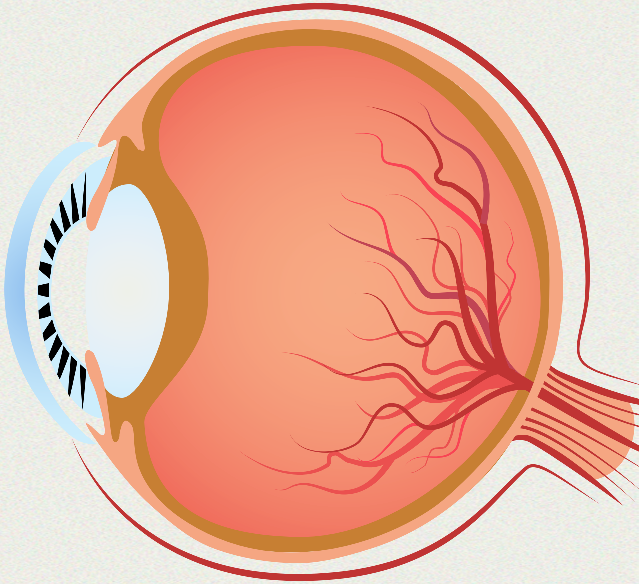
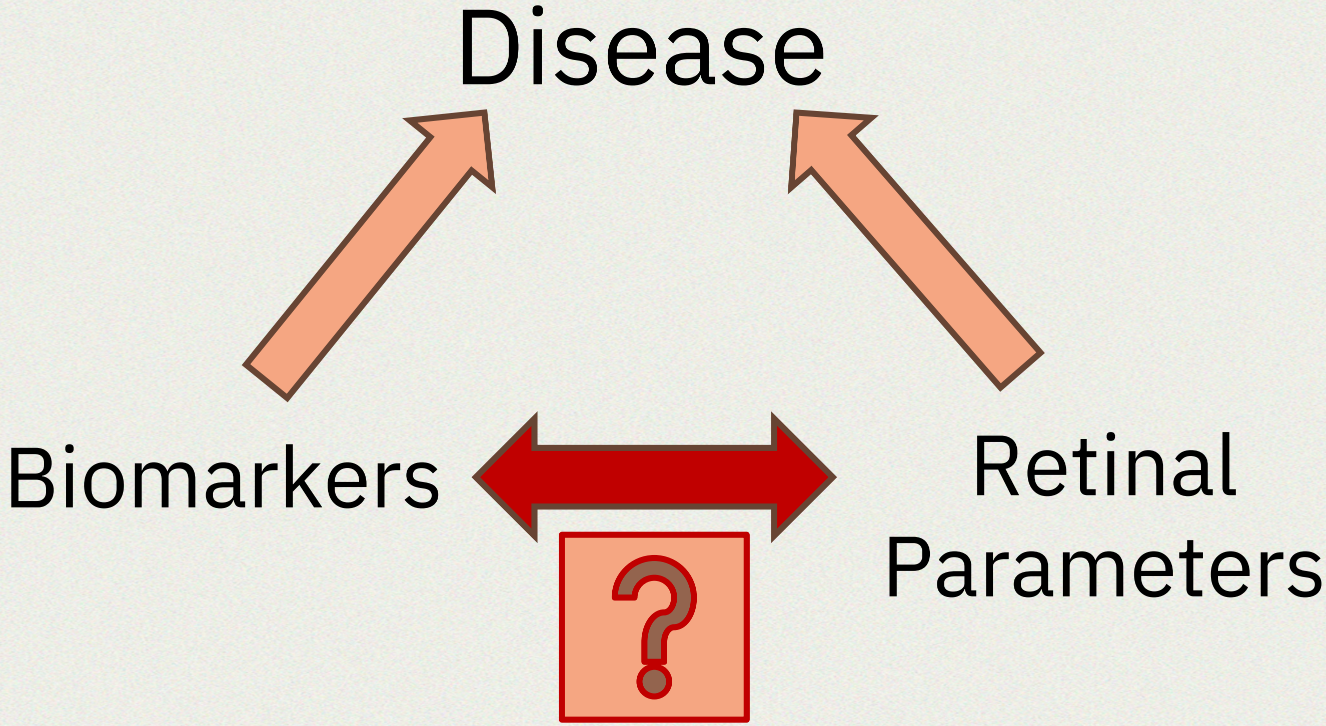
RETINAL PROPERTIES & DISEASE



Alessandro Gigliotti, Elia Quadri, Gionata Valerio

Supervisor: Sofía Ortín Vela

Introduction/Goal

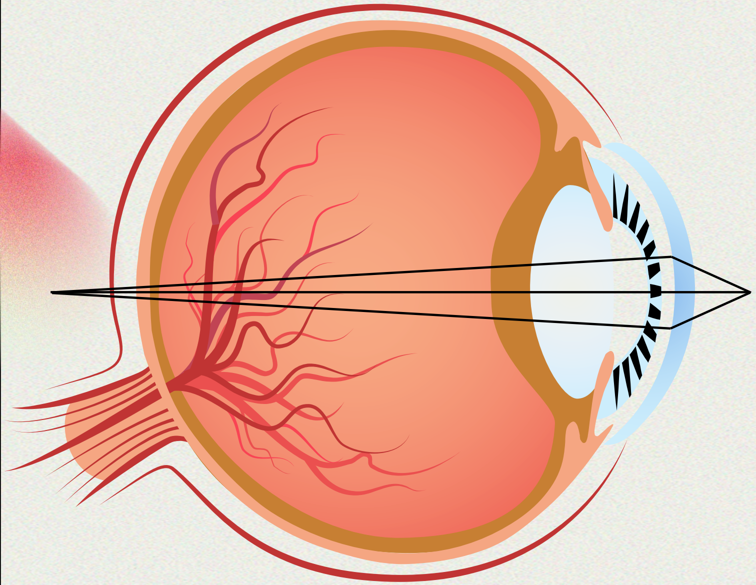


Learning Goals

- Discover the association between biomarkers and retinal parameters in relation to disease prediction

- Learn new analytical methods and statistical applications, and apply them to a practical case study

- Understand how to interpret results and draw appropriate conclusions to implement the work effectively and grasp the practical implications



01

THE DISEASE

ABOUT THE DISEASE

Diabetes

A chronic condition where the body cannot regulate blood sugar levels properly.

