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Outcome of initial inquiry into concerns raised regarding 2014 Cell Metabolism paper

Public statement by the Deputy Vice-Chancellor (Research), Professor Duncan Ivison

The University has recently completed an initial inquiry into allegations made by Mr Rory Robertson in respect of research carried out by Professor Stephen Simpson and other University researchers based at the Charles Perkins Centre. The allegations relate to a paper titled '*The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging and longevity in ad libitum fed mice*,' published in 2014 in *Cell Metabolism.*

The initial inquiry, which included a review and recommendation by an independent expert, found no breaches of the *Research Code of Conduct* and no research misconduct on the part of Professor Simpson and his colleagues.

The inquiry was conducted in accordance with the University's *Research Code of Conduct*, which incorporates the requirements of the *Australian Code for the Responsible Conduct of Research*, and holds the University's researchers to the highest standards of integrity and research practice. An initial inquiry in these circumstances is not an investigation of fraud, as Mr Robertson has been claiming.

In addition to the researchers' statistical analyses and conclusions being found to be acceptable through the University's initial inquiry, the paper was evaluated through the journal's peer review process prior to publication and in an extra independent review conducted by the journal in June in response to Mr Robertson's complaint. The University is satisfied that there is no basis for any of the matters raised by Mr Robertson to be investigated further.

Background

On 1 March 2019, the NHMRC referred to the University concerns raised by Mr Robertson, a member of the public, about a paper titled 'The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum fed-mice', *Cell Metabolism* 2014, 19(3), 418-430 (the **2014 Cell Metabolism paper**). The paper was authored by Professors Stephen Simpson, David Le Couteur, David Raubenheimer and Victoria Cogger and Dr Samantha Solon-Biet (the **Researchers**) and researchers from other institutions.

In summary, the concerns raised by Mr Robertson were that:

1. certain groups of mice were excluded from the experiment and their exclusion was not adequately communicated. Specifically, he has stated that "*the authors have skillfully (sic) misrepresented their 30-diet longevity results including by obscuring 100+ dead mice on five low-protein diets*";
2. a simpler analysis of median lifespan should have been used and this would have changed the outcome (i.e. the alternative analysis/modelling proposed by Mr Robertson would have indicated that longevity is greatest for mice fed a high-protein, low-carbohydrate diet);

3. the C57BL/6 mouse is not an appropriate animal model for investigating obesity, type 2 diabetes, cardiovascular disease and longevity in humans, and that humans and C57BL/6 mice have different metabolic responses to low-carbohydrate diets;
4. the findings of the 2014 Cell Metabolism paper have not been communicated responsibly to the general public;
5. Professor Simpson was highly motivated to find that a low-protein, high-carbohydrate diet results in the longest lifespan. Mr Robertson has stated that "*[Professor] Simpson's preferred finding for the 30-diet experiment was published in his 2012 book, and before that, in a 2009 paper*"; and
6. mice fed certain low-protein, high-carbohydrate diets required euthanasia in the 2014 Cell Metabolism study while mice fed the same diets actually lived longest according to a 2018 mouse-dementia paper by the University of Sydney researchers.

Process

An initial inquiry was conducted in accordance with the University's *Research Code of Conduct 2013* (the **Research Code**).

The initial inquiry was conducted by Professor Stephen Garton, Senior Deputy Vice-Chancellor (then Provost and Deputy Vice-Chancellor), as the designated person under the University's process for managing allegations of breaches of the Research Code (see section 23 of the Research Code).

Given the complex and technical nature of the concerns raised, Professor Garton sought specialist advice from an academic expert. Professor Peter Koopman, a University of Queensland senior academic, Fellow of the Australian Academy of Science, former Australian Research Council (**ARC**) Federation Fellow and NHMRC Senior Principal Research Fellow was engaged for this purpose. In addition to having over 30 years of experience in animal-based biomedical research, Professor Koopman was the University of Queensland's Executive Director of Research Ethics and Integrity from 2012 to 2017 and has expertise in research integrity, including familiarity with the standards of data integrity and presentation.

