Smart Phone based Fundus Imaging for Diabetic Retinopathy Detection

Adarsh Benjamin¹, Farha Fatina Wahid^{2, *} and Jenefa J³

¹Department of Artificial Intelligence and Machine Learning, CMR Institute of Technology, Bengaluru - 560037, Karnataka, India ²Department of Information Technology, Kannur University, Kannur - 670567, Kerala, India

³Department of Computer Science and Engineering, Christ (Deemed to be University), Kengeri Campus, Bengaluru - 560074, Karnataka, India

Abstract

INTRODUCTION: Diabetic retinopathy (DR) is one of the consequences of diabetes which if untreated may lead to loss of vision. Generally, for DR detection, retinal images are obtained using a traditional fundus camera. A recent trend in the acquisition of eye fundus images is the usage of smartphones to acquire images.

OBJECTIVES: This paper focuses on the study of existing works which incorporated smartphones for obtaining fundus images and various devices available in the market. Also, the common datasets used for carrying out DR detection using smartphone-based fundus images as well as the classification models used for the diagnosis of DR are explored.

METHODS: A search of information was carried out on articles based on DR detection from fundus images published in the state-of-the-art literatures.

RESULTS: Majority of the works uses SBFI devices like 20D lens, EyeExaminer etc. to obtain fundus image. The common databases used for the study are EyePACS, Messidor, etc. and the classification models mostly rely on deep learning frameworks.

CONCLUSION: The use of smartphones for capturing fundus images for DR detection are explored. Smartphone devices, datasets used for the study and currently available classification models for SBFI based DR detection are discussed in detail. This paper portrays various approaches currently being employed in SBFI based DR detection.

Keywords: Fundus imaging, smartphone-based fundus imaging, diabetic retinopathy, deep learning

Received on 19 September 2023, accepted on 05 November 2023, published on 13 November 2023

Copyright © 2023 A. Benjamin *et al.*, licensed to EAI. This is an open access article distributed under the terms of the <u>CC BY-NC-SA</u> <u>4.0</u>, which permits copying, redistributing, remixing, transformation, and building upon the material in any medium so long as the original work is properly cited.

doi: 10.4108/eetpht.9.4376

*Corresponding author. Email: <u>farhawahid@gmail.com</u>

1. Introduction

Diabetic Retinopathy (DR) is an eye disease which when untreated may result in partial or complete blindness of the eye. Study has shown that the causes of DR may be old age, cardiovascular diseases, unhealthy diet, unchecked diabetes, smoking/drinking, high cholesterol levels, pregnancy, etc. (1). Diabetic Retinopathy has been classified into mainly two types: non-proliferative DR and proliferative DR. Non-proliferative DR is further classified into mild, moderate and severe (1). Patients with DR above or with severe NPDR may lead to vision loss. The process of degeneration starts with the swelling of retinal blood vessels called microaneurysms creating clots/hemorrhages in the retina. The presence of DR can be acknowledged pictorially with the presence of cotton wool like spots, hemorrhages and abnormal growth of blood vessels. Diabetes affects almost 10% of the population and is estimated to be even more in third world or developing countries which do not have the basic amenities or the infrastructure to set up the diagnosis of DR in rural or downtrodden areas. The Diabetic Eye Diseases include DR, Diabetic Macular Edema and Glaucoma where DR is the most prominent of all. Study shows that DR is present in one-third of the patients with diabetes. The World Health



Organization (WHO) estimates that by 2030 around 400 million people will have diabetes and among them 10% would face the risk of diabetic retinopathy, diabetic macular edema, cataract and glaucoma (2,3). Vision threatening diseases unfortunately do not show any symptoms and therefore it is vital that regular screening of the retina is carried out. With early diagnosis, the chances of vision loss can be minimized with early treatment (4,5).

The diagnosis of any retinal image is done with the use of a fundus camera. The fundus camera is a highly functional, costly, non-transportable microscope that is used to take the image of interior surface of the eye. Its working requires the illumination of retina and can capture a field of vision of up to 140 degrees. The retina is then subjected to diagnosis by an ophthalmologist or an optometrist who distinguishes the characteristics of the retina in frame. The incorporation of Artificial Intelligence (AI) in the research arena of Diabetic Retinopathy has increased manifold from the advent of 2016 and 2017. The rise in AI for DR screening is continuously on the rise keeping in mind the number of articles published in the non-ophthalmology sector promising the importance and potential of AI and deep learning solutions in the detection and preliminary screening of DR. The leading countries in ophthalmology have been the United Kingdom and the United States of America. The drawback in retinal studies in third world and developing countries has been due to the lack of infrastructure present and hence leading to a dearth in the collection and availability of data required for such studies (6,7).