Hypertension

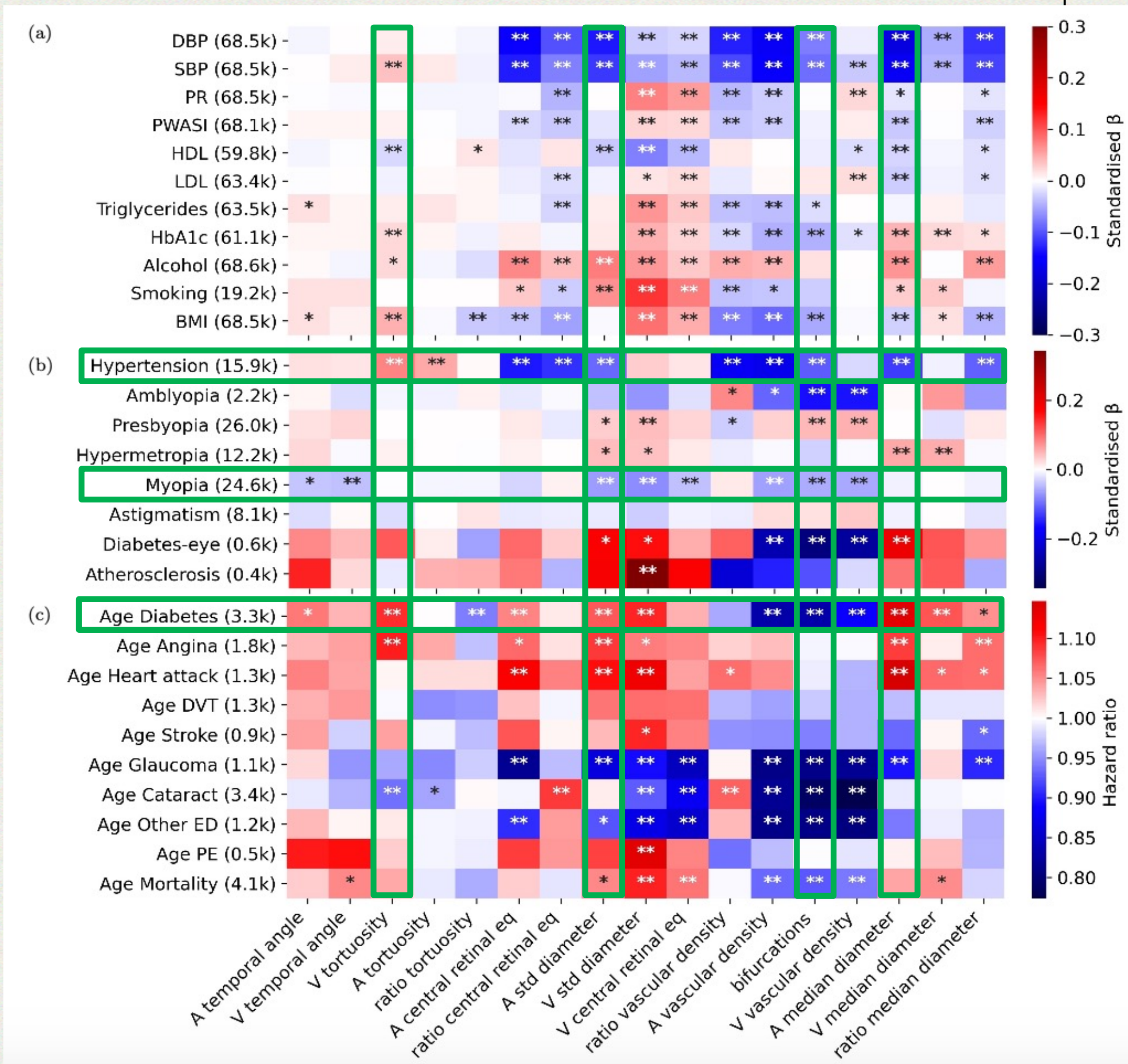
A condition where blood pressure is consistently too high, increasing the risk of heart disease and stroke.

Myopia

A vision condition where close objects appear clear, but distant ones are blurry.

Retinal parameters

1. Vein tortuosity
2. Standard deviation of artery diameter
3. Bifurcation
4. Median diameter of artery
5. Average retinal nerve fiber layer thickness



Ortín Vela, S., Beyeler, M.J., Trofimova, O., Iuliani, I., Vargas Quiros, J.D., de Vries, V.A., Meloni, I., Elwakil, A., Hoogewoud, F., Liefers, B., Presby, D., Ramdas, W.D., Tomasoni, M., Schlingemann, R., Klaver, C.C.W., Bergmann, S. (2023). "Phenotypic and Genetic Characteristics of Retinal Vascular Parameters and their Association with Diseases." medRxiv. doi: https://doi.org/10.1101/2023.07.07.23292368

Diabetes

Glucose

Blood level

HbA1c

Glycated haemoglobin

IDL

Cholesterol in IDL

PRS_d1/d2

Polygenic risk score for
Diabetes type 1
Diabetes type 2

PRS_coronary

Polygenic risk score for
Coronary artery disease

Glucose vs HbA1c

Diagnosis	**Monitor**
Acute	**Chronic** 3 months
Fasting needed	**$$**

Enzo Bonora, Jaakko Tuomilehto; The Pros and Cons of Diagnosing Diabetes With A1C. *Diabetes Care* 1 May 2011; 34 (Supplement_2): S184–S190.
https://doi.org/10.2337/dc11-s216

IDL-C

Diabetes

>LDL/VLDL-C

< IDL-C

Positive correlation

Negative correlation

Winocour, P. H., Durrington, P. N., Bhatnagar, D., Ishola, M., Arrol, S., & Mackness, M. (1992). Abnormalities of VLDL, IDL, and LDL characterize insulin-dependent diabetes mellitus. *Arteriosclerosis and Thrombosis: A Journal of Vascular Biology*, 12(8), 920-928. https://doi.org/10.1161/01.ATV.12.8.920

PRS Diabetes

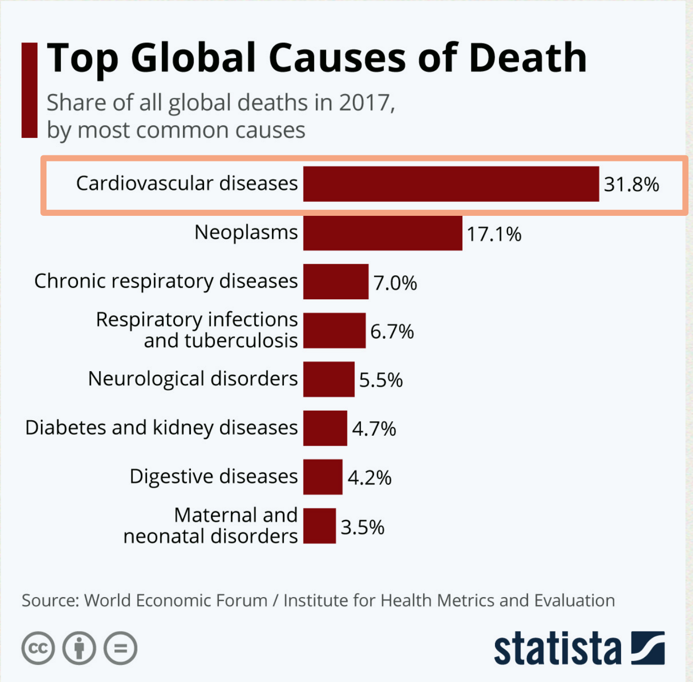
Polygenic Risk Score

multiple genetic variants in several genes → cause → predisposition to Diabetes

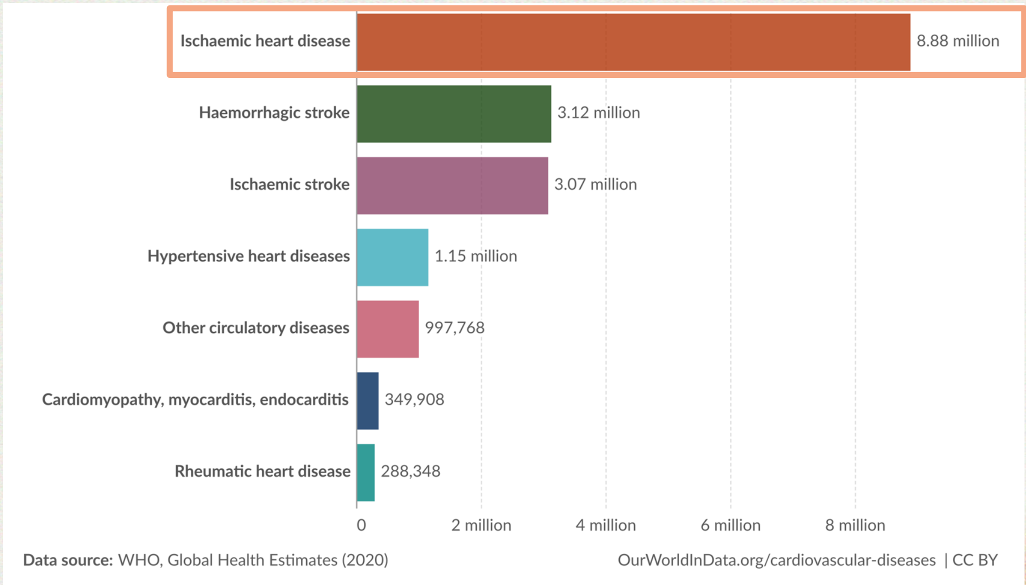
Type 1	Type 2
5%	95%

PRS coronary

32% of global deaths



80% for people with diabetes 1 or 2



Otvos, J. D., Mora, S., Shalaurova, I., Greenland, P., & Mackey, R. H. Clinical Implications of Discordance Between LDL Cholesterol and LDL Particle Number. Journal of Clinical Lipidology, 5(2), 105. https://doi.org/10.1016/j.jacl.2011.02.001

Liou, L., & Kaptoge, S. (2020). Association of small, dense LDL-cholesterol concentration and lipoprotein particle characteristics with coronary heart disease: A systematic review and meta-analysis. *PLoS ONE, 15*(11). https://doi.org/10.1371/journal.pone.0241993

