PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A new and automated risk prediction of coronary artery disease using clinical endpoints and medical imaging-derived patient-specific insights: protocol for the retrospective GeoCAD cohort study
AUTHORS	Adikari, Dona; Gharleghi, Ramtin; Zhang, Shisheng; Jorm, Louisa; Sowmya, Arcot; Moses, Daniel; Ooi, Sze-Yuan; Beier, Susann

VERSION 1 – REVIEW

REVIEWER	Aravind Akella Qualicel Global Inc
REVIEW RETURNED	18-Oct-2021

GENERAL COMMENTS	This is a very interesting attempt to identify CAD in patients using several measurable clinical variables and imaging with the aid of Machine Learning. This is a novel and very judicious attempt. While the clinical and imaging parts of the protocols are very well addressed, absolutely nothing is presented on the ML side other than citing their past work. I would have felt that ML should have been discussed equally for the protocol to claim ML prediction in the title. I encourage the authors to come up with a set of ML algorithms they would look into (such as Neural Networks, Random Forest, to start with) and discuss how each algorithm will be evaluated with the use of the standard parameters. (As the ML presentation is substantially lacking, several items in the Reviewer Checklist are rated as N/A).

REVIEWER	Wullianallur Raghupathi Fordham University
REVIEW RETURNED	04-Feb-2022

GENERAL COMMENTS	My most serious concern is lack of specific on the 'machine learning.' More details are needed, for e.g., is it deep learning image recognition using convolutional neural networks? The proposal outlines outdated approach. There is a lot of advanced work already done which is not even cited. I recommend researchers search and look at articles in NATURE journals. Chao, H., Shan, H., Homayounieh, F. et al. Deep learning predicts cardiovascular disease risks from lung cancer screening low dose computed tomography. Nat Commun 12, 2963 (2021). Cheung, C.Y., Xu, D., Cheng, CY. et al. A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre. Nat Biomed Eng 5, 498–508 (2021). Poplin, R., Varadarajan, A.V., Blumer, K. et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng 2, 158–164 (2018).

	Zeleznik, R., Foldyna, B., Eslami, P. et al. Deep convolutional neural networks to predict cardiovascular risk from computed tomography. Nat Commun 12, 715 (2021). Huang, W., Ying, T.W., Chin, W.L.C. et al. Application of ensemble machine learning algorithms on lifestyle factors and wearables for cardiovascular risk prediction. Sci Rep 12, 1033 (2022).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

While the clinical and imaging parts of the protocols are very well addressed, absolutely nothing is presented on the ML side other than citing their past work. I would have felt that ML should have been discussed equally for the protocol to claim ML prediction in the title. I encourage the authors to come up with a set of ML algorithms they would look into (such as Neural Networks, Random Forest, to start with) and discuss how each algorithm will be evaluated with the use of the standard parameters.

We agree with the reviewer and have added a detailed discussion on existing ML methods for CAD risk stratification in the introduction and discussion sections. (pg. 6 line 11 – pg. 7 line 15, pg. 16 line 15-28). [37-41, 68-77] Additionally we have extensively extended the data analysis section including proposed machine learning methods (pg. 12 line 6 – pg. 13 line 12), Briefly, Convolutional neural networks and random forest models will be investigated for risk prediction, with AUC metric reported for comparison against existing literature.

Reviewer 2

My most serious concern is lack of specific on the 'machine learning.' More details are needed, for e.g., is it deep learning image recognition using convolutional neural networks?

We have now elaborated on the proposed ML algorithm and the evaluation metrics (pg. 12 line 6 – pg. 13 line 12), and also expanded on existing ML methods for CAD risk stratification (pg. 6 line 11 – pg. 7 line 15, pg. 16 line 15-28).

The proposal outlines outdated approach. There is a lot of advanced work already done which is not even cited. I recommend researchers search and look at articles in NATURE journals.

Chao, H., Shan, H., Homayounieh, F. et al. Deep learning predicts cardiovascular disease risks from lung cancer screening low dose computed tomography. Nat Commun 12, 2963 (2021).

Cheung, C.Y., Xu, D., Cheng, CY. et al. A deep-learning system for the assessment of cardiovascular disease risk via the measurement of retinal-vessel calibre. Nat Biomed Eng 5, 498–508 (2021).

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Zeleznik, R., Foldyna, B., Eslami, P. et al. Deep convolutional neural networks to predict cardiovascular risk from computed tomography. Nat Commun 12, 715 (2021).

Huang, W., Ying, T.W., Chin, W.L.C. et al. Application of ensemble machine learning algorithms on lifestyle factors and wearables for cardiovascular risk prediction. Sci Rep 12, 1033 (2022).

We have updated and expanded our ML-based literature discussion based on the cited work and additional references. We also expanded the data analysis section to better explain our intended methods. Below is a brief summary of the discussion of the added studies.

We discuss Chao et al. [37] and Zeleznik et al. [41] published in Nature Communications as they use deep learning methods to predict cardiovascular risks from computed tomography. This work showed the ability of DL methods to quantify CVD mortality risk and automatically quantify coronary calcium from computed tomography. We also included Kurkure et al., Lessmann et al. and Martin et al. [73-75] as prior ML methods in investigating calcium scoring from computed tomography images, although the correlation to risk was not directly performed. Prior work based on different approaches, for example physical activity status by Huang et al. [40], retinal images by Poplin et al. and Cheung et al. [38,39] and echocardiography by Samad et al. and Ulloa Cerna et al. [71,72] and review of recent methods by Kadem et al. [69] are also now included. We note that the approaches used in these works do not have the capability of considering local risk factor identification, which we intend to build upon through the addition of haemodynamic considerations as proposed (pg. 16 line 20-28). We also mentioned Benjamin et al. [68] on the challenges in comparability and reproducibility in existing machine learning methods, as well as Tesche et al. [77] , an editorial comment highlighting the need for a new machine learning-based cardiovascular risk assessment system that outperforms the conventional Framingham assessment, in an effort to better highlight the need for our efforts.

VERSION 2 – REVIEW

REVIEWER	Aravind Akella Qualicel Global Inc
REVIEW RETURNED	30-May-2022

GENERAL COMMENTS	The authors have made considerable effort in revising the protocol manuscript to include discussion on their planned use of the ML algorithms (pgs. 22 through 24). They also rightly recognized the current ML CAD landscape only includes risk models and they plan to go deeper than that. The addition of advanced imaging should no doubt help further their goal. It would have been nicer, as I initially suggested, if they had also included a discussion on how they would evaluate the ML algorithms with the use of standard parameters (see for example: Akella and Akella (2021) (https://www.future-science.com/doi/10.2144/fsoa-2020-0206). In spite to this weakness I would gladly recommend this manuscript for publication.