The solution to look for is an alternative source of retinal imaging that that is affordable, portable and effective at the same time. The smartphone in many ways has been the extension of many solutions to make it more portable and reaching to the larger target audience. There have been many models created for data acquisition that primarily use the lens of the camera built in the smartphones of the age. The lens of the smartphone by itself is not in a position to capture the details of the retina because of its lack in specification but secondary devices can be attached to the smartphone in order to capture these minute details that are necessary for characterization of the captured images.

This motivated to have a study on the use of Smartphone Based Fundus Imaging (SBFI) and a comparison of various SBFI devices. The study further looks into classification of the captured image post image filtering techniques (which is optional), with the use of deep learning algorithms. The motivation therefore is twofold in nature:

- The area of study is fast growing and has good potential for research and development.
- The gap in implementation and research findings is alarming in the context of rural Indian territories.

The paper is articulated as follows. Section 2 gives an overview of the currently available SBFI devices followed by a detailed review on the works focusing on diabetic retinopathy detection using SBFI devices. Section 4 gives a discussion on the review and finally section 5 concludes the paper.

2. Smartphone based Fundus Imaging Devices

Fundus camera is a costly machine and is too big and heavy to be transported therefore, a viable alternative needs to be found for retinal imaging. With the advent of smartphones and its vast capabilities, smartphone-based fundus imaging (SBFI) devices can be attached to smartphones for satisfactory retinal images. Studies support the use of SBFI for diabetic retinopathy(DR) screening purposes (8).

The most basic device that can be used for retinal imaging is a 20D lens (9). The lens can be held at a certain distance from the patients' eye provided there is a coaxial light source such as the light source from the smartphone. Filmic Pro application was used to record the retina and later screenshots were taken to fetch the desired image from the video. Koeppe lens is optional which can be used to keep the eyelids open with or without sedation techniques. Figure 1 demonstrates capturing retina image using 20D lens.



Figure 1. Capturing retina from a 20D lens (9)

The iExaminer is an SBFI system that is manufactured by Welch Allyn. The iExaminer is to be coupled with a PanOptic ophthalmoscope. Welch Allyn also provides an iExaminer app to store, retrieve and send fundus images (10). A smartphone needs to be attached to this device.

Russo et al developed the D-Eye system (10). It uses cross polarization technique which is aimed at reducing corneal reflections and it is integrated with a smartphone's autofocus feature to prevent refractive error. It makes use of the smartphone's light source.

The Peek Retina imaging system has its own light source for illumination. The iNView SBFI system is developed by Volk Optical. The light source from the smartphone is reflected for illumination. Dilation of pupil to 50 degrees is not a prerequisite for this device (10). All the other devices mentioned above are dilation dependent except iExaminer These are all direct ophthalmoscopy. Figure 2 depicts various SBFI available in the market and their specifications are given in Table 1 (10).





Figure 2 SBFI devices - (a) iExaminer (b) Peek Retina (c) D-Eye (d) iNview. (10)

Table 1. Specifications of SBFI devices (10)

	iExaminer	D-Eye	Peek Retina	iNview
Light source	Self	Phone	Self	Phone
Degree of Retinal View	25	6-20	20-30	50
Working distance (mm)	22	22	22	65
Size (mm)	70/220/162	68/135/7	25/75/ 35	180/76 /180
Weight (g) Price (\$)	390 750	25 400	43 235	332 995

3. Diabetic Retinopathy Detection using SBFI Devices

The use of SBFI devices for diabetic retinopathy detection is much easier compared to the traditional fundus camera. There are many works in literature which focuses on the use of SBFI devices. We have carried out an extensive review on the existing literatures and found that these literatures can be expressed in terms of the datasets, the SBFI devices and the classification model used for retinopathy detection.

