Author's response to reviews

Title: WEARCON: Wearable home monitoring in children with asthma reveals a strong association with hospital based assessment of asthma control.

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Author's response to reviews:

Editor Comments:

EDITOR: When responding to many points raised by the reviewers, please do also remember about adequate, transparent presentation of the results of multivariate analysis in updated version of the manuscript (please see comments of the Reviewer 4).

RESPONSE: We would like to thank all the reviewers for their many points. We believe the updates we implemented in the manuscript according to their comments strengthen the adequate presentation of the results and the overall quality of the manuscript. We re-analysed the multivariate results according to the comments of reviewer 4.

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Reviewer 1:

REV1: This manuscript reports what to this reviewer is a novel wearable monitoring device, and assesses its performance when combined with other home monitoring devices which have been used before in the assessment of children with asthma. There can be no question but that the current clinical evaluation of asthma in children is far too subjective, casual and intermittent. Also, any sort of home monitoring that requires the child/family actively to make recordings is doomed to failure. The authors should make the point and cite literature that home peak flow monitoring often only results in a stream of fabricated data! This program, with a wearable device, overcomes the problem of relying on patient cooperation to gather at least some data, and this is one of its strengths that could be stressed further; the Smartinhaler measures activation of the device (not correct technique), also without requiring cooperation, and I presume although not overtly stated (apologies if
overlooked) that spirometry is electronically recorded; this of course does rely on patient effort. In this regard, I would like to see data on the percentage of satisfactory measurements which were achieved The overall study is for sure innovative, and the authors have certainly discovered some interesting physiology of uncontrolled asthma, such as respiratory rate recovery time after exercise and the earlier waking, and the effects of the latter in particular would merit further study. But I have reservations as to whether in fact they have made the case that we should be exploring the use of home monitoring for clinical purposes, and I am certain their conclusions are overcalled.

RESPONSE: We added data of the compliance to home-measurements and the percentage of satisfactory spirometry measurements to the first paragraph of the result section (page 12). Our choice of devices did indeed strongly consider the ease of use so that it would be feasible for children to cooperate to use the device for 2 weeks. We also provided an individual instruction session (of approx. 45min), allowing the children to properly use the devices and training the children to perform satisfactory spirometry measurements. We agree that these strengths could be stressed further and therefore emphasized this in the manuscript (page 7 paragraph 1 + page 19 last paragraph).

MAJOR POINTS

1.1 The authors define uncontrolled asthma either on GINA guided questions or on a positive exercise challenge or both. What I could not discern is how predictive GINA questions on their own were of the results of their home monitoring. If in fact the GINA questions on their own performed equally well as home monitoring, the need for sophisticated home testing evaporates.

1.1 RESPONSE: In general questionnaires for childhood asthma control have a weak correlation to extensive clinical evaluations of asthma control (Peijnenburg et al. 2015: https://erj.ersjournals.com/content/45/4/906.full), literature suggests this is due to the variable perception and recall bias of report of symptoms (Carroll et al. 2012; https://erj.ersjournals.com/content/39/1/90). Gina guided questions have the same limitations as other asthma questionnaires as they issue the same domains. Therefore objective provocation

testing (exercise challenge testing) as also described in GINA (report 2018) could add to the definition of uncontrolled asthma and provide complimentary objective information. This is also provided by our home-monitoring approach and indicates the need for non-obtrusive wearable home-monitoring.

1.2 Paediatrician-diagnosed asthma is a slightly iffy concept. How were they diagnosed? A recent Dutch primary care study has highlighted that at least out in the community, diagnosis is wildly inaccurate [Br J Gen Pract. 2016; 66: e152-7]. The UK is no better for accuracy of diagnosis. Were those with "well-controlled asthma" in fact children who did not have asthma at all? This could be settled with a table of diagnostic criteria utilised.

