PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome in Patients with Clinical Vertebral Fracture: A Nationwide Population-based Cohort Study in Taiwan
AUTHORS	Lee, Feng-You; Chen, Wei-Kung; Lin, Cheng-Li; Kao, Chia-Hung; Yang, Tse-Yen; Lai, Ching-Yuan

VERSION 1 – REVIEW

REVIEWER	Joonghee Kim Seoul National University Bundang Hospital
REVIEW RETURNED	08-May-2019

GENERAL COMMENTS	I thank the editors and authors for giving me an opportunity to review an interesting paper. General comments: The study is about the association between vertebral fracture event and cardiopulmonary events including aortic dissection, CHF, pneumonia and ARDS. My major concern is on how the claim data was processed to build the analytical dataset. I would appreciate more clear definitions and acceptable level of efforts to deal with the issues raised below. I also suggest authors to re-process and re-analyze the raw data if it is required. Introduction Appropriately done. The association between vertebral fracture and pneumonia has already been reported by me an my colleagues. Please consider to include it in the reference. - Risk of Pneumonia After Vertebral Compression Fracture in Women with Low Bone Density: a Population Based Study, Spine, 2017 Methods #1. How did you define 'newly diagnosed'? Please specify its operational definition (both for exposure and outcome events). #2. Please include a table summarizing the ICD-9 codes and their matching disease names as a supplemental table. In addition, it is required to be presented which criteria you used, for example, 1) there are principal and secondary diagnoses, 2) how many times an ICD group should appear to meet the criteria, 3) the duration of pre-enroll time used to define a comorbidity. #3. Were the ICD-9 criteria used for the definition of chronic conditions validated or commonly used by others? If so please add references.

	#4. "age every 5-year span" -> please specify. #5. Can you be sure that the exposure and the outcome events are not the same event? For example, a young man had a car accident and got a diagnosis of spine fracture in a hospital and then was transferred to another hospital where he got a new diagnosis of (traumatic) aortic dissection. How did you handle this issue? #6. There is no mention about how you checked the proportionality assumption and model fit of Cox regression models. Results #7. Risk of the outcome events is much higher in younger patients and those without comorbidities. This is counter-intuitive as a harmful exposure has more severe impact on the unhealthy persons. This may suggest the injury was more severe in the healthier patients. This is plausible because vertebral fracture in young/healthy population is not common unless the injury is severe. In addition, please analyze the interaction between the exposure and the age/comorbidity(possible using CCI?) variables. #8. Please be sure to check and report the validity of the proportionality assumption, because I suspect some violation of the assumption in the plots. I believe the effect size of VCF exposure should be disproportionately high in earlier period. If there is any violation you can use extended Cox model. https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf #9. The lack of the injury severity scale is somewhat critical. You can calculate ICD-based injury serverity score. Or you can just use cases with isolated vertebral fracture. If it is impossible, it should be clearly discussed as a major limitation of the study in a separate paragraph. Discussion I want to review the discussion part after the issues I mentioned above are resolved.

REVIEWER	Joshua Lewis Edith Cowan University, Australia
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	The manuscript by Lee and colleagues entitled “Risk of Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome in Patients with Vertebral Fracture: A Nationwide Population based Cohort Study” describes an association between vertebral column fractures with increased risk of cardiopulmonary diseases, including aortic dissection, congestive heart failure, pneumonia, and acute respiratory distress syndrome in a very large case-control study. The manuscript results are of interest, however there are a number of concerns that limit my enthusiasm for the manuscript in its present form. Primarily, the manuscripts introduction and discussion ignore the wealth of genetic and epidemiological data demonstrating osteoporosis and fracture are associated cardiopulmonary data albeit mostly with cardiovascular disease and vice versa, e.g. Sennerby, Ulf, et al. "Cardiovascular diseases and risk of hip fracture." Jama 302.15 (2009) 1666-1673; Veronese, Nicola, et al. "Relationship between low bone mineral density and fractures with incident cardiovascular disease: a systematic review and meta-analysis." Journal of Bone and Mineral Research 32.5 (2017):