Hypertension

Red blood cell count

IDL

Cholesterol in IDL

Body fat percentage

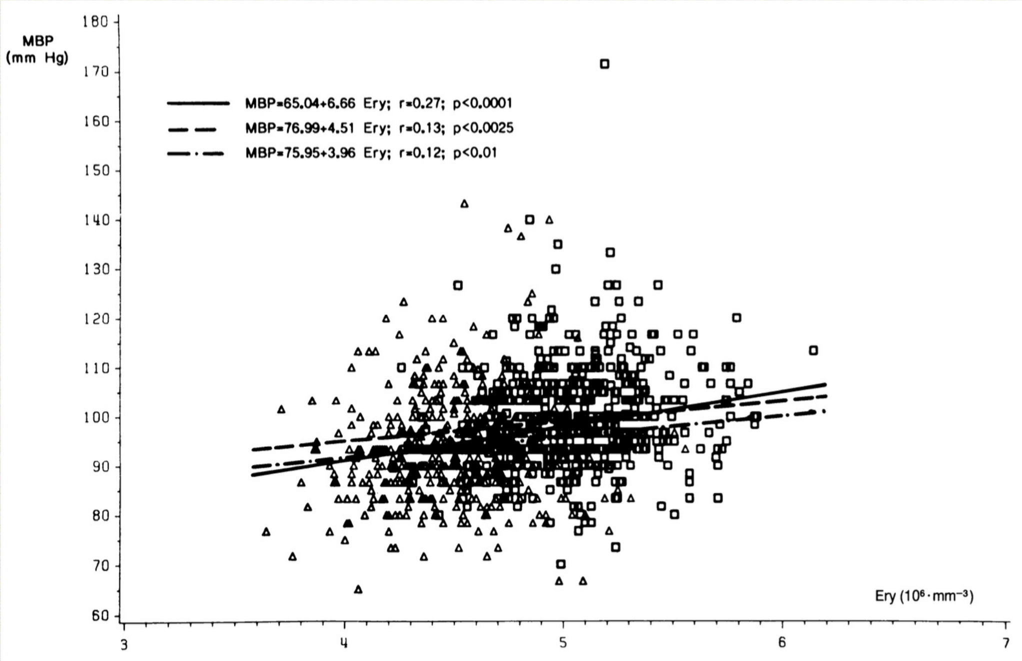
Pulse rate

bpm

PRS_coronary

Polygenic risk score for Coronary artery disease

Red blood cell count



- Red blood cell -> blood viscosity

Göbel, B. O., Schulte-Göbel, A., Weisser, B., Glänzer, K., Vetter, H., & Düsing, R. Arterial Blood Pressure: Correlation With Erythrocyte Count, Hematocrit, and Hemoglobin Concentration. American Journal of Hypertension, 4(1 Pt 1), 14. https://doi.org/10.1093/ajh/4.1.14

Cholesterol in IDL

Table 2. Correlations of lipid, lipoprotein, and apolipoprotein parameters with systolic and diastolic blood pressure in 200 male employees aged 26 ± 7 years (covariance analysis performed for covariates BMI and age)

Parameter	Systolic blood pressure		Diastolic blood pressure	
	r	*P*	*r*	*P*
Trglycerides	0.056	NS	0.053	NS
Total cholesterol	0.177	<0.05	0.200	<0.01
VLDL cholesterol	0.103	NS	0.099	NS
IDL cholesterol	0.201	<0.01	0.195	<0.01
LDL cholesterol	0.126	NS	0.160	<0.05
Apolipoprotein B	0.191	<0.01	0.194	<0.01
Lipoprotein (a)	−0.054	NS	−0.004	NS

Steinmetz, A., Kirklies, A., Schlosser, G., Cassel, W., Peter, J. H., Ehlenz, K., Schäfer, J. R., Wichert, P. v., & Kaffarnik, H. (1993). Lipoprotein (a), low-density, intermediate-density lipoprotein, and blood pressure in a young male population. Clinical Investigator, Springer-Verlag.
https://doi.org/10.1007/BF00179996

Body fat percentage

TABLE 2 Hazard ratios (HRs) and 95% confidence intervals (CI) for hypertension according to body fat percentage (BF%) quintile

Characteristics	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Men (BF%)	(7.1-16.9)	(17.0-19.8)	(19.9-22.4)	(22.5-25.3)	(25.4-38.3)
Unadjusted HR	1.00 (Reference)	1.06 (0.81-1.37)	1.33 (1.04-1.71)	1.52 (1.20-1.94)	1.83 (1.45-2.31)
Model 1	1.00 (Reference)	1.09 (0.84-1.43)	1.42 (1.10-1.85)	1.58 (1.22-2.05)	1.82 (1.40-2.36)
Model 1 plus BMI	1.00 (Reference)	0.99 (0.75-1.31)	1.16 (0.88-1.55)	1.20 (0.89-1.63)	1.23 (0.87-1.74)
Model 1 plus WC	1.00 (Reference)	0.99 (0.76-1.31)	1.17 (0.88-1.55)	1.21 (0.90-1.64)	1.27 (0.91-1.77)
Model 1 plus WHR	1.00 (Reference)	1.04 (0.80-1.37)	1.30 (0.99-1.69)	1.38 (1.05-1.81)	1.50 (1.13-2.00)
Incidence cases	116	111	138	152	176
Incidence density	32.5	33.8	41.5	47.5	57.2
Women	(11.6-26.7)	(26.8-30.3)	(30.4-32.4)	(32.5-35.1)	(35.2-47.2)
Unadjusted HR	1.00 (Reference)	1.02 (0.79-1.32)	1.01 (0.77-1.31)	1.34 (1.05-1.72)	1.78 (1.40-2.25)
Model 1	1.00 (Reference)	1.13 (0.86-1.49)	1.12 (0.85-1.49)	1.48 (1.12-1.94)	1.56 (1.20-2.04)
Model 1 plus BMI	1.00 (Reference)	1.03 (0.77-1.37)	0.96 (0.71-1.31)	1.20 (0.87-1.65)	1.10 (0.75-1.62)
Model 1 plus WC	1.00 (Reference)	1.05 (0.79-1.39)	0.98 (0.73-1.32)	1.24 (0.92-1.68)	1.22 (0.89-1.68)
Model 1 plus WHR	1.00 (Reference)	1.10 (0.83-1.46)	1.07 (0.80-1.42)	1.38 (1.04-1.83)	1.45 (1.10-1.91)
Incidence cases	113	118	110	139	175
Incidence density	28.6	28.9	28.5	37.2	48.9

Model 1: adjusted for age, study area (Ansan or Ansung), diabetes mellitus (baseline, follow-up), regular exercise, smoking, alcohol intake, HOMA-IR, CRP, HDL-C, total calorie intake, sodium intake. Incidence density: incidence cases per 1000 person-year.

Park, S. K., Ryoo, J.-H., Oh, C.-M., Choi, J.-M., Chung, P.-W., & Jung, J. Y. Body fat percentage, obesity, and their relation to the incidental risk of hypertension. Original Paper. https://doi.org/10.1111/jch.13667

Pulse rate

Heart rate (HR) is strongly associated with both peripheral and central blood pressures. This association has implications in hypertension (HTN) prognosis and management. Elevated HR in HTN further elevates the risk of adverse outcomes. Evidence suggests that HR is an independent risk factor for cardiovascular (CV) and total mortality in patients with HTN. With objective to engage physicians and researchers in India to identify and discuss the implications related to HR management in HTN, experts in the HTN management provided consensus recommendations. The key expert recommendations included the following. (i) Heart rate (HR) has inverse relationship with the central aortic pressure, whereby reduction in HR is associated with an increase in central aortic pressure. This counter-balances the benefit of HR reduction with the harmful effects of rising central aortic pressure. (ii) Increase in the resting HR is associated with increased risk of incident HTN. A linear association between the two is observed especially in individuals with HR >80 bpm. (iii) A reduced HR variability further adds to the propensity for the development of HTN, especially in men. (iv) Each 10 beats per minute increase in the resting HR can substantially increase the risk of adverse CV and mortality outcomes. On treatment HR provides a better prognostic guide. (v) Ambulatory HR with day-time and night-time HR evaluation may also suggest different impact on outcomes. (vi) Target HR in patients with HTN remains unclear. Generally, HR<70 bpm on beta blocker (BB) treatment is advised which may be further lowered in patients with comorbidities like heart failure and coronary artery disease. (vii) Adopting healthy lifestyle approaches to keep check on BP and HR is essential. (viii) Use selective beta-1 blocker in *symptomatic* cases with elevated HR beyond 80-85 mmHg. BBs are expected to benefit by lowering HR by nearly 10 bpm. Preference should be given to newer beta-blockers which reduce HR and both peripheral and central blood pressure to derive comprehensive advantage of this dual action. (ix) It still remains unclear whether reducing HR in HTN without comorbidities alters the CV and mortality outcomes.