1.2 RESPONSE: We agree diagnosis of asthma in children is inaccurate in primary care. However, our study was performed in a referral centre for childhood asthma, where we review kids not only schedually but also with acute symptoms. Furthermore, we have excellent laboratory facilities enabling us to identify asthma at different ages. All children had a history of asthma attacks which in our health care system is the indication to manage these children in a referral centre. We clarified this in the subject section of the methods (page 5 and page 6).

1.3 Of course, the risk of making any measurements is that it alters the very thing you are trying to measure. So wearing a device which monitors my activity may make it more likely that I will try to be more active. The authors need to discuss this in my view/

1.3 RESPONSE: The dynamics of observed physical activity did not suggest a direct effect of the wearable activity trackers, as there was no transient burst of activity following application. The trackers did not show interpretable data to the subjects and were only readable through electronic means (software possessed by the researchers), so children did not get feedback of their results. Moreover, all children followed the same 2 week home-monitoring protocol with the same devices, so if the effect was present, it would assumed to be similar in all groups. The section wearable devices in the methods (page 7) includes the sentence: “Wearables did not show interpretable data to the subjects to prevent any influence and data was stored anonymously.”

1.4 I am concerned about the interpretation of exercise data in the community. These are very variable and I would invite the authors to reflect on Powell CV, White RD, Primhak RA. Longitudinal study of free running exercise challenge: reproducibility. Arch Dis Child. 1996; 74: 108-14 and consider their data in the light of this manuscript.

1.4 RESPONSE: We studied the article of Powell and share their reservations about an exercise challenge test (ECT) as a screening tool for childhood asthma in the community. However, we selected children with diagnosed asthma from a referral centre. Furthermore our exercise test methodology differs vastly from theirs as we use a climate chamber (<10degree Celsius and dry air), increasing sensitivity of the test, and meticulously titrate and monitor exercise intensity and monitor FEV1 (and not PEFR) frequently after the challenge starting at 1 minute after exercise. Children commonly have breakthrough exercise induced bronchoconstriction (EIB) (van Leeuwen et al. 2011 https://adc.bmj.com/content/96/7/664) and starting measurements at 5 minutes , as Powell did , after exercise will reduce sensitivity of the test as lung function is already recovering. An ECT is a highly specific test for childhood asthma and in cold and dry air

conditions also a sensitive test (Coates et al. 2017 https://erj.ersjournals.com/content/49/5/1601526) able to discern a bronchial response even if asthma is quiescent, which is important for a screening tool, as Powell stated.
Powell measured EIB monthly over the course of a year and showed that there was a variation which is understandable as EIB follows the waves of asthma. However ECT's are acceptably reproducible on short term, within 2 weeks (as Powell mentioned in his paper) when there have been no major changes in the condition of the child.

1.5 The statistical section is beyond this reviewer's expertise, and should be looked at by an expert. There should be a statement about power calculation within this section and not at the start of the methods.

1.5 RESPONSE: We moved the sample size section to the end of the methods and implemented the comments of reviewer 4 (the statistical expert).

1.6 Table 2 and Figure 3 are textbook illustrations of the difference between what is statistically significant, and what is actually useful to a clinician treating an individual patient. There is tremendous overlap between the groups; other than reliever use, about half the uncontrolled asthmatics lie within the controlled box and whisker plot. So these parameters in isolation will be of no use to me for monitoring an individual, as opposed to showing differences between groups

1.6 RESPONSE: We totally agree, and this is why we aimed to combine multiple parameters in a multivariate model. This also holds true for the daily clinical practise. No clinician will let him/herself be guided by a single question/answer during a patient visit. Clinicians are trained to combine all the factors to come up with the right diagnosis and treatment. So despite the fact that some single parameters being statistically significant and do reveal a suggestion for the individual patient whether his/her asthma is controlled or not, we agree that a combining approach, as proposed in this study, is needed to be able to reach a high level of accuracy (high sensitivity and specificity).