	1126-1135. Additionally there is also extensive mechanistic data and studies, again not mentioned by the authors, e.g. Thompson, Bithika, and Dwight A. Towler. "Arterial calcification and bone physiology: role of the bone–vascular axis." Nature Reviews Endocrinology 8.9 (2012): 529. The association with aortic dissection and CHF may be due to the strong relationship between abdominal aortic calcification and vertebral fractures (Szulc, Pawel. "Abdominal aortic calcification: a reappraisal of epidemiological and pathophysiological data." Bone 84 (2016): 25-37). Again this was not mentioned by the authors. Finally, as mentioned by the authors the association with pulmonary diseases has been shown previously and is likely due to restrictive thoracic changes as a consequence of vertebral fractures. These aspects should be discussed in much more detail and describing the novel aspects such as the Taiwanese population and the strengths (being able to give more precise estimates of the strength of the association). Secondly, because there is so much of the published data left out the rationale for the study is not well developed. It is unclear how these outcomes were selected and the rationale for selecting these outcomes rather than other cardiopulmonary outcomes that have previously been associated with vertebral fractures e.g. CVD and COPD? Was this a priori? From the description it appears as though this was a case-control study. If so this should be made clear in the title, abstract etc. Clinical vertebral fracture rather than vertebral column fracture may be easier for the readers as VCFs can be either clinical or asymptomatic vertebral fractures. Minor 1. Abstract should have confidence intervals for the HRs 2. Two different fonts in Table 1. 3. The authors state “According to recent studies, the prevalence of women older than 50 years who experienced at least one VCF event was 23% - 26%, which was higher than that of men (21.5%). However the studies referenced are prevalence’s based on vertebral deformities rather than clinical vertebral fractures. 4. Number of decimal places varies in Table 1. 5. Page 11 line 42 “The relative risk of AD was higher in the VCF cohort than in the non-VCF cohort for patients without comorbidities (aHR = 1.44, 95% CI = 1.18–1.76). In all stratifications” should read relative hazard or aHR was higher.

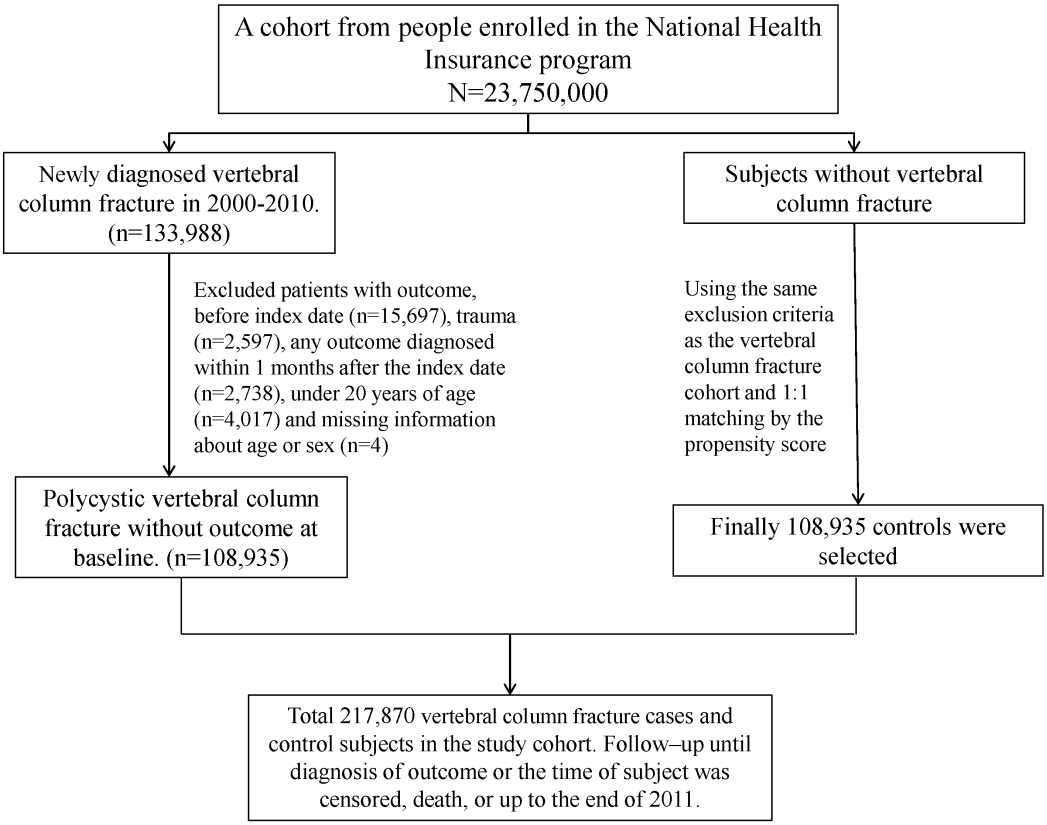
REVIEWER	Pawel Szulc INSERM UMR 1033, University of Lyon, Lyon, France
REVIEW RETURNED	27-May-2019