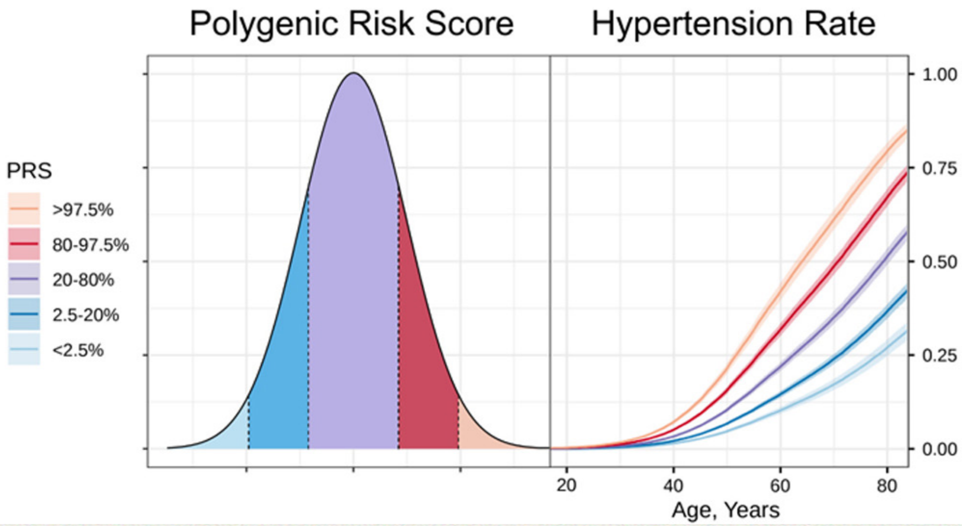
Dalal, J., Dasbiswas, A., Sathyamurthy, I., Maddury, S. R., Kerkar, P., Bansal, S., Thomas, J., Mandal, S. C., Mookerjee, S., Natarajan, S., Kumar, V., Chandra, N., Khan, A., Vijayakumar, R., & Sawhney, J. P. S. Heart Rate in Hypertension: Review and Expert Opinion. Review Article. https://doi.org/10.1155/2019/2087064

PRS for coronary artery disease (CAD)

GENETICS

Polygenic Risk Scores Predict Hypertension Onset and Cardiovascular Risk

Felix Vaura, Anni Kauko, Karri Suvila, Aki S. Havulinna, Nina Mars, Veikko Salomaa, FinnGen, Susan Cheng, Teemu Niiranen



7. HYPERTENSION AND CORONARY HEART DISEASE

Dr Mirjana Cubrilo-Turek, MD, Ph.D.

Department of Internal Medicine, Sveti Duh General Hospital, Zagreb

Hypertension is the most prevalent treatable cardiovascular disease affecting approximately one in four adults or 140 million USA residents. It affects men and women in all socioeconomic groups equally. If untreated, hypertension is a major cause of stroke, coronary heart disease and renal failure as well as other conditions. Easily diagnosed, and in most instances readily controlled, hypertension is often unsuspected or inadequately treated.

Vaura, F., Kauko, A., Suvila, K., Havulinna, A. S., Mars, N., Salomaa, V., FinnGen, Cheng, S., & Niiranen, T. Polygenic Risk Scores Predict Hypertension Onset and Cardiovascular Risk. Genetics. https://doi.org/10.1161/HYPERTENSIONAHA.120.16471
Cubrilo-Turek, M. Hypertension and Coronary Heart Disease. Department of Internal Medicine, Sveti Duh General Hospital, Zagreb. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6169140/pdf/ejifcc-14-067.pdf

Myopia

Intra-ocular pressure, Goldmann correlated (right eye)

Intra-ocular pressure, Goldmann correlated (left eye)

Body fat percentage

Red blood cells

Glucose/HbA1c

Intra-ocular pressure, Goldmann correlated (L/R)

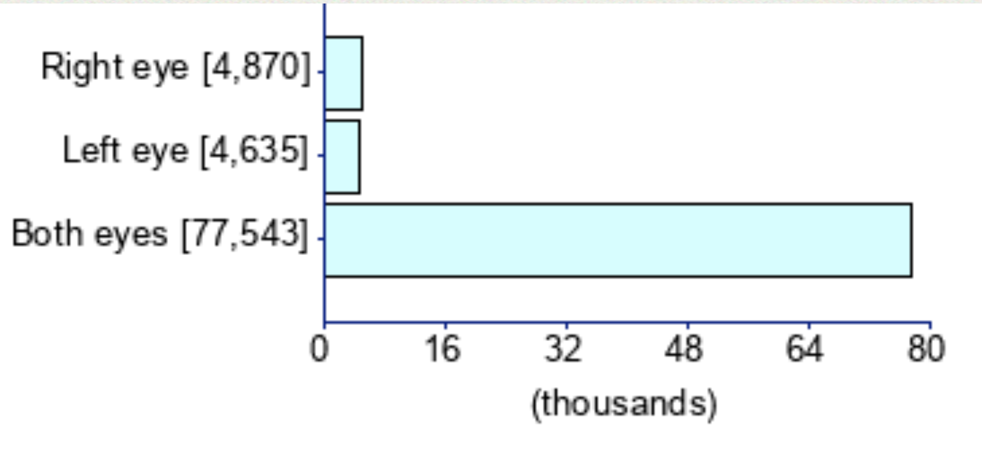


Table 2: Co-relation of Refractive Status and IOP

Refractive status	No	IOP (mm Hg)	t-test	p value
Emmetropia (Control)	120	14.78±1.65		
High myopia	30	18.00±2.4	5.67	<0.01***
Moderate myopia	30	16±2	0.95	>0.05
Low myopia	30	15.28±2.03	0.65	>0.05
Hypermetropics	30	15.12±1.53	0.82	>0.05

***Highly significant, indicating that high myopic are more prone for increased IOP.

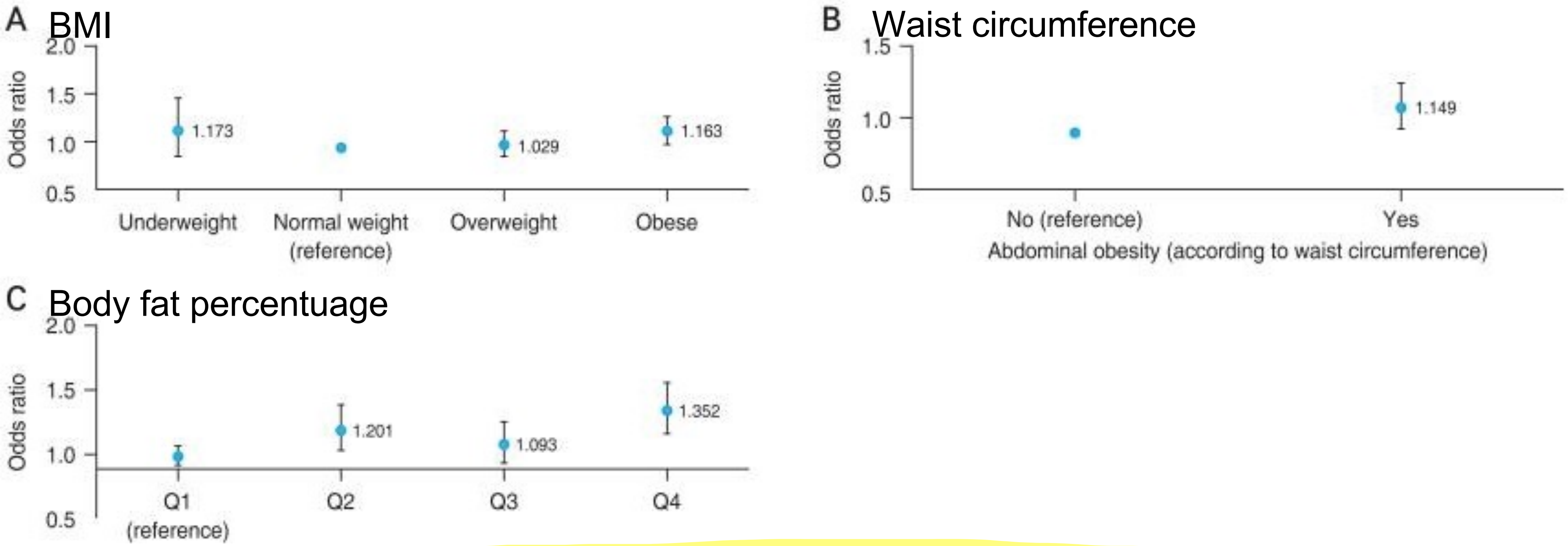
Table 3: Correlation of IOP with Refractive Errors