1.7 However, the authors then go on to combine variables which are excellent in separating controlled from uncontrolled asthma. These analyses are a post hoc fishing expedition. There is nothing at all wrong with this, but until the findings are verified in another cohort, they can only be seen as hypothesis generating. The authors thus overcall the significance of their study. They do acknowledge the need for further research, but they absolutely must acknowledge that they cannot make these sorts of positive conclusions from a post-hoc analysis.

1.7 RESPONSE: We agree on this and therefore the revised discussion also contains this paragraph: "Although the results of this study emphasize the potential relevance of home-monitoring, further studies should validate the model of the WEARCON study. The model has been built on a training dataset of 60 asthmatic children, but has to be validated with a validation dataset of home-monitoring data in asthmatic children to determine the exact effect size." We therefore also adapted the text in the conclusion so that it now says that this study showed a correlation between data of home-monitoring device and asthma control and explicitly not state that we can classify asthma control, as this has to be validated.

1.8 My hunch which the authors can refute from their data or otherwise is that actually all that is needed for determining whether a child has well controlled asthma is putting a smartinhaler on their salbutamol. In this regard, children often have multiple inhalers, in the car, at school, with grandparents, etc. Did they have Smartinhalers on every one? Or could they have missed doses

1.8 RESPONSE: From the data of the study we indeed saw that the reliever use is one of the most important parameters to distinguish between controlled and non-controlled asthma. However, we also believe (and did see) that this does not count for every individual asthmatic child. For example some children are poor perceivers resulting in reliever misuse or almost no use at all. For these children another parameter such as the lung function variation, respiratory rate recovery time or the wake-up time might be reflecting their asthma control more sufficiently. This is why we think combining parameters results in a better classification of asthma control. For this study they received two Smart inhalers (one for reliever use and one for controller use). We instructed them to use those inhalers for 2 weeks. Parents indicated this was feasible for a period of 2 weeks.

1.9 A weakness of this study is the absence of any qualitative data. How acceptable were these devices for children and their families? Likewise there is no health economics, which will also be important in determining whether we can use the device clinically.

1.9 RESPONSE: We added qualitative data about the compliance to measurements and satisfactory spirometry measurements to the results in the manuscript (page 12). It is of note that this study was aimed to identify relevant physiologic monitoring parameters with state-of-the art non-obtrusive home-use technology, and to which level these parameters correlated with asthma control (a hypothesis generating study as reviewer 1 commented in point 7). The implementation strategies with regard to patients acceptance, economic efficiency, but also social and healthcare barriers is a broad and different research question. Furthermore, for the purpose of this study the children were monitored for 2 weeks, which is not comparable to long-term monitoring in terms of acceptance and health economics.

MINOR POINTS

1.10 This manuscript is generally extremely well and clearly written, but there are some minor typos and incorrect grammatical usage which should be corrected

1.10 RESPONSE: We addressed all typos/incorrect grammar use indicated by the reviewers.

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Reviewer 2:

General comments
I recommend changing some of the terminology:
2.1 Rather than investigate whether asthma control can be "correctly" assessed, I would say something along the lines of "accurately" or comparable to existing strategies, etc.
2.1 RESPONSE: We agree and updated correctly to accurately throughout the manuscript.

2.2 Would use a term such as "non-asthmatic" children rather than "healthy" children
2.2 RESPONSE: We agree non-asthmatic is a better term and updated it throughout the manuscript.

2.3 When you say "hospital" do you mean inpatient hospital ward?
2.3: RESPONSE: No we meant the outpatient clinic. We updated this in the manuscript to clarify this issue.

2.4 You report negatively about composite asthma control questionnaires, yet I believe that's a large part of how you measure your device. You may want to word this differently (page 3, 3rd paragraph) or comment on this in the discussion.

2.4 RESPONSE: What we meant and what is known in literature is that composite questionnaire scores have not been able to improve symptom management (Peijnenburg et al, 2015, http://dx.doi.org/10.1183/09031936.00088814). But we agree this could lead to confusion as our study does composite objective monitoring parameters. Therefore we rephrased the sentence on page 3, 3rd paragraph to: “Monitoring the questionnaire scores alone has yet not been able to improve symptom management or impact daily life (13).”