GENERAL COMMENTS	This study assesses the association between vertebral fractures and the risk of cardiovascular and pulmonary complications. 1. I suggest the Authors should use the more traditional term “vertebral fracture”. 2. The term “newly diagnosed vertebral fracture” is not clear. It may be a clinical vertebral fracture (sudden backache most frequently after a minor trauma + vertebral fracture on the radiography) or simply the moment of the diagnosis of vertebral fracture which may have occurred much earlier. It should be clarified.

	3. Table 3 – the term “Non-Vertebral column fracture” is misleading and should be replaced, e.g. “No vertebral fracture”. This “Non-vertebral” suggests implicitly that the controls had non-vertebral fracture, i.e. peripheral fractures. 4. Are cardiovascular diseases really more frequent in women than in men? Please, provide a reference. 5. An interesting finding of this study is that the association between the investigated diseases is found even before the age of 50. This point should be discussed. 6. I agree with the Authors that some controls could have vertebral fractures which were not diagnosed. The Authors should add a comment that such bias could underestimate the associations. 7. One limitation is unavoidable in such studies and should be signaled. Different criteria for the diagnosis of vertebral fracture could be used in different hospitals. It is not sure whether the same criteria were used for the diagnosis of cardiovascular diseases in various hospitals.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
My major concern is on how the claim data was processed to build the analytical dataset. I would appreciate more clear definitions and acceptable level of efforts to deal with the issues raised below. I also suggest authors to re-process and re-analyze the raw data if it is required.
Reply: Thanks a lot for your comment. The attached flow chart below (the new Figure 1) shows the selection process of the study participants:



The association between vertebral fracture and pneumonia has already been reported by me and my colleagues. Please consider to include it in the reference.
- Risk of Pneumonia After Vertebral Compression Fracture in Women with Low Bone Density: a Population Based Study, Spine, 2017
Reply: Thanks a lot for your precious comment. We have included this work in our references and made some revision in the section of introduction and discussion as follows:
"Recently, Kim et al.[22] reported an association between isolated VCF and future development of pneumonia in women with low bone density."
"Finally, similar to rib fractures, worsening pain related to VCF might impair cough and secretion clearance, leading to atelectasis and subsequent lung infection[22]."
"22. Kim B, Kim J, Jo YH, et al. Risk of Pneumonia After Vertebral Compression Fracture in Women With Low Bone Density: A Population-Based Study. Spine (Phila Pa 1976) 2018;43(14):E830-E35. doi: 10.1097/BRS.0000000000002536"

How did you define 'newly diagnosed'? Please specify its operational definition (both for exposure and outcome events).
Reply: Thanks for your comment. Study subjects with the diagnosis of vertebral fracture from 1996-1999 were excluded at the baseline to begin the identification of patients with vertebral fracture newly diagnosed from 2000-2010. Therefore, most of prevalent cases of vertebral fracture were not likely to be included in the study cohort.
In addition, we excluded patients with a diagnosis of AD (ICD-9-CM codes, 441.0, 441.00, 441.01, 441.02, and 441.03), CHF (ICD-9-CM code, 428), pneumonia (ICD-9-CM codes, 480-488), and ARDS (ICD-9-CM codes, 518.82 and 518.5) before 1999 and before the index date, and any outcome (AD, CHF, pneumonia, ARDS events) diagnosed within 1 months after the index date.

Please include a table summarizing the ICD-9 codes and their matching disease names as a supplemental table.
Reply: Thanks for your comment. We have provided the supplementary table that summarizes all ICD-9-CM codes used in this study and the corresponding diseases.

