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<tr><th colspan="2">Article details: 2016-0101</th></tr>
<tr><td>Title</td><td>Family physician-led, team-based, lifestyle intervention in patients with metabolic syndrome: results of a multicentre demonstration project</td></tr>
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<tr><td>Reviewer 1</td><td>Dr. Dick Bijl</td></tr>
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<tr><td>General comments (author response in bold)</td><td>1. I have read the article by Khursheed et al. with interest. It studies the feasibility of a multicenter demonstration project of identifying and treating patients with metabolic syndrome in primary care. The results show that it is feasible. And that is a positive message, especially that it is possible to reduce weight and blood pressure. But then the rest of the article is disappointing. We do not read anything about the problems the researchers have come up to which might be interesting for researchers of any other intervention project in primary care. What problems did the researchers face, what was the impact of this program in the practice, how much extra work for the GP, how did the patients react, etc.
We thank the reviewer for this observation. Some participants faced difficulty in attending the supervised exercise visits due to scheduling conflicts, as already mentioned in the first paragraph of the interpretation section. Group visits were felt to be a more feasible option for many participants and the clinic staff. Family MD follow up visits were manageable as the focus was assessing progress and nudging the patients to continue their efforts rather than counselling on nutrition and physical activity which was managed by the dietitians and kinesiologists. Patient experiences were extremely positive, the program increased their knowledge, was felt to be life changing and patients expressed gratitude for being able to participate and felt it was a “privilege” to be part of the program.
The following quote is from one of the lead Family MD: “The CHANGE Program has helped physicians in our clinic successfully manage patients with deteriorating cardio-metabolic profiles. Some participants no longer have hypertension and metabolic syndrome, others have reduced diabetes or dyslipidemia medication. Patients that for 20 years hadn’t reduced their waist circumference saw improvement and found the health benefits of lifestyle intervention.
The team approach provides patients with the motivation to do regular physical activity and eat well with pleasure, and physicians are more confident to recommend a non-pharmacological treatment. Barriers: patients had to go outside of the family medicine unit to do exercise. Implementation effort: very easy to implant with all the work of the health professional.”
We were unable to add these details due to the word count limitation. The details of the qualitative analysis of the patient experiences are part of a separate publication.
2. The authors also have difficulty in the naming of their study, in the abstract it states that it is a cohort study. In fact it is a single arm study without a control group.
We have now accurately described the study as a longitudinal, before-after cohort study. This has been reflected in the Abstract and Methods
3. There is no power calculation. But the authors state that they have primary and secondary outcomes which I do not understand when you have not done a power calculation.
The sample size was based largely on feasibility rather than testing a hypothesis. We chose this sample size because we believed it was feasible in real-life practice and would allow us to meet our overall study goals. We have added the following sample size justification to the methods section page 4:
Sample Size
We aimed to enroll a total of 300 patients because this was feasible and we believed would be adequate to demonstrate feasibility of the program and detect small within patient changes in MetS outcomes. For example, for continuous outcomes this sample would provide over 90% power at two-sided alpha=0.05 to detect a within patient change that is 1/5th of the standard deviation of the change values, which is considered a small effect size by Cohen’s convention (29). Furthermore, this sample size would provide us a 95% chance of estimating the MetS reversal rate to within 5%, assuming the rate was ≤25%, as was observed.
The authors use correlation coefficients that are in my opinion useless statistics.
We have responded to this comment by removing all text related to the correlations from the manuscript
4. We know from other studies that it is possible to reduce weight in an intensive</td></tr>
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controlled study. The problem is of course that after the study people cannot sustain adherence to such a program.

We agree with the reviewer that weight loss sustainability is a concern. Contrary to this, we have shown weight loss being sustained until 12 months. It should be noted that the focus of our program is not only weight loss, but rather improvement in all MetS components. The sustainability of our program beyond 12 months is being examined as part of a separate research proposal.

