Author’s response to reviews

Title: KIDNEY FUNCTION AND NEPHROTOXIC DRUG USE AMONG OLDER HOMEDWELLING PERSONS WITH OR WITHOUT DIABETES IN FINLAND

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Dear Editor,

We appreciate the comments of the manuscript BNEP-D-19-00817 “KIDNEY FUNCTION AND NEPHROTOXIC DRUG USE AMONG OLDER HOME-DWELLING PERSONS WITH OR WITHOUT DIABETES IN FINLAND”. The manuscript has been modified according to the comments and a point-by-point response is provided below. Modifications in the revised manuscript have been highlighted in yellow.

Reviewer reports:

Lisbet Brandi (Reviewer 1): Potential drug interactions especially in older patients and patients with and without diabetes are important. Development of decision support system providing a risk profile for adverse events could be helpful to the clinician. PHARAO and RENbase as used in the present paper are examples of that
PHARAO is a new pharmacological risk assessment system (ref 31), which have low sensitivity for renal adverse events and is known not to include drugs which in other databases are characterized as potential nephrotoxic (ace inhibitor, diuretics e.g.). A recent paper on "clinical relevance of alerts form PHARAO" - BMC geriatric 2019, article number 164 concluded that, inclusion of drug doses should be considered to increase the sensitivity. TThis is not done in the present paper

RESPONSE: Unfortunately, we are not able to add dosage information. However, we added in the Discussion the lack of dosage information as limitation and possibility in future studies.

The aim of the present paper was to compare kidney function and use of potentially nephrotoxic drugs occurring among older home-dwelling persons with and without diabetes. 259 patients with an 259 patients without DM were invited to a health care examination. The drug use was collected by the physician and a risk profile provided based on PHARAO. The kidney function was evaluated by eGFR. No difference between the 2 groups were fund. Only 2 patients in both groups were treated by "potentially nephrotoxic drugs". The scientific question therefore cannot be answered. The number of patients are too few to support the conclusion that potentially nephrotoxic drug plays only a minor role in the worse renal function between diabetes and non-diabetes older home-dwelling persons.

RESPONSE: We agree with reviewer and therefore the need for larger sample sizes is added in Discussion.

Members of the author group has recently published an article on the same cohort as the present paper - Clinically relevant drug interactions and the risk for drug adverse effects among home dwelling older persons with and without diabetes - Journal of Clinical pharmacy and therapeutics 2019 vol 44 (5), 735-741. In that paper discussion of renal adverse events are omitted. Most of the other results presented in the present paper are published previously

RESPONSE: Unfortunately, this another paper was written and published meanwhile this paper went through previous review process. We have looked through this paper and paper concerning Drug interaction to avoid possible similarities. We modified table 2 to gather only clinical characteristics and removed irrelevant for present study with similarities with our previous study.

Comments to the author:

The issue is important.

The paper should be more focused on the methodology and the validity of risk assessment system and renal function.
RESPONSE: We added Hedna et al (2019) manuscript concerning specificity and sensitivity of PHARAO system as reference and added this in Discussion.

The other results are already published and should only be mentioned There are two table 1

RESPONSE: We have compared this paper and paper concerning Drug interaction to avoid possible similarities. We have modified table to gather only clinical characteristics relevant for present manuscript. Methods and results are changed accordingly.

Masa Knehtl (Reviewer 2): Heinjoki M and co-workers presented interesting study comparing kidney function and potentially nephrotoxic drug use among older home-dwelling persons with or without diabetes.

The cross-sectional study, conducted in one primary care district, included 363 subjects. The authors used mostly appropriate methodology, correctly stressed the limitations of their study and found some interesting results and added some novelty to the knowledge in this field.

However, some minor comments have been raised:

-It is not clear from the abstract how many participants were actually included in the study. After a random selection of 259 persons with diabetes AND 259 persons without diabetes, complete data was gathered for 187 persons with diabetes and 176 without diabetes, so totally 363 participants were included.

RESPONSE: We added actual participants in abstract.

-The methodology of the study population is not clearly represented in Figure1; two age and gender matching controls were supposed to be selected for each person diagnosed with diabetes, which is not clear from figure 1.

RESPONSE: We clarified in methods that randomization 1:2 was made first in the beginning of study, before questionnaire-part of the study and using primary health care system. Of the persons who responded to questionnaire study, 259 persons with diabetes and 259 without diabetes (1:1) was randomized to participate in health examination. We decided to remove the Figure 1 and clarify the flow only in text.

-Figure 2: if the eGFR was calculated by using CKD EPI equation, it should be expressed as ml/min/1,73m2 -Since the results have shown that persons with diabetes had a higher body mass index and a larger waist than non-diabetics, this difference should be considered when evaluating renal function. I suggest using Cockcroft-Gault equation to assess renal function, which includes participant's weight as well.

RESPONSE: In figure 2 (now figure 1) expression changed to ml/min/1,73 m2.
We added eGFR calculated by using Cockcroft-Gault equation as well. This changed the results in both groups and controversially among persons with diabetes. However, results remained indicating normal renal function in both analysis. In Discussion section is now mentioned as additional analyze. We added also in Methods that we did additional analyze with Cockcroft-Gault equation to observe the effect weight.