Refractive Error	No	Mean±SD
High myopia	30	18.0±2.4***
Moderate myopia	30	16±2
Low myopia	30	15.28±2.03
Hypermetropics	30	15.12±1.53

*** Highly significant. **ANOVA test** showed that there is highly significant association of mean IOP in high myopia compared to other groups of refractive errors.

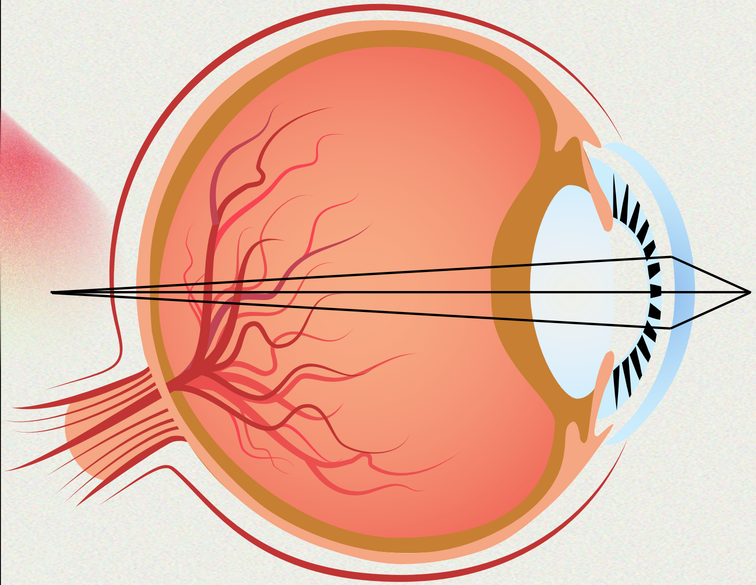
Roopa Somashekar Mathapathi1, Satish Sharanppagouda Patil2: Association of refractive errors with intraocular pressure and its relationship with age and gender , https://www.ijcap.org/journal-article-file/2966

Body fat percentage



In conclusion, obesity measured with direct assessment of fat mass was related to myopia in adults, especially among relatively young individuals. The development of myopia generally ends in adolescence, but obesity typically increases with age [50]. In adults with myopia, an increased awareness of the risk of obesity may be helpful in promoting the population's health and wellbeing.

Young Ho Noh and Kyoung In Jung, The Relationship between Myopia and Obesity in Adults,https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11016688/



02

Methods

Dataframe

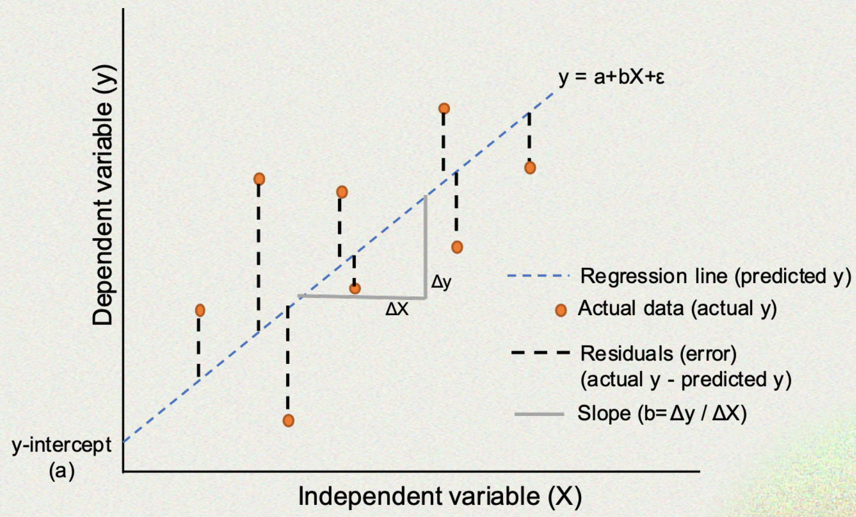
- Take the data from the UK Biobank
- Check the number of patients and missing values
- Check the type of data (binary, nomial,..)
- See the distribution of the data (+ normalization)
- Chek for eventual outliers

Regression

$$\hat{y} = \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \cdots \beta_n \cdot x_n$$

$$e = y - \hat{y}$$

y: observed value
$\hat{y}$: predicted value
e: residual



https://www.reneshbedre.com/blog/learn-to-calculate-residuals-regression.html

General parameters/covariates

Sex

City

Age

Age^2

Standing Height

Regression

1. $\widehat{disease} = covariates$

2. $\widehat{retina} = covariates \rightarrow$
   1. $\widehat{bifurcations} = covariates$
   2. $A\ \widehat{std\ diam} = covariates$
   3. ...

3. $\widehat{biomarker} = covariates$

   each one singularly

$$covariates = \beta 1_{sex} \times sex + \beta 2_{city} \times city + \beta_{age} \times age + \cdots$$

Regression

1. $e_{desease} = disease - \widehat{disease}$
2. $e_{retina} = retina - \widehat{retina}$
3. $e_{biomarker} = biomarker - \widehat{biomarker}$

Regression

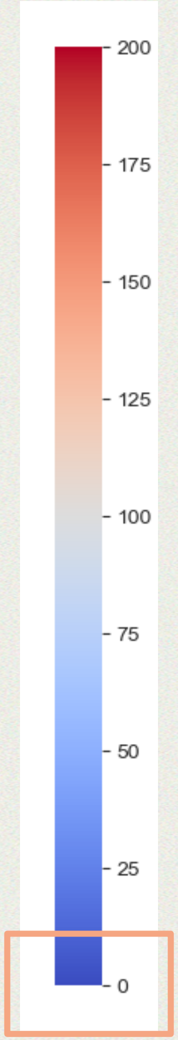
$$e_{disease} = \beta 1 \times e_{retina}$$

$$e_{disease} = \beta 2 \times e_{retina} + \beta 3 \times e_{biomarker}$$

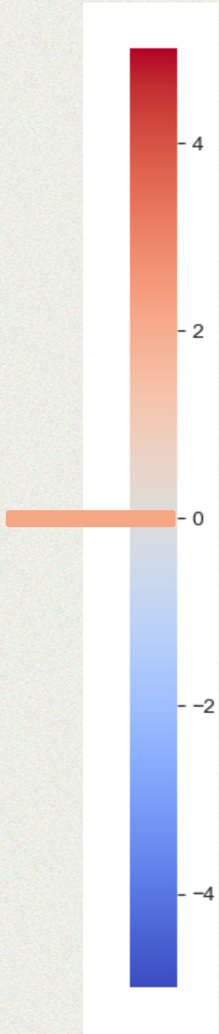
$$\beta 1 \times e_{retina} \stackrel{?}{=} \beta 2 \times e_{retina}$$

Control: $$e_{disease} = \beta 4 \times e_{biomarker}$$

Changing of beta value



$$\text{Score} = \log \frac{|\beta_{retina} - \beta_{retina\_biomarker}|}{|\beta_{biomarker} - \beta_{biomarker\_retina}|}$$