Professor Koopman is external to the University of Sydney and confirmed at the time of his appointment that he does not have any association with the researchers, any of the other authors of the 2014 Cell Metabolism paper or the Charles Perkins Centre. Professor Koopman stated that he is not an expert in metabolic studies or statistics, but conducted the review from the perspective of an independent experienced biomedical research scientist. Professor Koopman was paid by the University of Sydney on a fee-for-service basis. He was asked to provide advice in relation to the matters raised at points 1-3 above only as these were identified as requiring expert input.

As the University's delegate for overseeing the assessment of research-related complaints, I am satisfied that a thorough and rigorous assessment process has been conducted in accordance with the Research Codes. Given that expert advice was sought from an esteemed biomedical research scientist external to the University, and that Professor Koopman invested significant time and effort in evaluating the 2014 Cell Metabolism paper and the issues raised, I am satisfied that the research has been scrutinised impartially and to a high level.

Findings

The initial inquiry found no breaches of the Research Codes. These findings were made following an examination of a series of detailed submissions from Mr Robertson, responses from the researchers and expert advice from Professor Koopman.

The findings in relation to each of the concerns raised by Mr Robertson are summarised below:

1. **The concern that certain groups of mice were excluded from the experiment and their exclusion was not adequately communicated. Specifically, Mr Robertson has stated that "*the authors have skillfully (sic) misrepresented their 30-diet longevity results including by obscuring 100+ dead mice on five low-protein diets.*"**

Young mice that had been put on five of an initial 30 diets were euthanised and their diets were discontinued after the researchers observed weight loss, rectal prolapse or failure to thrive.

Professor Koopman noted that the euthanasia and subsequent removal of certain groups of mice had been mandated by the responsible ethics committee and were therefore appropriate actions on the part of the researchers.

Lifespan data for these mice were not included in the analysis, and on this point Professor Koopman observed that using age at euthanasia as a proxy for lifespan may not be scientifically valid, as it is not known whether mice would have died, or whether they may they may have lived long and healthy lives, had they not been euthanased.

Professor Koopman indicated that it would have been preferable if the paper had stated why weight loss, rectal prolapse or failure to thrive, as well as the consequent need for early euthanasia, were not considered relevant to the study. However he accepted the researchers' explanation that the study was about late-life health rather than health and longevity in general, and accordingly, there was a valid basis for excluding the younger mice that had been euthanased. Professor Koopman also indicated that it would have been preferable if it had been made clearer in the paper (for example, through using more consistent wording) that the study was about late-life health rather than health and longevity in general.

In relation to the way in which the exclusion of certain groups of mice was communicated (that is, in the legend of Table S1 of the Supplemental Information for the paper), Professor Koopman noted that field-specific norms exist, and observed that it may be the norm of the metabolic field to present important information such as dietary composition in the supplementary part of the paper. Professor Koopman also held the view that disclosure in the supplemental material that some mice were removed from the study due to weight loss, rectal prolapse and/or failure to thrive fulfills at the basic level the obligation to present a full account of their findings.

On the basis of the above assessment by Professor Koopman, Professor Garton did not consider that there was a breach of the Research Code.

Through the course of assessing this issue, Professor Koopman also identified a discrepancy between the total number of animals reported in the paper (N=858) and the actual number of animals used (N=715). However, he found no evidence to suggest that

mouse numbers had been deliberately misrepresented and on that basis Professor Garton found that the error in the number of mice reported did not amount to a breach of the Research Code.

2. **The concern that a simpler analysis of median lifespan should have been used and this would have changed the outcome (i.e. the alternative analysis/modelling proposed by Mr Robertson would have indicated that longevity is greatest for mice fed a high-protein, low-carbohydrate diet).**

For the purpose of considering Mr Robertson's claim, Professor Koopman conducted a series of simpler, independent analyses of the data to test whether the researchers' conclusions were robust. He noted his simpler analyses do not necessarily present a complete and accurate story, but were intended to examine whether the researchers' conclusions using the General Aggregate Model would be supported by a simpler means of regression analysis which takes into consideration the overall data set. The findings of Professor Koopman's analysis suggest an association between increased P:C ratio and lower lifespan, consistent with the conclusions in the 2014 Cell Metabolism paper.