-In general, the writing could use some tightening
Abstract
2.5 The conclusion sentence "home-monitoring of physiological parameters is associated with…" is a little unclear. I'd suggest replacing "associated" with another term such as corroborates/correlated/estimates/matches/etc

2.5 RESPONSE: We changed associated to correlates in the conclusion of the abstract and the conclusion section of the manuscript.

Background
2.6 Would remove the sentence "national and international respiratory associations…." Or if you keep it, cite reference(s)
2.6 RESPONSE: We included the references to this sentence.

2.7 An example of "tightening" would to remove words such as "on the other hand" (page 3, line 38)
2.7 RESPONSE: We removed this in the manuscript.

2.8 Paragraph 4 - consider this reference: https://www.ncbi.nlm.nih.gov/pubmed/23564399
2.8 RESPONSE: We added this reference to paragraph 4.

2.9 3rd paragraph. Aren't composite scores one of the ways you're considering that your device is "correct?" (see above comments).
2.9 RESPONSE: See comment 2.4, the sentence is rephrased.

2.10 Another reference perhaps https://www.ncbi.nlm.nih.gov/pubmed/16520675
2.10 RESPONSE: A very interesting suggestion. The more recently published study of C. Dinakar, "Clinical Tools to Assess Asthma Control in Children" https://www.ncbi.nlm.nih.gov/pubmed/28025241, does even better fit the manuscript as she states: "The tools available in a clinical practice setting can be classified as subjective ("patient reported") and objective ("physiologic and inflammatory measures"). A judicious combination of measures from each category may be needed to optimally assess asthma control." This is exactly the point we make in in the manuscript paragraph 3, as there is a need for "additional complementary objective methods to monitor asthma control at home". We therefore included this reference.

2.11 The tools available in a clinical practice setting can be classified as subjective ("patient reported") and objective ("physiologic and inflammatory measures"). A judicious combination of measures from each category may be needed to optimally assess asthma control.
--Consider this reference after the sentence "despite considerable interest in asthma home-monitoring in children…" (page 4, last paragraph): https://www.ncbi.nlm.nih.gov/pubmed/29688023
2.11 RESPONSE: Very interesting study indeed. We added this to the mentioned sentence.

Methods
2.12Page 5, line 15 and figure 1. What do you mean by "hospital visit"/In hospital evaluation of asthma? They were admitted to the inpatient ward for this study? Or did it take place in clinic and pulmonary function lab.
2.12 RESPONSE: See point 2.3. We did update in-hospital evaluation to outpatient-clinic evaluation. And also altered the figure legend.

2.13Were there really 4 year olds in the study? Doesn't seem like it based on Table 1. Also, were you able to obtain reliable BPT testing in the younger kids (especially under 10 years old)?
2.13 RESPONSE: Yes, there were 3 asthmatic and 2 non-asthmatic 4 year olds included. But as table one indeed indicates, the age of the children was normally distributed around the average of 9 year old, with standard deviations between 2 and 3, indicating that most children were in the category between 6 and 12 years old. We agree that young children often require more attention to learn to perform reliable and reproducible spirometry. The BPT was executed by experienced personnel and the exercise challenge was performed on a jumping castle for children below 8 years old (van Leeuwen et al. , 2013, https://pubmed.ncbi.nlm.nih.gov/23199614/). We included this description of the BPT protocol to the method section (page 6).

2.14 Page 6, lines 24-39 (asthmatic children section). Recommending using the sentence about "many children with poorly controlled asthma avoid…" to explain why a BPT was also used in addition to the GINA control composite questions.
2.14 RESPONSE: The following sentence does indirectly say that, but we agree it is better to explicitly state the explanation and therefore included the following sentence: "Therefore, the BPT was used in addition to the GINA recommendations to assess asthma control." Followed by the definition of uncontrolled asthma.