A mobile-phone based DR detection system was developed in (5). Here, the retinal images were obtained using 28D condensing lenses. The input query image was initially converted to gray image and resized to 256x256. On the resized image, DWT was applied to decompose it into four subimages. From these images, feature extraction was carried out to calculate the energy of decomposed images. The features of query image were compared with the features of all images (healthy and DR effected) in the database. The labelled features and the feature database were used by ANN to retrieve the most relevant images returned as the result. The databases used for the study were CVRUDB1 and CVRUDB2. Images were also collected from Luthra Hospital, Bilaspur and Shri Mahadevam Multispeciality Hospital, Raipur. Euclidean distance was used for comparison of images.

Retinal imaging system based on smartphones for DR detection using deep learning frameworks using transfer learning was proposed in (10). The authors had focused on improving DR accuracy and to study the effect of FoV of SBFI devices. Pretrained networks were used to counter the deficiency present in the amount of images required for training deep learning network. The CNN architectures used were AlexNet, ResNet50 and GoogLeNet with 25, 177 & 144 layers respectively. Convolution layers were followed by activation layer and max-pooling layers. The convolution layers followed with activation layers and max-pooling layers for low-level feature extraction. GoogLeNet and ResNet50 both use 1x1 convolutional layers. Dimension reduction led to decrease the number of parameters from 138 million to 4 million. The features extracted were fed into classifier. Classifier to softmax layers classify images based on probability. The last three layers from the pretrained network were replaced with fully connected, softmax and classification layers. The images were classified into DR and No DR. Learning rate of first 110 layers of GoogLeNet and ResNet were frozen to 0 to prevent overfitting. New network was retrained using SGD algorithm. Datasets used were EyePACS/ Messidor/ Messidor-2/ IDRiD/ UoA. To test DR accuracy for SBFI, synthetic images were generated from UoA dataset. There are no publicly available images for SBFI according to the paper. Vertical flip was used for data augmentation (10).

In (11), the five stages of diabetic retinopathy are detected using a smartphone based app. Initially, two deep neural networks were trained using transfer learning. The pretrained transfer learning of the proposed two stage approach for classification was achieved using Inception V3 model. The study was carried out using two data sets -EyePacs and APTOS. For the images in EyePACS dataset, the first network was used to classify the images into no, mild, moderate and profound DR and the second network was used to further classify profound DR into severe and proliferative DR. For the images from APTOS dataset, the first stage gives a simple classification as DR and no DR images. In the second stage, images are classified into the four stages. The models were developed using TensorFlow and Keras in Python. The accuracies obtained for the EyePACS dataset for stage 1 and 2 were 88.4% and 84.8% respectively. The overall accuracy reported for EyePACS was 87.4%. As far APTOS dataset is concerned, the overall accuracy obtained was 88.5% (11).

For the screening of DR in primary care, a mobile teleophthalmology system was developed in (12). The authors used EyeFundusScopeNEO system architecture. It consisted of 6 modules - EFS: Fundus camera, SiiMA, SiiMA Scheduler, SiiMA Clinical Reports, PACS and RNU. Screening was provided by clinicians or algorithms based on health records (12).



A mobile app along with machine learning (ML) methods embedded on cloud was proposed by (13). The dataset used for the study was Diavision, portable diavision and messidor. Initially, image acquisition was carried out using retinograph and portable devices. The authors used binary and multiclass approach. Each image went through two diagnoses – detection of disease and extent of disease. They worked on finding the best fit among CNN models. Using Messidor dataset, best performance were obtained with VGG16 and SVM (13).

A comparison of various smartphone based devices for DR detection using deep learning was discussed in (14). CNN based AlexNet was used as classification model and made use of transfer learning. The activation function used was ReLu.

In (15) a SBFI for DR screening in India as an outreach program was proposed. The SBFI devices used were Peek Retina, D-Eye, Paxos scope adapter and the one indigenously developed by Sankara Eye Foundation (indirect SBFI). The captured devices were used without any alteration. The authors have given a comparison between the images obtained from each SBFI device in terms of sensitivity, specificity and time taken.