Changing of beta value

Positive Score

β_{retina} *changes more than* $\beta_{biomarker}$

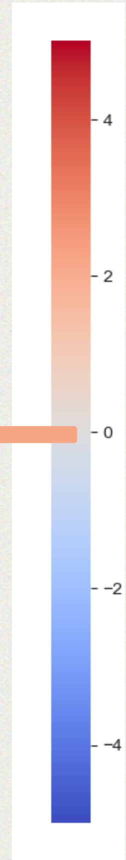
Biomarker –(explain)-> Retina

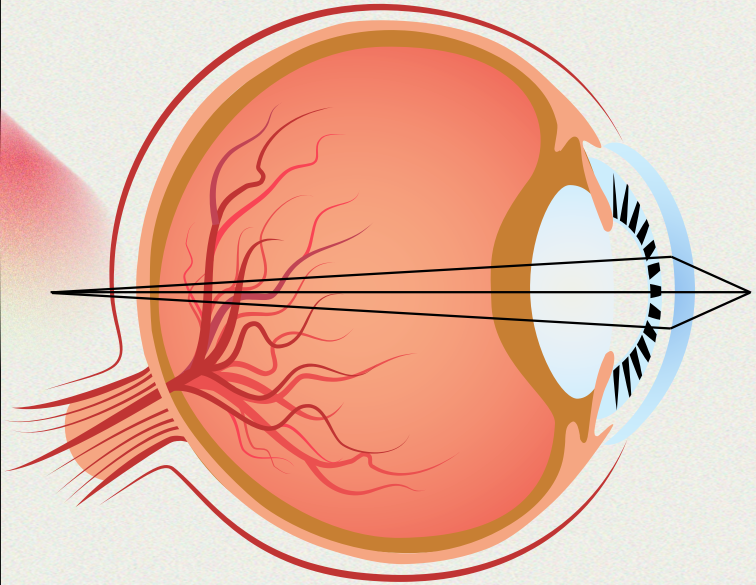
$$\text{Score} = \log\left(\frac{|\beta 2 - \beta 1|}{|\beta 4 - \beta 3|}\right)$$

Negative Score

$\beta_{biomarker}$ *changes more than* $\beta_{retinal}$

Retina –(explain)-> Biomarker





03

Results

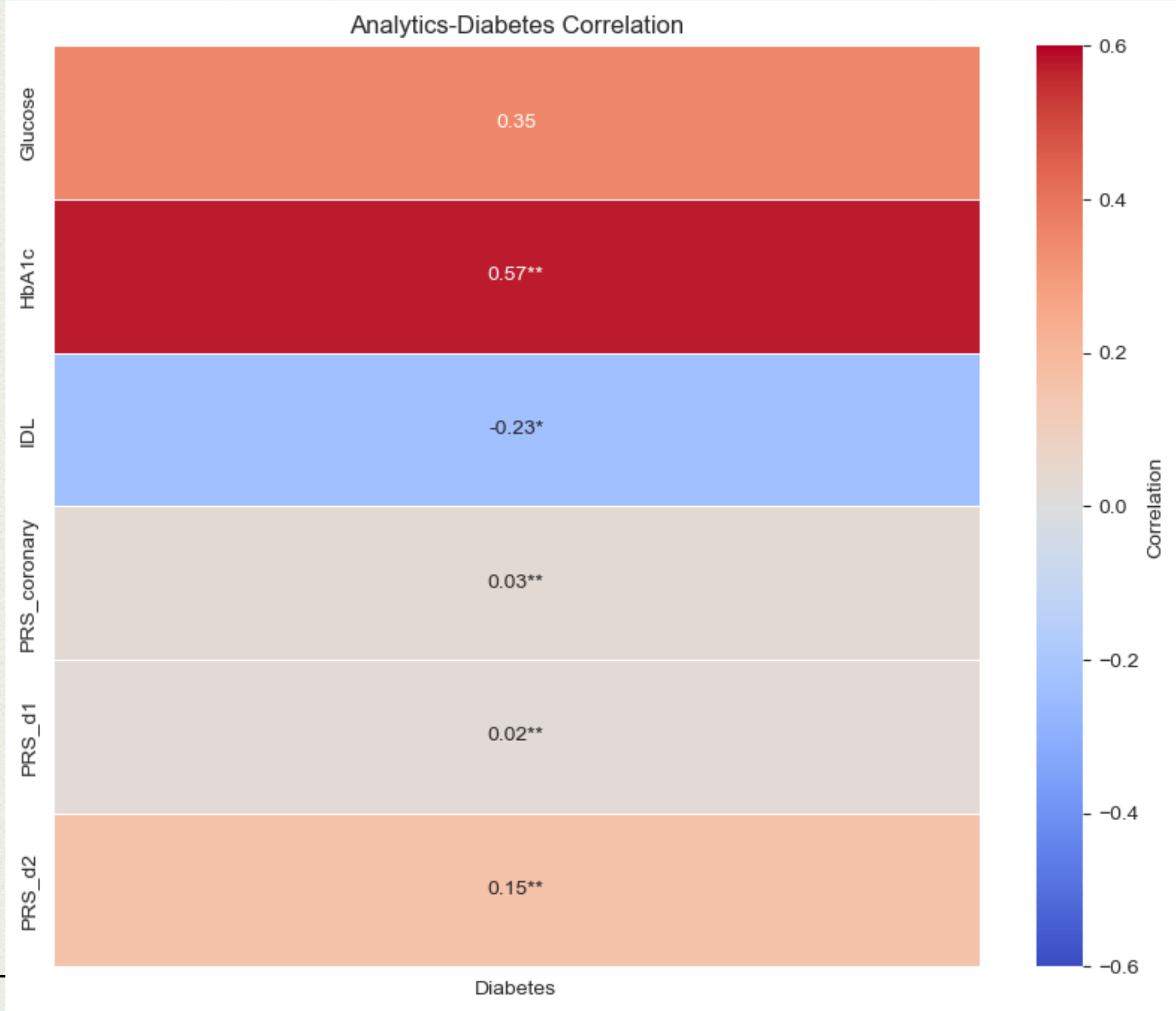
Diabetes - Retina

Hazard ratio of 1 = 0 correlation

Ortín Vela, S., Beyeler, M.J., Trofimova, O., Iuliani, I., Vargas Quiros, J.D., de Vries, V.A., Meloni, I., Elwakil, A., Hoogewoud, F., Liefers, B., Presby, D., Ramdas, W.D., Tomasoni, M., Schlingemann, R., Klaver, C.C.W., Bergmann, S. (2023). "Phenotypic and Genetic Characteristics of Retinal Vascular Parameters and their Association with Diseases." medRxiv. doi: https://doi.org/10.1101/2023.07.07.23292368

