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LETTER TO THE EDITOR

# Response to comments on "Gamma-glutamyl-transferase is associated with incident hip fractures in women and men ≥ 50 years: a large population-based cohort study"

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DearEditor,

With keen interest, we have read the comments by Lai [1] on our recently published paper on the association of GGT with hip fracture risk [2]. We thank the author for his critical thoughts on our research and take the opportunity to respond to the raised points.

First, we agree on the high relevance of falls and their prevention of hip fracture risk. However, this is only one side of the coin. Claiming the importance of falls only by the fact that they precede almost all osteoporotic hip fractures [3] is both trivial and misleading. If the total number of fractures could be substantially curtailed by reducing the proportion of falls that lead to a fracture and/or by reducing fall risk, almost all fractures would still occur after a fall even though the fracture burden decreases. Another important factor is the probability of a severe injury after a fall, i.e., the proportion of falls leading to a fracture, which depends e.g. upon bone status, i.e., bone quality and strength. This factor could be influenced by GGT, as shown and discussed in our paper [2]. For comparison, the situation is akin to efficacious strategies aimed at the reduction of injuries and deaths in road traffic that include measures to both prevent traffic accidents and prevent or mitigate injuries in case of accidents [4], because physical traffic injuries are virtually always due to accidents, and accidents will never be totally avoidable, respectively.

The hypothesis that alcohol intake acts as a confounder of GGT-related hip fracture risk, causing both elevated GGT serum levels and hip fractures via higher propensity for falls (as depicted in Lai's Fig. 1) [1], was our very rationale for the subgroup analysis including individuals with information on alcohol consumption [2]. That alcohol consumption is not the underlying factor that explains high hip fracture risk via increased risk of falls in individuals with elevated GGT levels in our study, however, should be sufficiently clear from the results therein [2]: Additional adjustment for alcohol intake did not alter the hazard ratio (HR) for hip fracture in women and even increased the hazard ratio in men. If alcohol consumption played a role as a confounder and real cause of fractures, HRs would be expected to decrease or even drop to 1. Nevertheless, we have herein conducted an additional analysis suggested by Lai [1] to examine hip fracture risk in individuals with vs. without alcohol intake stratified by serum GGT levels, using Cox regression models (Table 1). If hip fractures were due to alcohol, the risk would be expected to rise with vs. without alcohol intake among individuals with elevated GGT. This is not the case though, since HRs even decreased non-significantly, also upon adjustment for baseline age (see below) (Table 1). The gender-specific analysis yielded similar results that should, however, be interpreted cautiously because of the small numbers. Moreover, fracture risk among subjects with normal GGT levels did

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**Table 1** Hip fracture risk in subjects ≥50 years with no alcohol vs. alcohol consumption, stratified by GGT levels at baseline. *HR*, hazard ratio; *VHM&PP*, the Vorarlberg Health Monitoring and Promotion Program

| GGT | GGT normal (women, < 36 U/l; men, < 56 U/l) | | | | GGT elevated (women, ≥ 36 U/l; men, ≥ 56 U/l) | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* (subjects) | *n* (hip fractures, % of subjects) | Age at baseline (mean ± SD) | HR (95% CI) | *n* (subjects) | *n* (hip fractures, % of subjects) | Age at baseline (mean ± SD) | HR (95% CI) |
| All[a] | 4453 | 183, 4.1% | | | 992 | 49, 4.9% | | |
| No alcohol consumption | 2690 | 137, 5.1% | 69.1 ± 8.1 | Reference | 505 | 33, 6.5% | 68.5 ± 7.7 | Reference |
| Alcohol consumption | 1763 | 46, 2.6% | 61.2 ± 9.2 | 0.99 (0.68–1.43) | 487 | 16, 3.3% | 61.6 ± 8.6 | 0.58 (0.28–1.17) |
| Women[b] | 2274 | 137, 6.0% | | | 487 | 28, 5.7% | | |
| No alcohol consumption | 1701 | 111, 6.5% | 68.9 ± 8.4 | Reference | 357 | 24, 6.7% | 68.9 ± 7.6 | Reference |
| Alcohol consumption | 573 | 26, 4.5% | 59.9 ± 9.0 | 1.09 (0.68–1.73) | 130 | 4, 3.1% | 61.2 ± 8.8 | 0.43 (0.13–1.35) |
| Men[b] | 2179 | 46, 2.1% | | | 505 | 21, 4.2% | | |
| No alcohol consumption | 989 | 26, 2.6% | 69.3 ± 7.6 | Reference | 148 | 9, 6.1% | 67.5 ± 8.0 | Reference |
| Alcohol consumption | 1190 | 20, 1.7% | 61.9 ± 9.3 | 0.83 (0.44–1.57) | 357 | 12, 3.4% | 61.7 ± 8.5 | 0.70 (0.27–1.77) |