In (16), according to the authors even though the stages of DR are clearly defined, there existed discrepancy between ophthalmologists. The paper proposed their 3 CNN solutions with TTA and without TTA. No modifications were made to the dataset distribution. Quadratic weighted Cohen's kappa score was used as the main evaluation metric. Image cropping and resizing was done as a preprocessing step. The CNN architecture used had a feature extractor and decoder. CNN was pretrained from ImageNet. Multi-tasking approach was used: Three decoders, namely, Classification head, Regression head and Ordinal Regression head were used. Training was performed on IDRiD and MESSIDOR combined. Model regularisation was performed, and uniform noise was added. Ensemble models with 3 encoder architectures at different resolution were considered for the study. Use of ensemble increased generalization and reduced variance (16).

An optimized hybrid machine learning approach for smartphone based DR was proposed in (17). A new portable ophthalmoscope was designed - DIY model. It had retinal lens and a frame that can be attached to the smartphone. Initially, preprocessing was carried out by applying CLAHE algorithm on green channel of image. Further, segmentation using Watershed Transform and THFB was implemented to detect exudates, optic disc, microaneurysms, etc. From the segmented images, feature extraction was done using Haralick and ADTCWT. The Haralick features were utilized based on the second-order statistics and directional features were extracted through ADTCWT. To select the best feature, LIBO was used. Two features utilized exploration and exploitation. Hybrid Machine Learning algorithm was used with combination of NN and DCNN. SSD was used choose ideal weights. Datasets used were APTOS 2019 and EyePACS. 70/30



In (18), fundus image was taken using smartphone-based device called Remideo fundus on Phone. The captured images were validated with Ophthalmologist's grading. Number of patients examined were 301. An AI DR screening software called EyeArt was used. Pilot study was conducted on 50 patients to assess sensitivity and specificity of EyeArt software. Pupils were dilated by using Tropicamide eye drops. Grading of images were done by two ophthalmologists. Kappa grading between the two was 0.89. Third specialist was considered when the two could not come to an agreement. EyeArt was trained and validated using 78,685 images from EyePACS dataset. 2408 images of 301 patients were sent for screening via EyeArt to EyeNuk, Los Angeles, CA, USA (18).

Table 2 gives some of the prominent works on SBFI device-based DR detection.

SI	Paper	Data Sets	Model	Accuracy
1	(5)	CVRUDB1 CVRUDB2	Discrete Wavelet Transform	63% Precision
2	(10)	EyePACS, Messidor 1/2, IDRiD, UoA	ResNet, AlexNet, GoogLeN et	99.8% (ResNet) 99.3% (GoogLeNe t) 98.0%(AlexNet)
3	(11)	EyePACS, APTOS	Pre- trained Inception- V3	87.4% (EyePACS) 88.5% (APTOS)
4	(12)	SiiMA Clinical Reports	Indigenou s Algorithm and Clinicians	-
5	(13)	Diavision, Messidor	Portable Diavision Model	100%
6	(14)	EyePACS	AlexNet	75.31% (iNview) 68.89% (Peek Retina) 62.11% (D- Eye) 61.44% (iExaminer)
7	(15)	New Dataset	Manual Diagnosis	Indirect SBFI Device: 0.79/1.0 (Sensitivity/ Specificity)

 Table 2. Summary of prominent works on smart

 phone-based fundus imaging for DR detection.



8	(16)	IDRiD & Messidor	Ensemble	98.6% (without TTA) 99.3% (with TTA)
9	(17)	EyePACS APTOS	Hybrid	98.9% (EyePACS) 99% (APTOS)
10	(18)	EyePACS	AI (Not specified)	95.8%

4. Discussion

The study has shown that around 450 million people suffer from diabetes and among them 45 million of them suffer from diabetes related retinal diseases (2,3). The study has also shown that these deformities characterize themselves in the retina. Regular checkups and timely diagnosis states that the degenerative factor of these diseases can be reduced to a large extent but if it goes unchecked, the same may lead to human vision loss (4,5). It is found that the study and experimentation of the same is of much importance in India. Approximately 80% of all people with diabetes and suffering from DR are from low and middleincome countries (7). They are also faced with the challenge of ill equipped infrastructure and healthcare to tackle the situation (6,7).

The study in ophthalmology has also extended to the use of smartphones in the support of diagnosis of DR. It is understood that although smartphones are equipped computationally, they are not in terms of data acquisition and hence, the need to create adaptable and suitable smartphone-based image devices has become essential. In this paper, we have reviewed recent papers on diabetic retinopathy detection which uses smartphones for capturing fundus images. Based on the review, it is clearly visible that we can categorize the existing works based on the datasets they have used or based on the devices used to capture images as well as classification models incorporated for DR detection.