Diseases	ICD-9-CM codes
Clinical vertebral fracture (CVF)	805, 806
Cervical spine CVF	805.0-805.18, 806.0-806.19
Thoracic spine CVF	805.2, 805.3, 806.2-806.39
Lumbar spine CVF	805.4, 805.5, 806.4, 806.5
Sacrum plus coccyx CVF	805.6, 805.7, 806.6-806.79
CVF without spinal cord injury (SCI)	805-805.9
CVF with spinal cord injury (SCI)	806-806.9
Aortic dissection (AD)	441.0, 441.00, 441.01, 441.02, 441.03
Congestive heart failure (CHF)	428
Pneumonia	480-488
Acute respiratory distress syndrome (ARDS)	518.82, 518.5
Comorbidities	
Hypertension	401–405
Diabetes mellitus	250
Hyperlipidemia	272
Atrial fibrillation	427.31
Chronic kidney disease	580-589
Chronic obstructive pulmonary disease	491,492,496

In addition, it is required to be presented which criteria you used, for example, 1) there are principal and secondary diagnoses, 2) how many times an ICD group should appear to meet the criteria, 3) the duration of pre-enroll time used to define a comorbidity.
Reply: Thanks for your directions. In our study, coexisting comorbidities were identified before the index date, with at least one time of principal or secondary diagnoses documented in hospitalizations during the period 2000 to 2010. We have mentioned this in the section of sampled participants.

Were the ICD-9 criteria used for the definition of chronic conditions validated or commonly used by others? If so please add references.
Reply: Thanks for your precious comments. ICD-9 coding for cardiovascular disease definition was validated in previous studies and commonly used in many published retrospective studies. We have included these works in our references and revised the section of “Data Source” as follows:
“Validation of the NHIRD with cardiovascular diseases were investigated and appeared to be a valid resource for population research[32-35]”.
Referrences:
25. Peng YC, Lin CL, Yeh HZ, et al. Diverticular disease and additional comorbidities associated with increased risk of dementia. J Gastroenterol Hepatol 2016;31(11):1816-22. doi: 10.1111/jgh.13389
26. Chen YT, Su JS, Tseng CW, et al. Inflammatory bowel disease on the risk of acute pancreatitis: A population-based cohort study. J Gastroenterol Hepatol 2016;31(4):782-7. doi: 10.1111/jgh.13171
27. Lee CH, Hsu WC, Ko JY, et al. Trends in the management of peritonsillar abscess in children: A nationwide population-based study in Taiwan. Int J Pediatr Otorhinolaryngol 2019;125:32-37. doi: 10.1016/j.ijporl.2019.06.016
28. Su JA, Chang CC, Wang HM, et al. Antidepressant treatment and mortality risk in patients with dementia and depression: a nationwide population cohort study in Taiwan. Ther Adv Chronic Dis 2019;10:2040622319853719. doi: 10.1177/2040622319853719
29. Hong WJ, Chen W, Yeo KJ, et al. Increased risk of osteoporotic vertebral fracture in rheumatoid arthritis patients with new-onset cardiovascular diseases: a retrospective nationwide cohort study in Taiwan. Osteoporos Int 2019 doi: 10.1007/s00198-019-04966-z
30. Huang KL, Yeh CC, Wu SI, et al. Risk of Dementia Among Individuals With Psoriasis: A Nationwide Population-Based Cohort Study in Taiwan. J Clin Psychiatry 2019;80(3) doi: 10.4088/JCP.18m12462
31. Lin CE, Chung CH, Chen LF, et al. Risk of incident hypertension, diabetes, and dyslipidemia after first posttraumatic stress disorder diagnosis: A nationwide cohort study in Taiwan. General hospital psychiatry 2019;58:59-66. doi: 10.1016/j.genhosppsych.2019.03.004
32. Cheng CL, Chien HC, Lee CH, et al. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. International journal of cardiology 2015;201:96-101. doi: 10.1016/j.ijcard.2015.07.075
33. Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 2011;20(3):236-42. doi: 10.1002/pds.2087
34. Cheng CL, Lee CH, Chen PS, et al. Validation of acute myocardial infarction cases in the national health insurance research database in taiwan. J Epidemiol 2014;24(6):500-7. doi: 10.2188/jea.je20140076
35. Ho TW, Ruan SY, Huang CT, et al. Validity of ICD9-CM codes to diagnose chronic obstructive pulmonary disease from National Health Insurance claim data in Taiwan. Int J Chron Obstruct Pulmon Dis 2018;13:3055-63. doi: 10.2147/COPD.S174265

"age every 5-year span" -> please specify.
Reply: Thanks for your comment. Participants in each year stratum were further stratified by age in 5-year span: 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 and 65+ years. Based on the specific range of age of each vertebral fracture case, one comparison subjects were selected from non-vertebral fracture subjects with the appropriate age span.