2.15 Page 6, line 54. How did you determine asthma symptoms? What determined if they were "prevalent" or not?
2.15 RESPONSE: Before inclusion we asked the parents if the child was never diagnosed with asthma, used asthma medications or had/have asthma related symptoms (such as shortness of breath, wheezing etc). This was solely to pre-screen the controls to prevent possible "accidental findings of children with asthma". Due to these questions we did exclude some volunteers from participation. During the outpatient-clinic visit, after the 2 weeks of home-monitoring, all children from the non-asthmatic group were fully assessed with a medical history and the BPT. None of these non-asthmatic children revealed asthma symptoms. In order to make it more clear we adjusted "prevalent" to "self-reported" asthmatic symptoms in the method section of the manuscript.

Discussion
2.16 Page 15, line 10. I'm unclear about what "assessed in the hospital during extensive evaluation" means (see above comment in methods section)
2.16 RESPONSE: An outpatient-visit in combination with the BPT. This test takes about an hour and therefore is quit extensive. We adjusted the sentence to the following: "as assessed in the outpatient-clinic during an extensive evaluation including a bronchoprovocation test."

2.17 Were the subjects paid?
2.17 RESPONSE: No they were not, as this could have influenced their behaviour. They were only thanked for their participation by a small gift afterwards (step-counter > worth approx. 3 euro's).

2.18 What do you think kids adherence to wearing the device will be outside of a research setting (i.e. would this be feasible in the "real world" to have the kids wear all this equipment)?
2.18 RESPONSE: Good point, we included some data of the compliance to home-monitoring in the result section and expanded the implication paragraph (p.18 last paragraph) in the discussion session to review our perspective on this.

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Reviewer 3:
3.1 This is a very interesting paper, well designed and performed within the small sample size limitations. Because of the small sample size, I think the title should include the words" a pilot study".
3.1 RESPONSE: We agree that for extensive multivariate analyses a larger sample size would be desirable, so that besides the most important parameters also other predictors (like age, gender etc.) could be entered in the analysis. However, we do believe that 2 weeks of multi-parameter home-monitoring data of 90 children is sufficient to adequately substantiate our findings on relevant monitoring parameters and therefore answer our primary research question of this study. We carefully selected the monitoring parameters and devices beforehand based on literature research and in our view this study has both a hypothesis generating as hypothesis confirming character. Moreover, we hesitate to classify this as a "pilot" study, because in the field of eHealth research the term pilot-study is often confused with a feasibility study.

REV3: The authors present a prospective observational design that includes sixty children with paediatrician-diagnosed asthma and thirty healthy children asthmathic childrem with the aim of investigating whether asthma control can be correctly assessed in the home situation by combining parameters from respiratory physiology sensors-

3.2 The level of the severity if asthma and consequently the actual maintenance therapy remain incompletely clarified, so it is not clear whether these aspects have been considered in multivariate analyses: I think these aspects should further be explored in larger studies.
3.2 RESPONSE: The maintenance therapy and an indication of the severity of the included patients can be retrieved from the baseline characteristics in the result section. These aspects were not included in the multivariate analyses, but as indicated could indeed be explored in al larger study. We included a statement in the statistical analysis section of the methods (as also indicated by reviewer 4), that possible other predictors (like age, gender etc.) were not added to the multivariate analysis.

3.3 Furthermore, I think that the 2-week time interval is too short to evaluate the control status since usually the control status is evaluated with 4-week intervals according to the GINA guidelines.
3.3 RESPONSE: GINA indeed uses a 4-week interval (for both adults and children from 6years old). It could be argued that for (young) children this period may be long as their course of asthma is very variable. Multiple validated paediatric measurements (i.e. the childhood asthma control test = 1week) also use shorter intervals to assess asthma control. We had to balance the monitoring interval based on the fact that the bronchoprovocation results have a limited time of reproducibility. To avoid anticipated compliance issues we had to contain the monitoring period. This brought us to the compromise of 2 weeks of monitoring.