5. The use of pioglitazone does not relate to rational pharmacotherapy as this drug has a negative balance of efficacy and side effects.

We chose to illustrate pioglitazone as it is the only clinically approved drug that addresses the core basis of the MetS i.e. insulin resistance, rather than the drugs that target the consequences of insulin resistance. Given this we feel that it is justified to keep this in the interpretation. We have changed the wording in the interpretation, page 6 to reflect this as follows

In high risk patients with insulin resistance, the use of the insulin sensitizing drug, a clinically approved drug aimed to target this resistance, pioglitazone, was associated with a significantly lower incidence of stroke or myocardial infarction compared to placebo (9% vs.11.8%, $p<0.007$) over 4.8 years.....

6. The term 'holistic' is not appropriate and should not be used when there are not workers of social sciences involved in the performance of the multicenter program.

Thank you for pointing this out, we have removed the tern "holistic" from the first sentence, last paragraph, page 6.

7. In the statistical analysis there is the problem of multiple comparison because too many tests are performed and there is no attention for this by the authors in the paper only in the protocol.

We considered statistical significance confirmed when the False Discover Rate remained below 5%. To address the reviewer's concerns, the following additions have been made with new references added to support the analyses.

a. Methods, statistical analyses, page 4 last paragraph

All p-values are two sided without adjustment for multiplicity of tests. To address the multiplicity of outcome testing, a False Discovery Rate was calculated for all outcome p-values (31). We considered statistical significance confirmed when the False Discovery rate remained below 0.05.

b. Interpretation, page 6, first paragraph

When the False Discover Rate was calculated to account for the multiplicity of outcome testing, all outcomes with a nominal $p<0.05$ had a False Discover Rate below 5% and thus all conclusions remained intact. This robustness to adjustment for multiple comparisons is a consequence of most of the p-values being so highly statistically significant.

8. The study results show that there are positive results on surrogate parameters, which is not interesting. Performing such a big study and concluding that the risk has decreased is in my opinion not the kind of studies we would need . What we need is a study on hard clinical end points.

We would like to confirm our position that there have been several large RCTs that have already demonstrated the positive effect of diet and exercise on clinically hard outcomes, (Diabetes Prevention Program Research Group N Engl J Med. 2002; Estruch et al N Engl J Med. 2013, Hambrecht R et al Circulation. 2004 Mar 23;109(11):1371-8, Knowler et al. NEJM 2002:346:393-403, Lancet 2002;360:1455-61, Singh et al Lancet. 2002 Nov 9;360(9344):1455-61, Mente A et al Arch Intern Med. 2009;169(7):659-69). As we have already stated in the introduction, the purpose of this study was to demonstrate the feasibility of the diet and exercise intervention within real life settings..

Metabolic syndrome is recognized as a major and prevalent risk factor for cardiovascular disease by the World Health Organization (Diabet. Med. 15, 539–553 (1998), the National Cholesterol Education Program–Adult Treatment Panel III (J. Am. Med. Assoc. 285, 2486–2497, 2001) and the International Diabetes Federation (Lancet 366, 1059–1062 (2005) and we are in fact measuring valid end points of metabolic syndrome (Circulation. 2009;120:1640-1645). Hence our objective of demonstrating the feasibility of using diet-exercise in reducing metabolic syndrome is of clinical significance

To clarify the need for the present study, we have added the following to the introduction, page 3

Despite these promising results, uptake of lifestyle-focused preventive care for cardiovascular risk into Canadian primary care settings remains limited (20). Demonstration of the feasibility of efficacious interventions is needed.

9. Another problem with this study is that there is no critical analysis of the status of the metabolic syndrome. It is not enough that the authors state the importance of the syndrome in the introduction, they should also state the critics. And the question might also why this study has actually been performed. References 11 and 12 do not mention the existence of the metabolic syndrome yet the authors bring them in relation to it.