Can you be sure that the exposure and the outcome events are not the same event? For example, a young man had a car accident and got a diagnosis of spine fracture in a hospital and then was transferred to another hospital where he got a new diagnosis of (traumatic) aortic dissection. How did you handle this issue?
Reply: Thanks for your precious comment. We have excluded participants with a diagnosis of AD (ICD-9-CM codes, 441.0, 441.00, 441.01, 441.02, and 441.03), CHF (ICD-9-CM code, 428), pneumonia (ICD-9-CM codes, 480-488), and ARDS (ICD-9-CM codes, 518.82 and 518.5) before 1999 and before the index date, and also, any outcome diagnosed within 1 months after the index date. We consider this process can help excluding the condition mentioned above.

There is no mention about how you checked the proportionality assumption and model fit of Cox regression models.
Reply: Thank so much for your comments. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals.

Results showed that there was no significant relationship between Schoenfeld residuals for VCF and follow-up time (p-value = 0.06) in the model evaluating the aortic dissection risk and Schoenfeld residuals for VCF and follow-up time (p-value = 0.18) in the model evaluating the acute respiratory distress syndrome risk. In the model evaluating the congestive heart failure and pneumonia risk throughout overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for VCF and follow-up time, suggesting the proportionality assumption was violated. In the subsequent analyses, we stratified the follow-up duration to deal with the violation of proportional hazard assumption in the revised table 2.

Risk of the outcome events is much higher in younger patients and those without comorbidities. This is counter-intuitive as a harmful exposure has more severe impact on the unhealthy persons. This may suggest the injury was more severe in the healthier patients. This is plausible because vertebral fracture in young/healthy population is not common unless the injury is severe. In addition, please analyze the interaction between the exposure and the age/comorbidity (possible using CCI?) variables.
Reply: Thank you for your comments. We have added interaction between the exposure and the age and the comorbidity in the revised Table 2. The comorbidities included comorbidities of CCI score, hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD, which were incorporated into the multivariable analysis on the risk of outcome between VF patients and non-VF cohort.

Please be sure to check and report the validity of the proportionality assumption, because I suspect some violation of the assumption in the plots. I believe the effect size of VCF exposure should be disproportionately high in earlier period. If there is any violation you can use extended Cox model. https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf
Reply: Thank so much for your comments. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. Results showed that there was no significant relationship between Schoenfeld residuals for CVF and follow-up time (p-value = 0.06) in the model evaluating the aortic dissection risk and Schoenfeld residuals for CVF and follow-up time (p-value = 0.18) in the model evaluating the acute respiratory distress syndrome risk. In the model evaluating the congestive heart failure and pneumonia risk throughout overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for CVF and follow-up time, suggesting the proportionality assumption was violated. In the subsequent analyses, we stratified the follow-up duration to deal with the violation of proportional hazard assumption in the revised table 2. Further analysis of the extended Cox models with time-dependent terms showed similar results for pneumonia, indicating that the strength of the association reduced over time (HR [p value], for CVF, 1.41 [p<0.001]; for interaction term of CVF and time, 0.98 [p<0.001]). Further analysis of the extended Cox models with time-dependent terms shows results for congestive heart failure, indicating that interaction term of CVF and time was not significant, 1.01 [p=0.36].

The lack of the injury severity scale is somewhat critical. You can calculate ICD-based injury serverity score. Or you can just use cases with isolated vertebral fracture. If it is impossible, it should be clearly discussed as a major limitation of the study in a separate paragraph.
Reply: Thanks so much. To address the concern that injury severity could be a crucial confounding factor to outcome events, we conducted a re-analysis by excluding trauma codes of all other systems (ICD-9-CM 800-959, except vertebral trauma 805, 806) to achieve “isolated vertebral fracture”.

Reviewer: 2
Primarily, the manuscripts introduction and discussion ignore the wealth of genetic and epidemiological data demonstrating osteoporosis and fracture are associated cardiopulmonary data albeit mostly with cardiovascular disease and vice versa, e.g. Sennerby, Ulf, et al. "Cardiovascular diseases and risk of hip fracture." Jama 302.15 (2009) 1666-1673; Veronese, Nicola, et al. "Relationship between low bone mineral density and fractures with incident cardiovascular disease: a systematic review and meta-analysis." Journal of Bone and Mineral Research 32.5 (2017): 1126-1135. Additionally there is also extensive mechanistic data and studies, again not mentioned by the authors, e.g. Thompson, Bithika, and Dwight A. Towler. "Arterial calcification and bone physiology: role of the bone–vascular axis." Nature Reviews Endocrinology 8.9 (2012): 529. The association with aortic dissection and CHF may be due to the strong relationship between abdominal aortic calcification and vertebral fractures (Szulc, Pawel. "Abdominal aortic calcification: a reappraisal of