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Reviewer 4:
The authors of this manuscript have addressed an important topic related to home-monitoring of asthma control. They have done a good job of only drawing appropriate conclusions based on the results presented. Nonetheless, there are several statistical points that must be addressed.

4.1 Generally speaking, p-values less than 0.05 are considered statistically significant, not less than or equal to.
4.1 RESPONSE: This is adapted in the manuscript. It had no consequences with regard to the results.

4.2 How many imputed datasets were created? Just one or multiple? This needs to be explicitly stated.
4.2 RESPONSE: We did the analysis based on a single imputed dataset, but in consult with a statistician we decided to reanalyse the data based on a pooled dataset of multiple imputations. Therefore, we created 5 imputed datasets (the default of SPSS) and pooled the data according to the "bar procedure" (Baranzini, 2018, DOI: 10.13140/RG.2.2.33750.70722). We updated the method section in the manuscript: "Five imputed datasets were created and pooled according to the bar procedure (32)". Also the multivariate result section was updated based on the new analysis.

In tables 1 and 2:
4.3 Some indication of the overall p-value for the ANOVA or Kruskall-Wallis test across the three groups should be indicated in the tables. Without this information, there is no justification for including information about the specific pairwise comparisons.
4.3 RESPONSE: A column is added to table 1 and 2, which shows the p-value of the ANOVA or Kruskal-Wallis test.

4.4 An indication of which variables were non-normally distributed would also be helpful. Though this can be inferred by looking at whether the statistic shown is mean +/- SD or median (IQR), it would be helpful to have this indicated more explicitly.
4.4 RESPONSE: Along with the added P-value, we included signs to indicate whether the data was normally distributed and which test was used per variable.

4.5 It would be helpful to have the order of columns in these tables reflect the hypothesized ordering of the asthma predictors. For example: healthy, controlled, uncontrolled, or vice versa.
4.5 RESPONSE: We changed the columns to: uncontrolled – controlled – healthy.

Regarding the multivariate analysis:
4.6 The methods section states that a multinomial logistic regression was used but the results seem to indicate that a binary logistic regression was used? This is an important distinction that needs to be clarified further! As the paper currently stands, it looks like the results reported are from a binary logistic regression predicting either controlled or uncontrolled asthma, but this is in contrast with the methods described in the "Statistical Analysis" section.

4.6 RESPONSE: We do agree on this. We chose to exclude the multinomial regression results (controlled, non-controlled, non-asthmatic) from the manuscript and focused on the binary logistic regression analysis (controlled versus non-controlled) but this was not adapted in the method section. We updated the method section accordingly.

4.7 The reference group used for the multivariate analysis (whether it is a multinomial or binary logistic regression) needs to be explicitly stated and should also be used in helping interpret the odds ratios (for example, higher FEV1 was associated with higher odds of XX asthma group, compared to YY asthma group).
4.7 RESPONSE: The reference group was the controlled asthma group. (so when interpreting; higher odds of the non-controlled group, compared to the controlled asthma group). We emphasized this in the method and results section.

4.8 It is not clear exactly which variables were included in the final multivariate model. A table or figure showing the results of this multivariate model is needed to better understand exactly which variables were included. Did the models control for potential confounders like age and gender? Were all home monitoring parameters assessed for inclusion in this final multivariate model or only the ones with significant results on univariate analysis?
4.8 RESPONSE: All variables which are shown in table 2 (which were also analysed for univariate analysis) were assessed for inclusion in the analyses. The model did not include potential other predictors (like age, gender etc) as we would like to focus on the home-monitoring parameters. We added this information to the methods of the manuscript.

4.9 This multivariate model seems to be at the heart of the results/implications for this manuscript, but as it currently stands it is not well-explained, which weakens the manuscript considerably. I strongly encourage the authors to provide more detail and reconcile contradictions in the writing to help improve the quality of the results.
4.9 RESPONSE: We updated the manuscript according to your comments. We also included the detailed model characteristics (table 4) so that other professionals could use the model as well.