Some of the devices that have been created and experimented upon, which became beneficial for the research includes D-Eye, iNView, Peek-Retina, 20D lenses, iExaminer and Paxos Scope adapter (10). A traditional fundus camera is situated in only highly equipped health facilities. The infrastructure to make this available in most parts of the country is highly inadequate. A traditional fundus camera is a costly investment and the charges to provide its services are also a costly affair. Therefore, it is in the best interest of the study to provide an affordable service without compromising on the quality of the retinal images acquired for diagnosis. Study has shown that nowadays, the computation capability of smartphones is endless and preliminary medical diagnosis can be extended to mobile devices. The smartphone provides accurate results, it is portable, it is cheaper than traditional systems and it is available in most places.

Although it is advisable that the computational capabilities from the smartphone not be relied upon independently but can be used with the support of application program interfaces. It is found that the lens of the smartphone is not capable of taking a fundus image. The requirement for DR diagnosis is the posterior image of the retina. The captured image should be able to capture minor exudates or spots present in the retinal image. Images of blood vessels and analysis of the same can also prove to be useful. It is therefore necessary to use the in-built lens of the smartphone with a secondary lens which will be able to capture these details in the image.

As far as the classification models are concerned, there are many learning algorithms present in the market today. Algorithms such as GoogLeNet, AlexNet, ResNet, Inception v-3 and many more are present under Convolution Neural Networks. Neural networks require a lot of data to work with. Features are extracted from the images and parameters are set. Therefore, a database containing a large number of accurately classified images must be available. The study has shown that training and validation can be done in many ways to increase the accuracy of the model. There are multiple CNNs that are available. The depth of the networks can be set in such a way that it does not create overhead on the system. Hybrid algorithms have been developed like the Inception v-3 model that makes use of a three head architecture.

Traditionally, a model requires data from a single repository but may make use of single, multiple and cross datasets. Different datasets have been considered for smartphone-based DR detection. EyePACS, Messidor 1 & 2, IDRiD, UoA-DR & APTOS are some of the datasets used in the existing literatures.

Data collection methodology has also been analyzed in the study. There are repositories that contain synthetic images. Synthetic data generators generate data from already existing data. A 20D lens has been chosen to capture the retinal image. The study has discussed other forms of data collection such as SBFI devices like D-Eye, iExaminer, Peek Retina, iNview and others. The characteristics of these devices that should be considered are the cost, illumination capabilities, compatibility with different smartphones, degree of retinal view, the working distance, size, weight and the price. The study also discusses indigenously developed devices. A secondary attachment to the smartphone is mandatory as the existing lens on the smartphone is incapable of capturing the details of the retina.

5. Conclusion

In this paper, DR detection using smartphone-based fundus imaging is discussed. The study focuses on works which has incorporated on the usage of smartphones for DR detection. A set of existing works are reviewed, and it is found that majority of the works uses SBFI devices like 20D lens, EyeExaminer etc. to obtain fundus image. The



common databases used are EyePACS, Messidor, etc. and the classification models mostly rely on deep learning frameworks. This survey has no aim to find the best method from the existing works rather focuses on portraying various approaches currently being employed in SBFI based DR detection. Extensive study is yet to be carried out to find the optimal methodology in smartphone-based fundus imaging for DR detection and to propose new model for accurate diagnosis of diabetic retinopathy based on SBFI.