Professor Koopman regarded the General Aggregate Model that had been used by the researchers to have been an appropriate choice of data analysis to examine broad trends in the overall data set, rather than specific data points. He also held the view that because the purpose of the study was to examine broad trends in the overall data set, rather than to examine the response diet-by-diet, the presentation of data in Table S2 was not misleading. In addition, Professor Koopman considered that it was unnecessary to explain in detail in the paper how the analysis works, as the paper was published in a scientific journal intended for an audience specialising in metabolic studies. He also concluded that, based on their method of data analysis, the researchers' conclusion that longevity was greatest for mice fed a low-protein, high-carbohydrate diet appeared to have been appropriate.

While the details of Professor Koopman's analyses are not provided here, interested parties may obtain them from the University's Research Integrity Office at research.integrity@sydney.edu.au.

Professor Koopman also considered the data presented in Figure 2B, which Mr Robertson had asserted was inconsistent with data presented in Table S2. Specifically, Mr Robertson had asserted that Table S2 shows median lifespans all less than 140 weeks, whereas he interprets Figure 2B as showing maximum lifespans of over 150 weeks. In this matter Professor Koopman held the view that Mr Robertson may have taken the label "*Intake based, median lifespan*" to pertain to all parts of Figure 2, where it applies only to Figure 2A. He held the view that the figure legend clearly identifies Figure 2B as a Kaplan-Meier survival curve, which does not indicate median survival, but rather indicates the number of animals remaining alive after a given number of weeks. Professor Koopman held the view that Figure 2B shows that some mice were still alive after 150 weeks, and therefore that there is no inconsistency between the data presented in Figure 2B and Table S2.

Taking into account the views of Professor Koopman, and the fact the 2014 Cell Metabolism paper and its statistical analyses have undergone extensive peer review, Professor Garton was satisfied that neither the researchers' data analysis nor their conclusions involved any breach of the Research Code.

3. The concern that the C57BL/6 mouse is not an appropriate animal model for investigating obesity, type 2 diabetes, cardiovascular disease and longevity in humans, and that humans and C57BL/6 mice have different metabolic responses to low-carbohydrate diets.

Professor Koopman observed that "*mice represent a powerful model for many aspects of human biology, as they are mammals, are small, are relatively cheap to maintain, and breed quickly. They have been used for over a century to study many aspects of mammalian biology. Their genetics is extremely well characterised. Importantly, they are available as inbred strains, reducing the variability between individuals that can confound certain kinds of experiment.*"

Professor Koopman also noted that "*All studies involving an animal model suffer from the potential caveat that the model may not accurately reflect human biology. Simpler and cheaper animal models tend to poorly reflect human biology, whereas carrying out studies on animal models that more closely resemble human biology (such as chimpanzees and pigs) can be prohibitive in terms of logistics, cost, statistical power, or animal ethics*."

In Professor Koopman's view, mice represent a reasonable compromise, and he found that despite some potential limitations, the use of the C57BL/6 mouse strain for the study was justifiable. He noted that there was a need for a mouse model and use of the C57BL/6 strain aligns with current academic practices.

On the basis of Professor Koopman's assessment, Professor Garton found that use of the C57BL/6 strain did not involve any breach of the Research Code.

4. The concern that the findings of the 2014 Cell Metabolism paper have not been communicated responsibly to the general public.

Mr Robertson asserted that the outcomes of the study that was the subject of the 2014 Cell Metabolism paper had been misrepresented in media reports, in an ABC radio interview and in a University advertising campaign.

Professor Garton found that Mr Robertson's concerns about the reporting of the outcomes of the study were based on his view that the conclusions reported by the researchers did not reflect the actual study outcomes. For the reasons discussed in relation to issues 1 to 3 above, neither Professor Koopman nor Professor Garton accepted Mr Robertson's claim that the researchers had misrepresented the study outcomes in the 2014 Cell Metabolism paper. Accordingly, Professor Garton found that the research outcomes were not misrepresented in media reports and an ABC radio interview to which Mr Robertson has referred and that there is no breach of the Research Code.

