injury functional and ability levels increases the possibility of persistent depressive symptomatology [10, 26]. In a prospective cohort study of 240 older participants, those who experienced high levels of depressive symptoms prior to a medical event (hip fracture, stroke and heart attack), had a poorer likelihood of recovery in

activities of daily living [27]. Lastly, a recent study using a cultural models approach to understand how older women viewed osteoporosis reported that experiencing a fracture coincided with the acknowledgement of 'getting older' [28], thus we may expect a fracture to increase the likelihood of depression for some older women. It is plausible that stigma may be associated with a fracture in older age [28], and thus impact negatively on an older woman's self-identity. Taken in context, although a lower prevalence of depression overall has been reported among older women [3], the occurrence of a fracture may enhance the susceptibility to depression for a variety of reasons.

Our findings suggest no relationship between fracture and later depression among younger women. It is plausible that the causal pathway to fracture may differ across age groups, resulting in differing effects on psychological and physical outcomes. For instance, an internal locus of control (the belief one can control one's own life), high self-esteem, hope, acceptance, optimism, and a sense of mastery have all been associated with resilience or the ability to maintain or regain mental health following adversity [29]. Furthermore, differences in pre-morbid emotional and cognitive state may have existed between the younger and older women prior to fracture. This is an important factor, as high positive affect and motivation has been observed as increasing the chances of returning to pre-morbid levels of functioning after a major health event [27]. Lastly, compared to older women, younger women may have more access to social networks on which they can draw on for support, be less likely to remain homebound post-fracture, and be able to fulfil ongoing work and social commitments during recovery [30-32].

Some methodological issues should be considered when interpreting the study findings. The time lag between fracture and depression measurement and an inability to provide pre-event psychiatric status is a limitation and it has to be taken into consideration that depression is a long-term, recurrent disorder in most individuals [33]. Thus, it is likely that depression preceded fracture in at least some of the women. The use of a self-report instrument, rather than a clinical diagnostic interview must also be acknowledged, also sensitivity and specificity of this scale was not determined. Response bias may also have influenced the findings, with higher rates of psychopathology and other co-morbid conditions possibly present in the population declining participation. Last, as with all observational studies, our results could be biased by unrecognised confounders and may not be generalizable to other populations of women, men, or those with other medical conditions. To our knowledge, there are no published studies investigating post fracture depression among the younger, fracture sites other than the hip, or studies with longer follow up periods; these are all strengths of the current study.

CONCLUSION

In conclusion, this study demonstrated that differences in mood status exist between older and younger women following fracture and that fracture is associated with increased depression in older women. Assessment of mood status in both the short- and long-term following fracture in the elderly seems justified, with early detection and treatment of elevated levels of depression likely to result in improved outcomes.

Further research investigating a causal link between fracture and depression is warranted and is currently underway.

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AUTHORS' CONTRIBUTIONS

LJW took part in the conception and design of the study, data cleaning, statistical analysis, interpretation of the data and took primary responsibility for writing the manuscript. MB and SLB took part in the interpretation of data and critically revised the manuscript. MH and ALS took part in the conception and design of the study, statistical analysis, interpretation of the data and critically revised the manuscript.

FNJ took part in the conception and design of the study, acquisition of the data and critically revised the manuscript. JAP took part in the conception and design of the study, interpretation of the analysis and critically revised the manuscript. All authors read and approved the final manuscript.

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Table 1: Characteristics of the fracture vs. non-fracture cohorts according to age (≤65yr and >65 years). Values are given as median (interquartile range), mean (± standard deviation) or n (%).

	Women with fracture	Women with no fracture	p-values
≤65 years	**n = 170**	**n = 382**	
Age (yr)	54.0 (45.0-60.2)	50.6 (43.2-58.5)	0.019
Weight (kg)	69.1 (61.4-78.4)	67.6 (60.1-79.0)	0.386
Height (cm)	162.2 ± 6.5	161.9 ± 5.9	0.619
Depression (12-month)	17 (10.0%)	60 (15.7%)	0.074
Physical activity (active)	117 (79.6%)	275 (75.6%)	0.328
Alcohol consumption (current)	77 (52.4%)	198 (54.4%)	0.679
Smoking (current)	20 (26.7%)	40 (11.0%)	<0.001
>65 years	**n = 126**	**n = 208**	
Age (yr)	72.2 (69.2-76.4)	74.1 (70.3-81.0)	0.002
Weight (kg)	64.7 (57.0-70.6)	63.7 (56.0-71.9)	0.736
Height (cm)	157.21 ± 6.3	156.7 ± 6.4	0.502
Depression (12-month)	12 (9.5%)	7 (3.4%)	0.019
Physical activity (active)	48 (45.7%)	78 (50.0%)	0.497
Alcohol consumption (current)	40 (38.1%)	69 (44.2%)	0.324
Smoking (current)	3 (5.3%)	3 (1.9%)	0.192

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y
Methods			
Study design	4	Present key elements of study design early in the paper	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Y
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Y
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Y*
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	Y
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y
		(*b*) Describe any methods used to examine subgroups and interactions	Y
		(*c*) Explain how missing data were addressed	Y
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Y
		(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y
		(b) Give reasons for non-participation at each stage	Y
		(c) Consider use of a flow diagram	N
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y
		(b) Indicate number of participants with missing data for each variable of interest	Y
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*Y*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.