epidemiological and pathophysiological data." Bone 84 (2016): 25-37). Again this was not mentioned by the authors.
Reply: Thanks a lot for your precious directions. We have revised the discussion and included the relevant references as follows:
"Sennerby et al.[51] proposed that specific genes involved in cellular mechanisms that shared by the vasculature and bone might explain the close relationship between cardiovascular diseases and fractures."
"In a meta-analysis, Veronese et al.[56] provided evidence that low bone mineral density and fractures were modestly associated with increased risk of cardiovascular diseases. The authors speculated that alterations in signaling pathways of bone remodeling and arterial calcifications, low-grade inflammation, higher prevalence of vascular calcifications, and low estrogen levels could all contributed to the higher cardiovascular risk."
"Interestingly, prior studies have provided evidence for the strong correlation between abdominal aortic calcifications and poor bone health with major fragility fracture[47 48]. With the progressive destruction of intima-media layer accompanied with new bone-like tissue deposition in the aortic wall, aneurysm or dissection might tend to occur."
"Indeed, diffuse vascular calcifications which is strongly associated with bone loss, including abdominal aorta and coronary arteries, could result in a higher afterload on the left ventricle, leading to subsequent left ventricular hypertrophy and finally, congestive heart failure[47 48]."

Finally, as mentioned by the authors the association with pulmonary diseases has been shown previously and is likely due to restrictive thoracic changes as a consequence of vertebral fractures. These aspects should be discussed in much more detail and describing the novel aspects such as the Taiwanese population and the strengths (being able to give more precise estimates of the strength of the association).
Reply: Thanks for your precious directions. We have tried our best searching for any native research focusing on this issue and Taiwanese population, but the literature is scarce. Therefore, we have included other relative literatures and revised the content of the section in discussion as follows:
"Harrison et al.[67] conducted a systemic review of 4 case-control studies and reported that women with osteoporotic vertebral fractures or kyphosis were associated with decreased predicted vital capacity, as well as total lung capacity. Furthermore, Krege et al.[68] estimated that spine fracture burden was correlated with reduced lung volume, but not flow; indicating that spine fracture burden is linked with restrictive, but not obstructive lung disease. The authors further concluded that patients with marginally compensated pulmonary function may not tolerate the superimposed lung restrictive change resulting from vertebral fractures and thus, leading to a further compromised pulmonary function and subsequent lung diseases."

Secondly, because there is so much of the published data left out the rationale for the study is not well developed. It is unclear how these outcomes were selected and the rationale for selecting these outcomes rather than other cardiopulmonary outcomes that have previously been associated with vertebral fractures e.g. CVD and COPD? Was this a priori?
Reply: Thanks for your precious comments. The development of our research question includes outcome events selection was originally based on the clinical experience in the ED that we observed a considerable proportion of patients with backache related to vertebral fractures concomitantly presented with high blood pressure, palpitations(arrhythmias), stressful feeling, low physical activities and poor ability of expectoration, which all were considered crucial risk factors for cardiopulmonary diseases. Prior studies have demonstrated the close relationship between osteoporotic vertebral fractures in the elderly and coronary heart disease and, stroke, as we mentioned in the section of introduction. Therefore, we selected other most prevailing cardiopulmonary diseases that commonly encountered in the ED include aortic dissection, heart failure, pneumonia and ARDS for further analysis.

From the description it appears as though this was a case-control study. If so this should be made clear in the title, abstract etc.
Reply: Thanks for your comment. In our study design, we identified adult patients with newly diagnosed vertebral fracture from January 1, 2000, to December 31, 2010 as a study cohort, and frequency matched by the comparison cohort that comprised adult patients without vertebral fracture. The two cohorts were followed and traced until the outcome events (AD, CHF, pneumonia, ARDS) appeared or they were censored because of loss to follow-up, death, or the end of December 31, 2011, and we could calculate the relative hazard of outcome events. For the above reasons, we

modestly consider this work to be a retrospective matched cohort study (Szklo, M. Population-based cohort studies. Epidemiologic reviews, 1998; 20:81-90.).