[a]Adjustment for sex, age at baseline, BMI, systolic blood pressure, diastolic blood pressure, triglycerides, cholesterol, serum uric acid, diabetes, and smoking status

[b]Adjustment for age at baseline, BMI, systolic blood pressure, diastolic blood pressure, triglycerides, cholesterol, serum uric acid, diabetes, and smoking status

not differ according to alcohol status. Conspicuously, baseline age was considerably higher in subjects without vs. with alcohol intake. These findings confirm our interpretation that the absence of alcohol intake in an elderly population might be reflective of worse health status and higher fracture propensity [2]. Moreover, heavy drinkers and alcoholics might already be dead at an advanced age [5], which could explain the difference in HRs between individuals with normal and elevated GGT (Table 1). Also, moderate alcohol intake has been associated with decreased fracture risk via increased bone mineral density [6–8]. Likewise in a population-based investigation, no modification of hip fracture risk by alcohol consumption at ≥60 years was reported except in abstinent and rarely drinking women who were at a slightly increased risk [9], which could confirm our assumption that teetotalism due to health reasons plays a role in an elderly population. Combined evidence thus demonstrates that in the real-world setting of a population-based study in elderly people, different mechanisms are at work that merit consideration, of which alcohol as a confounder of the association of GGT and hip fracture risk via falls as depicted in Lai's Fig. 1 is but one and seems to be of minor relevance only.

Concerning a potential role of fall-risk increasing medications as confounders, we emphasize that we were unable to account for medications as discussed as one limitation of our study [2]. Literature on a possible impact of such drugs on GGT levels in human adult populations is sparse. That said, some studies described a moderate increase in GGT by antipsychotics [10, 11] and opioids [12], the latter possibly caused by concomitant alcohol intake. Besides, the bulk of antihypertensives and diuretics whose application is widespread among the elderly, and which may cause hypotension and low blood pressure-related falls, usually affect renal rather than hepatic function without change in GGT serum levels (e.g., [13]). If any, such (small to moderate) effect might, however, hardly gain measurable relevance in a population-based study or be superimposed by other factors, much like with alcohol consumption (see above). For example, the drug use frequency and profile reported in a recent study in residents of aged care services [14] cited by Lai [1], representing a highly selected cohort, are certainly not comparable with those in a population-based investigation. In this study [14], participants' average age was roughly 88 years, which is considerably higher than in our study (around 81.5 and below 78 years at fracture for women and men, respectively, let alone average age at baseline [2]). It can hence be assumed that medication profiles in their study in geriatric patients [14] and in ours [2] hardly match. Finally, in view of the long-term follow-up in our study, a good proportion of participants might have initiated fall-risk increasing medications not until baseline. Thus, an increase in hip fractures caused by these drugs would be assigned to baseline GGT levels before drug initiation and the real effect size of the association between GGT and hip fracture risk would consequently be attenuated. Also, confounding should play no role for those who started taking fall-risk increasing medications after the baseline examination provided that baseline GGT levels are randomly distributed among

affected hip fracture patients. However, at a later baseline time point (at the last examination in our study), more participants might already be taking fall-risk increasing drugs as compared with an earlier time point (at the first examination in our study), potentially resulting in enhanced confounding as well as an increased effect size when GGT levels are considered at the last vs. first examination. A moderately increased effect at the last vs. first examination was indeed observed in our study [2]. Even though this one aspect would seem compatible with Lai's hypothesis, we deem the overall effect size is too large to be due to confounding by fall-risk increasing medications alone, also because alcohol is not a relevant factor (see above). However, to conclusively clarify a possible confounding role of fall-risk increasing drugs, future studies are warranted that account for information on relevant covariates and with an appropriate study design, conducted by experienced research groups including Lai's.

In summary, we contend that a hypothesis that explains the association between GGT and hip fracture risk solely on basis of alcohol intake and fall-risk-enhancing drugs is over-simplified and inadequate for the real-world situation encountered in a population-based investigation.

## Declarations

**Conflict of interest** None.

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