Thanks for this suggestion, we have now added a statement in the

	introduction about the critics of the MetS and added relevant references **Introduction, page 3, 3rd sentence has been added as follows:** **The concept of MetS has been criticized (6,7) despite its wide acceptance by the World Health Organization (8), the National Cholesterol Education Program–Adult Treatment Panel III (9) and the International Diabetes Federation (10).** **In our interpretation, we already have the following statement. Have added another reference and corrected the reference numbers as follows:** **The relevance of purely reversing MetS has been criticized by some (56, 7)** **As in our response to comment # 8 above, we maintain our position that MetS reversal plays an integral role in reducing risk of diabetes and CVD hence we feel that the reference #11 (now #16 Diabetes Prevention Program) and #12 (now #17) is highly applicable to our interpretation. In the Estruch et al 2013 study, the patients did have the components of MetS as illustrated in the baseline characteristics.** **For response to the question of why this study has been performed, please see our response to comment #8 above.**
Reviewer 2	Dr. Laura Rosella PhD MHSc
Institution	University of Toronto, Dalla Lana School of Public Health, Toronto, Ont.
General comments (author response in bold)	Summary Lifestyle interventions are important for the prevention of chronic diseases. This paper examines the effect of an intervention integrated into family practice for people with metabolic syndrome (MetS). The paper does not compare the intervention with a control group thus the ability to look at efficacy or effectiveness is limited. Overall the paper is quite short and would benefit from expanded details in the methods in particular. Major comments: 1. The paper would benefit from more detail on the intervention itself within the text. Several interventions exist for lifestyle/diet modification which have been tested in randomized trials (for e.g. DPP). It's not clear how/if this builds upon existing lifestyle modification interventions. For the physical activity part – was a trainer involved or did the participant do these activities on their own? Further, there is presumably information on how the program was developed (in terms of theories and informing practices/evidence) that would be helpful for the reader. While the long protocol provided as supplementary material is helpful, details of the interventions should be significantly expanded within the manuscript itself. **We agree with the reviewer and would like to point out that we have already made reference to the theories and practices for the program in the methods section as follows:** **Methods, Settings and Design, page 3, references 22-25** **Each patient was seen by the registered dietitian (RD) for individualized counselling, based on a care map that incorporated evidence from clinical trials and principles of health behaviour change from the integrated behavioural model (22), with an emphasis on the Mediterranean diet (23). Diet quality was determined by two 24-hour recalls one week apart that were used to calculate the Canadian Health Eating Index (HEI-C) (24) and Mediterranean Diet Score (MDS) (25).** **We have expanded the methods section, page 4 to add the following, as suggested by the reviewer:** **Each patient was also seen by the clinic kinesiologist for assessment of their fitness and physical activity habits and for an individualized fitness plan that included supervised and unsupervised aerobic activity, resistance training and flexibility exercises.** **The program prescribed follow up visits with the FP at 3, 6, 9 and 12 months for a review of blood pressure, glucose, lipids (triglycerides, high density lipoprotein cholesterol [HDL-C]), medications and changes in waist circumference and body weight. Weekly visits with the dietitian and kinesiologist for first 3 months were followed by monthly visits for 9 months. Ongoing encouragement was provided by all staff to support the patient in making lifestyle changes based on progress achieved in MetS components.** 2. Without a control group, it is difficult to say if these changes would have happened anyway simply on the advice on the physician or through patient initiative. The authors themselves describe this as a demonstration study. As a result, the concluding statements are quite bold. For example –it is not optimal to state "effective" in the concluding statement of the abstract. Also the conclusion of the discussion stating that family practices should include such a program based on this study can been seen as an overstatement since control groups were not included and the effectiveness of the intervention cannot be assessed. I suggest the language should be toned down to this effect throughout the manuscript. **See response to Editors comments point #1** 3. More details are required as per how the sites were chosen and the patients were