Clinical vertebral fracture rather than vertebral column fracture may be easier for the readers as VCFs can be either clinical or asymptomatic vertebral fractures.
Reply: Thanks for your precious comment. We have replaced all the words “VCF (vertebral column fracture)” with “CVF (clinical vertebral fracture)” throughout the whole work.

Abstract should have confidence intervals for the HRs
Reply: Thanks for your comment. We have corrected it.

Two different fonts in Table 1.
Reply: Thanks for your comment. We have corrected it.

The authors state “According to recent studies, the prevalence of women older than 50 years who experienced at least one VCF event was 23% - 26%, which was higher than that of men (21.5%). However, the studies referenced are prevalence’s based on vertebral deformities rather than clinical vertebral fractures.
Reply: Thanks a lot for your direction. We have revised the reference.

Number of decimal places varies in Table 1.
Reply: Thanks for your comment. We have corrected it.

Page 11 line 42 “The relative risk of AD was higher in the VCF cohort than in the non-VCF cohort for patients without comorbidities (aHR = 1.44, 95% CI = 1.18–1.76). In all stratifications” should read relative hazard or aHR was higher.
Reply: Thanks a lot for your precious comment. We have replaced the term “relative risk” with “relative hazard”.

Reviewer: 3
I suggest the Authors should use the more traditional term “vertebral fracture”.
Reply: Thanks for your precious comment. We have replaced all the words “VCF(vertebral column fracture)” with “CVF(clinical vertebral fracture)” throughout the whole work.

The term “newly diagnosed vertebral fracture” is not clear. It may be a clinical vertebral fracture (sudden backache most frequently after a minor trauma + vertebral fracture on the radiography) or simply the moment of the diagnosis of vertebral fracture which may have occurred much earlier. It should be clarified.
Reply: Thanks for your comment. Study subjects with the diagnosis of vertebral fracture from 1996-1999 were excluded at the baseline to begin the identification of patients with vertebral fracture newly diagnosed and also, hospitalized simultaneously from 2000-2010. Therefore, most of prevalent cases of vertebral fracture were not likely to be included in the study cohort.

Table 3 – the term “Non-Vertebral column fracture” is misleading and should be replaced, e.g. “No vertebral fracture”. This “Non-vertebral” suggests implicitly that the controls had non-vertebral fracture, i.e. peripheral fractures.
Reply: Thanks for your precious comment. We have corrected it.

Are cardiovascular diseases really more frequent in women than in men? Please, provide a reference.
Reply: Thanks for your precious comment. We have revised our discussion and added references as follows:
“Our study indicated one counterintuitive result that women bore a higher overall incidence of CHF than men did. However, previous investigations of sex-specific epidemiology of CHF have demonstrated that women with atrial fibrillation have a higher incidence of heart failure with preserved ejection fraction, especially in very old age compared with men[47-49].”
47. Hassanein M, Abdelhamid M, Ibrahim B, et al. Gender differences in Egyptian patients hospitalized with heart failure: insights from the European Society of Cardiology Heart Failure Long-Term Registry. ESC Heart Fail 2018;5(6):1159-64. doi: 10.1002/ehf2.12347

48. Madan N, Itchhaporia D, Albert CM, et al. Atrial Fibrillation and Heart Failure in Women. Heart Fail Clin 2019;15(1):55-64. doi: 10.1016/j.hfc.2018.08.006
49. Magnussen C, Niiranen TJ, Ojeda FM, et al. Sex-Specific Epidemiology of Heart Failure Risk and Mortality in Europe: Results From the BiomarCaRE Consortium. JACC Heart Fail 2019;7(3):204-13. doi: 10.1016/j.jchf.2018.08.008

An interesting finding of this study is that the association between the investigated diseases is found even before the age of 50. This point should be discussed.
Reply: Thanks a lot for your direction. We have revised our discussion and added words as follows:
It is noteworthy that young adults aged ≤49, though represented the minority of CVF patients, bore a significant heightened risk of developing adverse cardiopulmonary outcomes. We speculate that CVF could have more prominent influence on the outcome diseases without the interaction of multiple potential comorbidities and unknown confounders. Moreover, CVF is less frequent in a young, healthy population; it could be more severe, especially for hospitalized trauma victims and therefore, strengthening the correlations between the investigated diseases.

I agree with the Authors that some controls could have vertebral fractures which were not diagnosed. The Authors should add a comment that such bias could underestimate the associations.
Reply: Thanks for your precious recommendation. We have added the comment as follows:
“the true incidence of CVF and the inferred association between CVF and cardiopulmonary diseases could be underestimated.”