Diabetes - Biomarkers

- HbA1c > Glucose
- PRS_d1 < PRS_d2
  - 5% vs 95%



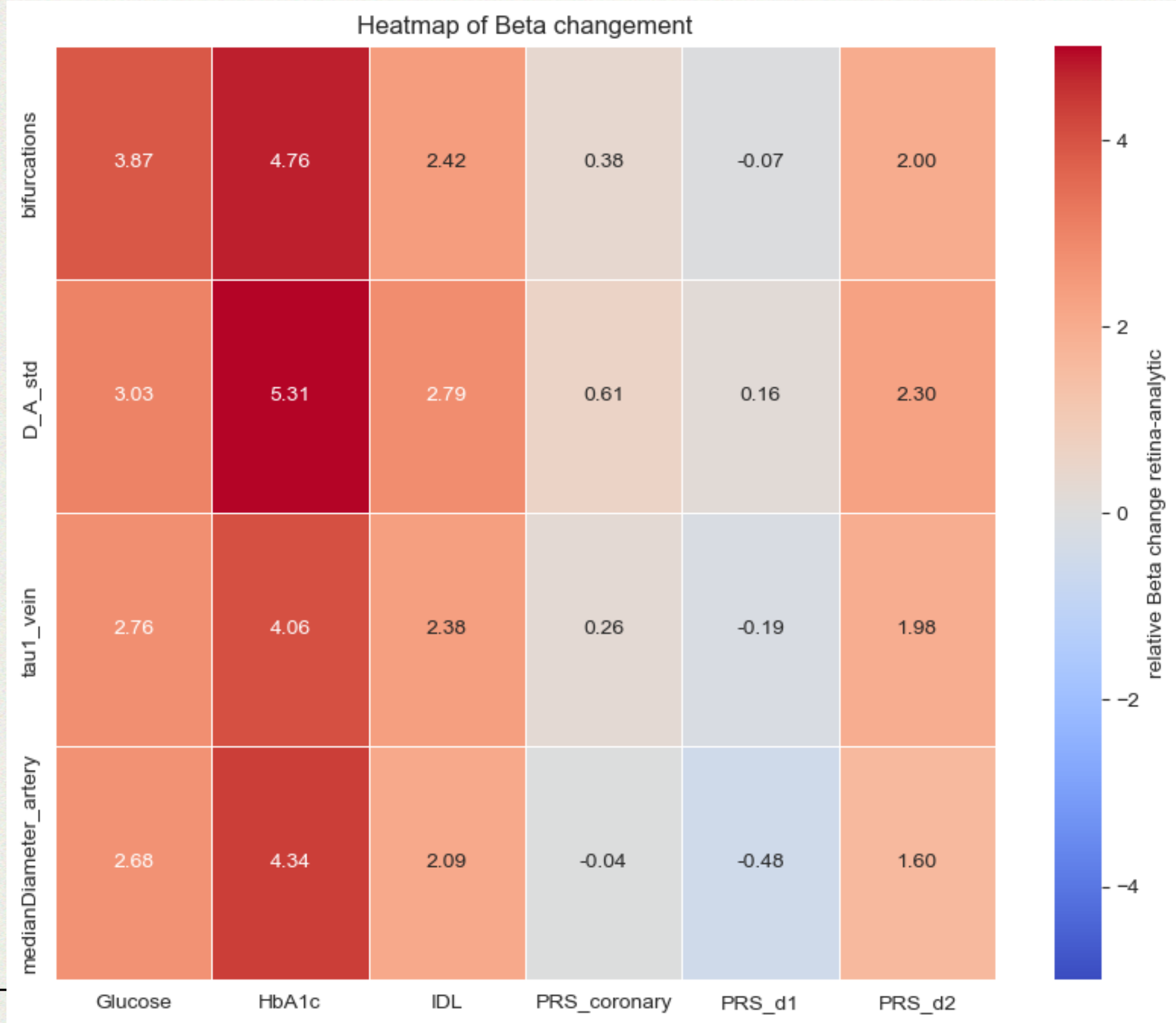
Retina - Biomarkers

$$\text{Score} = \log\left(\frac{|\beta 2 - \beta 1|}{|\beta 4 - \beta 3|}\right)$$