References

- Chandakkar, P.S., Venkatesan, R., Li, B.: Retrieving clinically relevant diabetic retinopathy images using a multi-class multiple-instance framework. SPIE. 8670, 86700Q (2013). <u>https://doi.org/10.1117/12.2008133</u>.
- [2] Bourne, R.R.A., Stevens, G.A., White, R.A., Smith, J.L., Flaxman, S.R., Price, H., Jonas, J.B., Keeffe, J., Leasher, J., Naidoo, K., Pesudovs, K., Resnikoff, S., Taylor, H.R.: Causes of vision loss worldwide, 1990-2010: A systematic analysis. Lancet Glob. Heal. 1, e339–e349 (2013). https://doi.org/10.1016/S2214-109X(13)70113-X.
- [3] CDC: National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. (2020).
- [4] Ramasamy, K., Raman, R., Tandon, M.: Current state of care for diabetic retinopathy in India. Curr. Diab. Rep. 13, 460–468 (2013). https://doi.org/10.1007/S11892-013-0388-6/METRICS.
- [5] Kashyap, N., Singh, D.K., Singh, G.K.: Mobile phone based diabetic retinopathy detection system using ANN-DWT. 2017 4th IEEE Uttar Pradesh Sect. Int. Conf. Electr. Comput. Electron. UPCON 2017. 2018-January, 463–467 (2017). https://doi.org/10.1109/UPCON.2017.8251092.
- [6] WHO Global Report: Global Report on Diabetes. Isbn. 978, 11 (2016).
- [7] Barometer, D.R.: The Diabetic Retinopathy Barometer Report: Global Findings. (2017).
- [8] Taylor, R., Broadbent, D.M., Greenwood, R., Hepburn, D., Owens, D.R., Simpson, H.: Mobile retinal screening in Britain. In: Diabetic Medicine (1998). https://doi.org/10.1002/(SICI)1096-9136(199804)15:4<344::AID-DIA588>3.0.CO;2-O.
- [9] Haddock, L.J., Kim, D.Y., Mukai, S.: Simple, inexpensive technique for high-quality smartphone fundus photography in human and animal eyes. J. Ophthalmol. 2013, (2013). https://doi.org/10.1155/2013/518479.
- [10] Hacisoftaoglu, R.E., Karakaya, M., Sallam, A.B.: Deep learning frameworks for diabetic retinopathy detection with smartphone-based retinal imaging systems. Pattern Recognit. Lett. 135, (2020). https://doi.org/10.1016/j.patrec.2020.04.009.
- [11] Majumder, S., Elloumi, Y., Akil, M., Kachouri, R., Kehtarnavaz, N.: A deep learning-based smartphone app for real-time detection of five stages of diabetic retinopathy. Presented at the (2020). https://doi.org/10.1117/12.2557554.

- [12] Nunes, F., Madureira, P., Rego, S., Braga, C., Moutinho, R., Oliveira, T., Soares, F.: A Mobile Tele-Ophthalmology System for Planned and Opportunistic Screening of Diabetic Retinopathy in Primary Care. IEEE Access. 9, (2021). https://doi.org/10.1109/ACCESS.2021.3085404.
- [13] Alves, S.S.A., Matos, A.G., Almeida, J.S., Benevides, C.A., Cunha, C.C.H., Santiago, R.V.C., Pereira, R.F., Reboucas Filho, P.P.: A New strategy for the detection of diabetic retinopathy using a smartphone app and machine learning methods embedded on cloud computer. In: Proceedings - IEEE Symposium on Computer-Based Medical Systems (2020). https://doi.org/10.1109/CBMS49503.2020.00108.
- [14] Karakaya, M., Hacisoftaoglu, R.E.: Comparison of smartphone-based retinal imaging systems for diabetic retinopathy detection using deep learning. BMC Bioinformatics. 21, (2020). https://doi.org/10.1186/s12859-020-03587-2.
- [15] Wintergerst, M.W.M., Mishra, D.K., Hartmann, L., Shah, P., Konana, V.K., Sagar, P., Berger, M., Murali, K., Holz, F.G., Shanmugam, M.P., Finger, R.P.: Diabetic Retinopathy Screening Using Smartphone-Based Fundus Imaging in India. Ophthalmology. 127, (2020). https://doi.org/10.1016/j.ophtha.2020.05.025.
- [16] Tymchenko, B., Marchenko, P., Spodarets, D.: Deep learning approach to diabetic retinopathy detection. In: ICPRAM 2020 - Proceedings of the 9th International Conference on Pattern Recognition Applications and Methods (2020). https://doi.org/10.5220/0008970805010509.
- [17] Gupta, S., Thakur, S., Gupta, A.: Optimized hybrid
- machine learning approach for smartphone based diabetic retinopathy detection. Multimed. Tools Appl. 81, (2022). https://doi.org/10.1007/s11042-022-12103y.
- [18] Rajalakshmi, R., Subashini, R., Anjana, R.M., Mohan, V.: Automated diabetic retinopathy detection in smartphone-based fundus photography using artificial intelligence. Eye 2018 326. 32, 1138–1144 (2018). <u>https://doi.org/10.1038/s41433-018-0064-9</u>.