One limitation is unavoidable in such studies and should be signaled. Different criteria for the diagnosis of vertebral fracture could be used in different hospitals. It is not sure whether the same criteria were used for the diagnosis of cardiovascular diseases in various hospitals.
Reply: Thanks for your comment. We have added this part in our limitation.
“Similarly, diagnostic criteria applied, as well as physician’s ability to diagnose the investigated diseases might vary among different hospitals and areas.”

VERSION 2 – REVIEW

REVIEWER	Joshua Lewis Edith Cowan University, Australia
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	The reviewers have addressed most of my concerns and the manuscript is substantially improved. Figures 1 & 2 need to be updated for clinical vertebral fractures rather than vertebral column fractures.

REVIEWER	Pawel Szulc INSERM UMR1033, University of Lyon, Lyon, France
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	This is a very interesting and important study which really adds to our knowledge on the link between fragility fracture and cardiovascular diseases. I have three remarks. The Authors need to improve the description of the results. At the moment, we are lost in minor details and we have to look for the major message by ourselves. However, it is the role of the Authors to show their most important message. 1. For aortic dissection, the figure shows clearly that after 10 years the proportionality of the risk is lost. Therefore, I suggest the Authors limit the analysis for the aortic dissection to the first ten years. 2. The presentation of the results needs work. The Authors describe aortic dissection in detail and add brief information on

	other diseases. The Authors should make separate sections: a) description (Table 1); b) aortic dissection and analyses in subgroups stratified using various criteria; c) heart failure and analyses in subgroups stratified using various criteria; d) pneumonia and analyses in subgroups stratified using various criteria; e) ARDS and analyses in subgroups stratified by various criteria; f) analyses in the groups stratified according to the level of vertebral fracture and the spinal cord injury. 3. The Discussion is very long – 8 pages! It should be condensed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Pawel Szulc
Institution and Country: INSERM UMR1033, University of Lyon, Lyon, France
This is a very interesting and important study which really adds to our knowledge on the link between fragility fracture and cardiovascular diseases. I have three remarks. The Authors need to improve the description of the results. At the moment, we are lost in minor details and we have to look for the major message by ourselves. However, it is the role of the Authors to show their most important message.
For aortic dissection, the figure shows clearly that after 10 years the proportionality of the risk is lost. Therefore, I suggest the Authors limit the analysis for the aortic dissection to the first ten years.
Reply: Thanks a lot for your precious comment. In our study, since the study subjects were identified from January 1, 2000, to December 31, 2010, we have modified the follow-up time to be terminated at the end of December 31, 2010, instead of the end of December 31, 2011. In this way, the analysis for the outcomes, including aortic dissection, will be limited to the first ten years,

The presentation of the results needs work. The Authors describe aortic dissection in detail and add brief information on other diseases. The Authors should make separate sections: a) description (Table 1); b) aortic dissection and analyses in subgroups stratified using various criteria; c) heart failure and analyses in subgroups stratified using various criteria; d) pneumonia and analyses in subgroups stratified using various criteria; e) ARDS and analyses in subgroups stratified by various criteria; f) analyses in the groups stratified according to the level of vertebral fracture and the spinal cord injury.
Reply: Thanks a lot for your precious comment and direction. In order to improve the readability of this work and avoid lengthy discussion, we have re-subdivided the discussion part into five separate sections as follows:
Demographics and comorbidity
Clinical vertebral fracture and aortic dissection
Clinical vertebral fracture and congestive heart failure
Clinical vertebral fracture and pneumonia, acute respiratory distress syndrome, and subtypes analysis
Limitations
Additionally, we also divided the content of “Results” into three separate sections: “Demographics and comorbidity”, “Primary outcomes”, and “Subtypes analysis”.

3. The Discussion is very long – 8 pages! It should be condensed.
Reply: Thanks a lot for your comment and direction. We have carefully reviewed this part and made some corrections by removing several redundant and less relevant contents.

Reviewer: 2
Reviewer Name: Joshua Lewis
Institution and Country: Edith Cowan University, Australia
The reviewers have addressed most of my concerns and the manuscript is substantially improved. Figures 1 & 2 need to be updated for clinical vertebral fractures rather than vertebral column fractures.
Reply: Thanks a lot for your comment. We have updated the figures.