	chosen within the sites to assess the possibility of selection bias. Further, the role of selection bias in the study findings needs to be discusses. In particular, those that were enrolled may not be representatives of all patients in a typical FP practice – they may have been more willing to change and thus the benefits of the program were overemphasized. In fact, selection bias could explain the results significantly – it is difficult to rule that our without more information. **See response to Editors comments point #5.** 4. Some information regarding enrollment is missing. For example, Figure 1 states that 305 patients were enrolled, but how many were approached. I.e. what is the basic study inclusion rate? This information is important as those that were enrolled likely differ from those that were not and depending on how high the enrollment rate was, this may affect study validity. **We acknowledge that inability to report an inclusion rate is a limitation of the demonstration project design. Given that this study was done is a real-life setting, the centres were unable to track all the patients that were approached.** 5. It is unclear how the analyses that involve waist circumference correlations with other outcomes fits in with the study as those correlations are not the aim of the intervention and not unsurprising given the nature of the measures. I would suggest removing this or adding additional information as to how/why these analyses contributes to the objective. **As suggested by the reviewer, we have removed all text related to the correlations from the manuscript** 6. The result on aerobic capacity are interesting, but it is not clear how this relates to MetS. Presumably if fitness is improved, this should help reduce some of the components of MetS but the objectives do not clearly outline this. Further the intervention itself does not include aerobic fitness in its program objectives. One can improve fitness without seeing changes in weight or MeTS components therefore these changes may not directly tie to program objectives. Can the authors be more explicit about the purpose of these analyses and their implication for the demonstration study? **Agree that we can make the association of aerobic capacity to MetS clearer. Accordingly, we have referred to a detailed study demonstrating how aerobic exercise alters the fundamental physiological abnormality of insulin resistance, in the introduction as follows** **Aerobic exercise training resulting in increased aerobic capacity has been shown to reduce insulin resistance, which is the basis of the metabolic syndrome (19)** 7. Some important limitations are not reported, for example the challenges/potential biases with diet recall. **Thanks for this comment. We have already addressed this under the response to the Editor's comment #5.** 8. Some of the results in table 4 are confusing – consider changing the scale or applying a transformation (for eg on LDL and fasting glucose) to make the results more interpretable. **Thanks for your observation of table 4. We have added the units to make this clearer** 9. The conclusions regarding the widespread implementation of this program within Canada'a universal healthcare system is challenging since family physicians do not all have staff dieticians and kinesiologists or other lifestyle coaches. Significant investments would be needed to roll out a program such as this and this should be acknowledged. **Thanks for this great suggestion. We have changed the conclusion on page 7 as follows:** **In conclusion, we demonstrate that it is feasible to recruit patients with MetS to a lifestyle program of diet and exercise in a family medicine primary care setting that includes the FP, dietitian and kinesiologist. Such a program may be associated with a reverse reversal of MetS by 19% and has the potential to improve clinical outcomes such as the risk of acute myocardial events. Given Canada's publicly funded universal healthcare, the widest possible coverage of the population to reverse MetS would be to institute a CHANGE-like program of diet and exercise treatment in family practice settings across Canada. Although not all primary care settings have access to dietitians and exercise specialists, several jurisdictions have recognized the importance of the patient's medical home incorporating an interdisciplinary team (38). Our work raises the need for FPs to recognize lifestyle as highly relevant (39) and for dietitian and exercise specialists to be on primary care teams.** Minor comments #1"evaluable follow-up" on p.4 line 10 – not sure what this means **Good point. We have changed the word "evaluable" to "any".** #2 P-values in table 1 are not needed, but the authors can leave if they wish. **We generally agree that p-values are not essential in tables describing patient characteristics and are nonsensical when comparing groups assigned by randomization. But, some readers might wonder if the observed differences are consistent with random sampling error or if there appear to be true**

	differences in the populations who did and did not complete the 12 month assessment. We're happy to remove the p-values if the editor prefers, but we do find they may are meaningful in this context