In relation to the number of mice reported in the media, Professor Garton accepted that in both the paper and subsequent reporting of its outcomes there was an error in the number of mice said to have been involved in the study. However, he accepted Professor Koopman's observation that there is no evidence to suggest that mouse numbers were deliberately misrepresented. As such he did not consider that the error in the reported number of mice constituted a breach of the Research Code.

In relation to Mr Robertson's concerns about the material which was included as part of the University's 'Unlearn' advertising campaign, Professor Garton noted that it is relevant that this was a promotional advertising campaign, the purpose of which was to raise awareness of the University's research activities generally and to highlight that universities are here to question received wisdom. The campaign was also intended to make the point that research findings can be controversial as this is how science works. It was not intended as a means of disseminating the outcomes of particular research projects. When viewed in this context, Professor Garton did not consider the 'Unlearn' advertisement to be misleading, and accordingly, he did not consider that that it was in breach of the Research Code.

That said, Professor Garton acknowledged that the wording of the advertisement in its original form was open to different interpretations. This was recognised by the University after receiving Mr Robertson's submissions, and the text in the "Unlearn" advertisement was changed from:

> "*By questioning how the body processes different foods, our researchers have discovered that a low protein, high carb diet can delay chronic disease and help us live a longer and healthier life.*"
>
> to
>
> *"By questioning how the body processes different foods, our researchers have discovered that a low protein, high carb diet* **may** *delay chronic disease and help us live a longer and healthier life.*"

While Professor Garton did not find any breaches of the Research Code, he has recommended a strengthening of the processes by which these communications are approved. The University's Marketing and Communications teams have received training in research integrity in line with the *Australian Code for the Responsible Conduct of Research 2018,* and the process by which advertisements are approved has been strengthened.

5. **The concern that Professor Simpson was highly motivated to find that a low-protein, high-carbohydrate diet results in the longest lifespan. Mr Robertson has stated that "*[Professor] Simpson's preferred finding for the 30-diet experiment was published in his 2012 book, and before that, in a 2009 paper.*"**

Professor Garton observed that all researchers must deal with the challenge of developing and testing theories, and noted that the publication of a hypothesis prior to the collection of data, or expressing support for a particular theory or result, is an unexceptional practice. He also noted that the publication of a hypothesis is actively promoted in some fields, including medical and biomedical science.

For the reasons outlined in the discussion of issues 1 to 3 above, the findings made by the researchers appeared to Professor Koopman to have been appropriate based on the method of data analysis that they had utilised, and there was no evidence of any manipulation of the data or any other improper conduct to support a preferred outcome. Accordingly, Professor Garton found no breach of the Research Code arising from the fact that the outcomes of the study underpinning the 2014 Cell Metabolism paper were consistent with hypotheses published in 2009 and 2012.

6. **The concern that mice fed certain low-protein, high-carbohydrate diets required euthanasia in the 2014 Cell Metabolism study while mice fed the same diets actually lived longest according to a 2018 mouse-dementia paper by the University of Sydney researchers.**

Professor Garton noted that as euthanasia of the mice in the 2014 study was mandated by the responsible ethics committee, it could not be known whether mice fed these diets would have died, or whether they would have lived long and healthy lives had they not been euthanased.

It was unnecessary for Professor Garton to consider whether the findings in the 2014 paper differed from those in the 2018 paper. He observed that it is not uncommon in research for experiments to yield different results, and a difference in results would not constitute a breach of the Research Code.

Given that Professor Garton's task was to consider whether there was conduct that could constitute a breach of the Research Code, there was no need for him to form any view on the question of whether there was any difference in the findings in the two papers.

Recommendations

On the basis of the above, Professor Garton recommended the following:

- That the 2014 Cell Metabolism paper is amended to correctly state the total number of mice fed one of 25 diets;
- That any University of Sydney communications about the 2014 Cell Metabolism paper are amended to correctly state the total number of mice fed one of 25 diets;
- That Mr Robertson and the researchers are notified of the outcome of this initial inquiry; and
- That information about the process and its outcomes are communicated to other interested parties as appropriate, noting the need to protect the reputations of those involved where allegations were found to be unproven.

Please direct any questions to the Research Integrity Office at research.integrity@sydney.edu.au or (02) 8627 0200.