- Biomarkers –(explain)-> Retina

- PRS_d1 exception !!
- Retina –(explain)-> PRS_d1
  - 5 %

- PRS_coronary ~ Retina



Conclusion

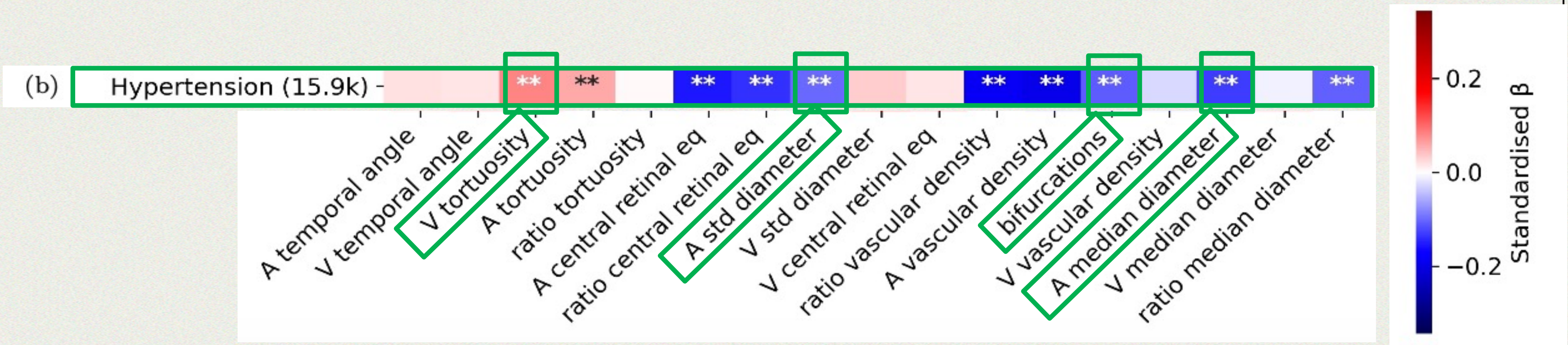
Diabetes

major causes of retinopathy

Biomarkers

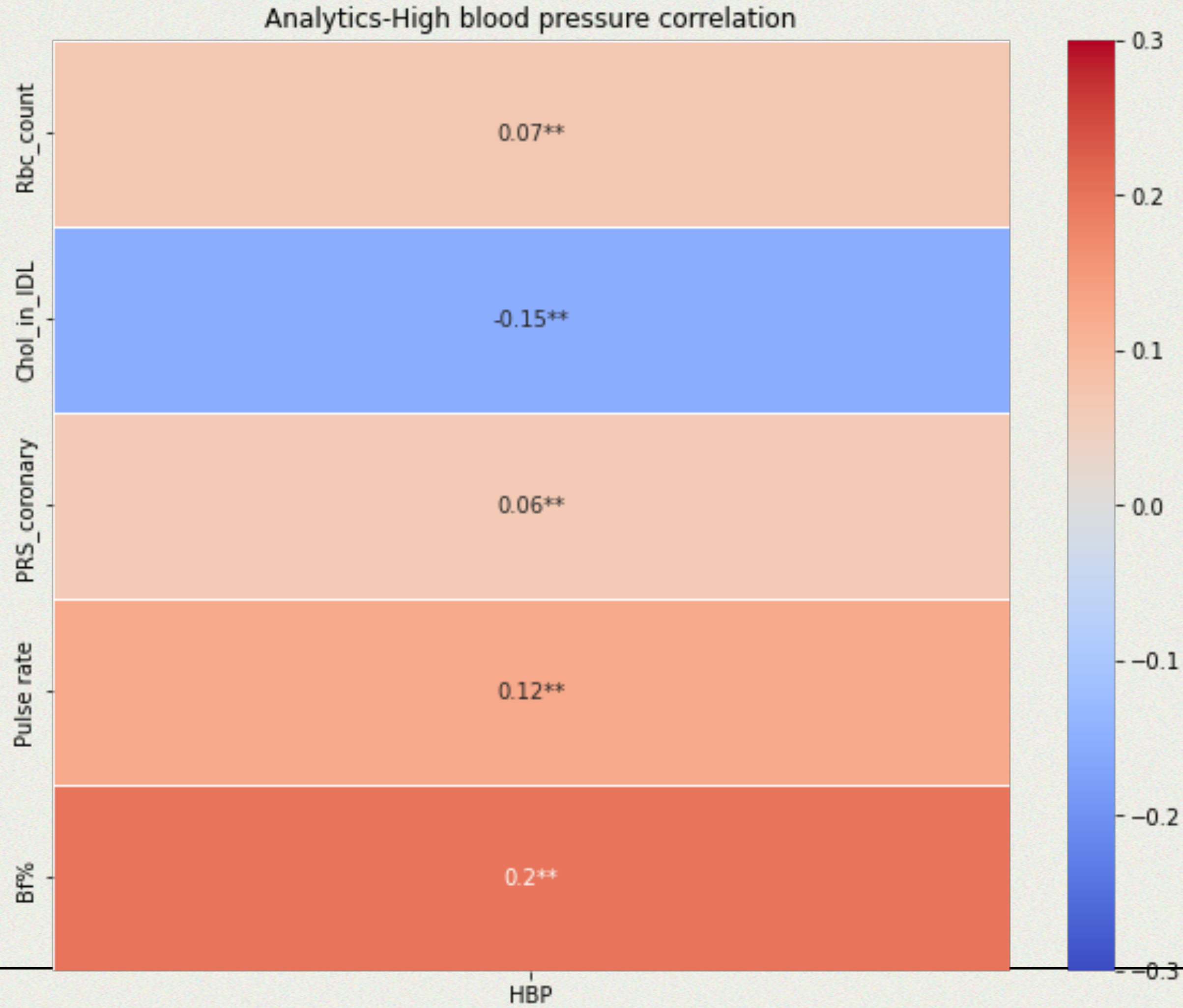
Retinal Parameters

Hypertension - Retina



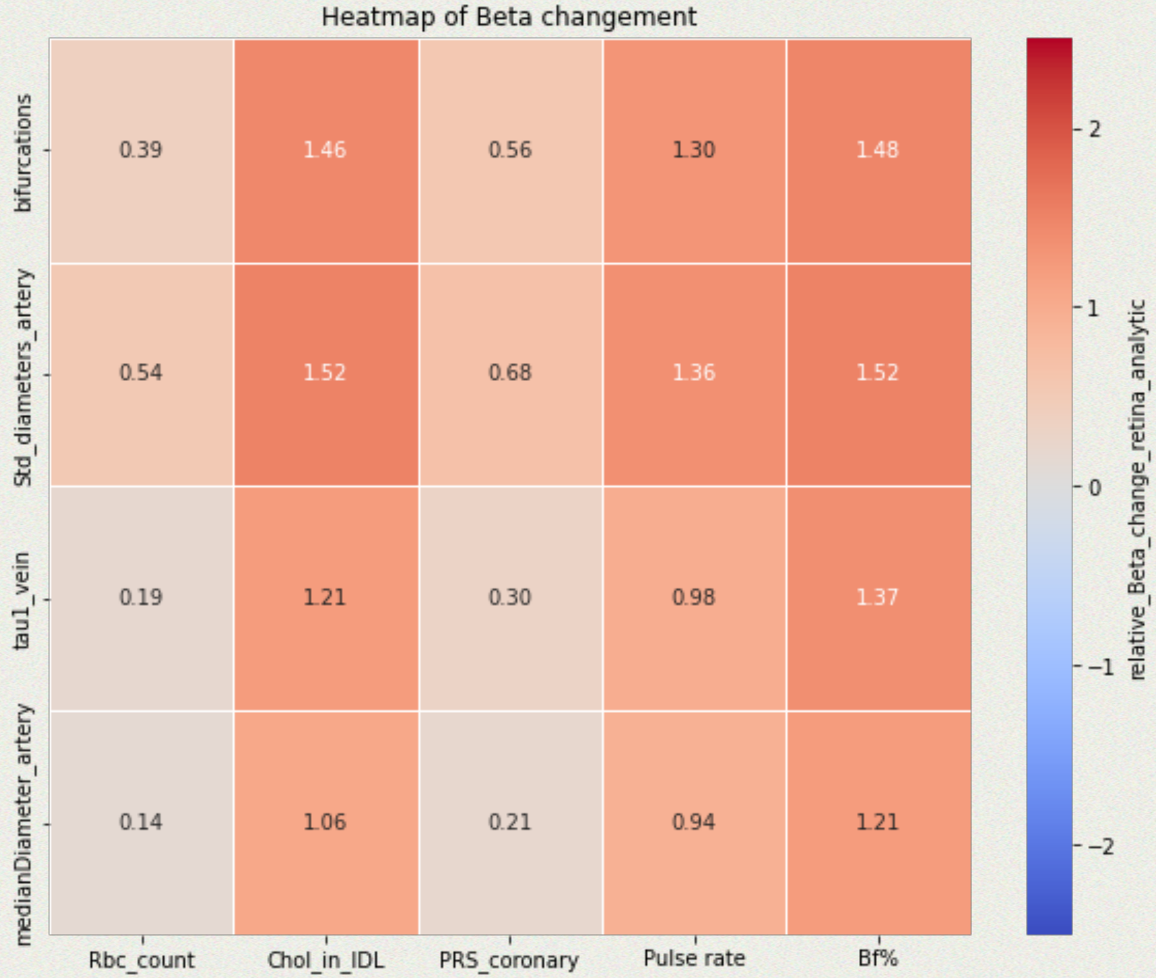
Hypertension - Biomarkers

- As expected
- Low values
- Cholesterol in IDL negative!!

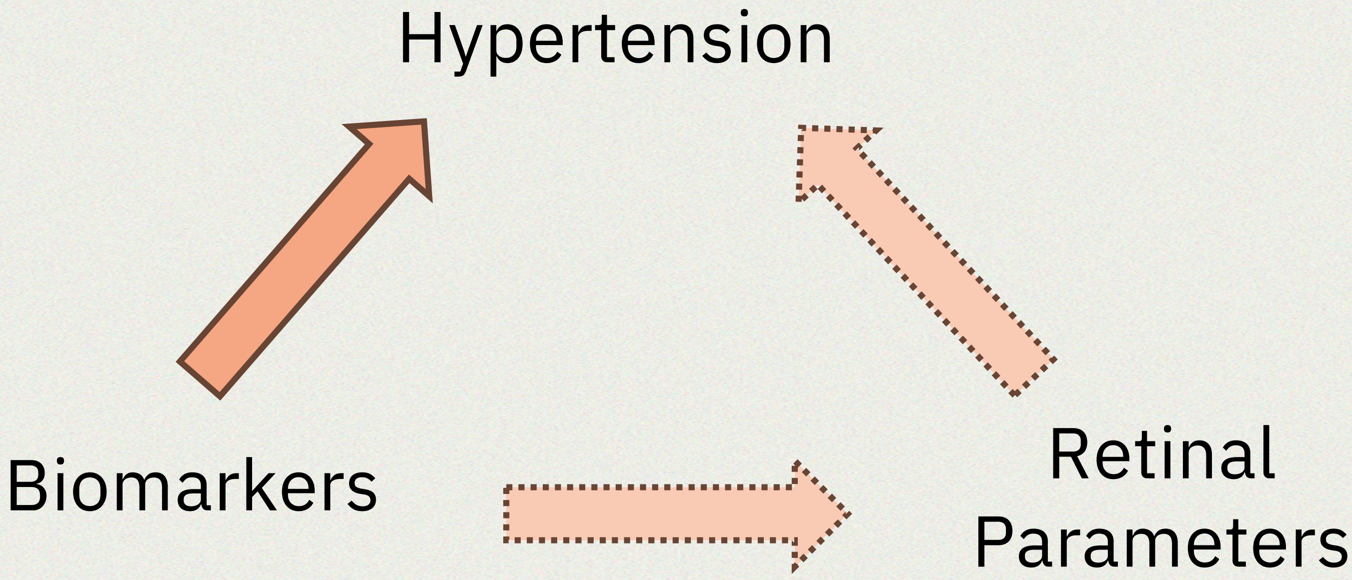


Retina - Biomarkers

- Always positive
- IDL, PR and Bf% highest values across all the retina parameters
- Not huge values
- Other variables?

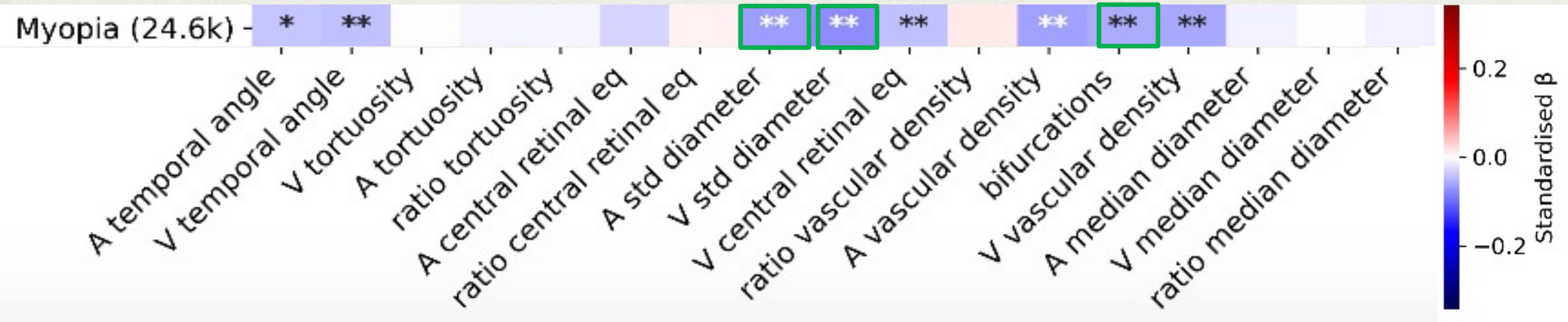


Conclusion



High blood pressure in retina artery ➔ damage

Results



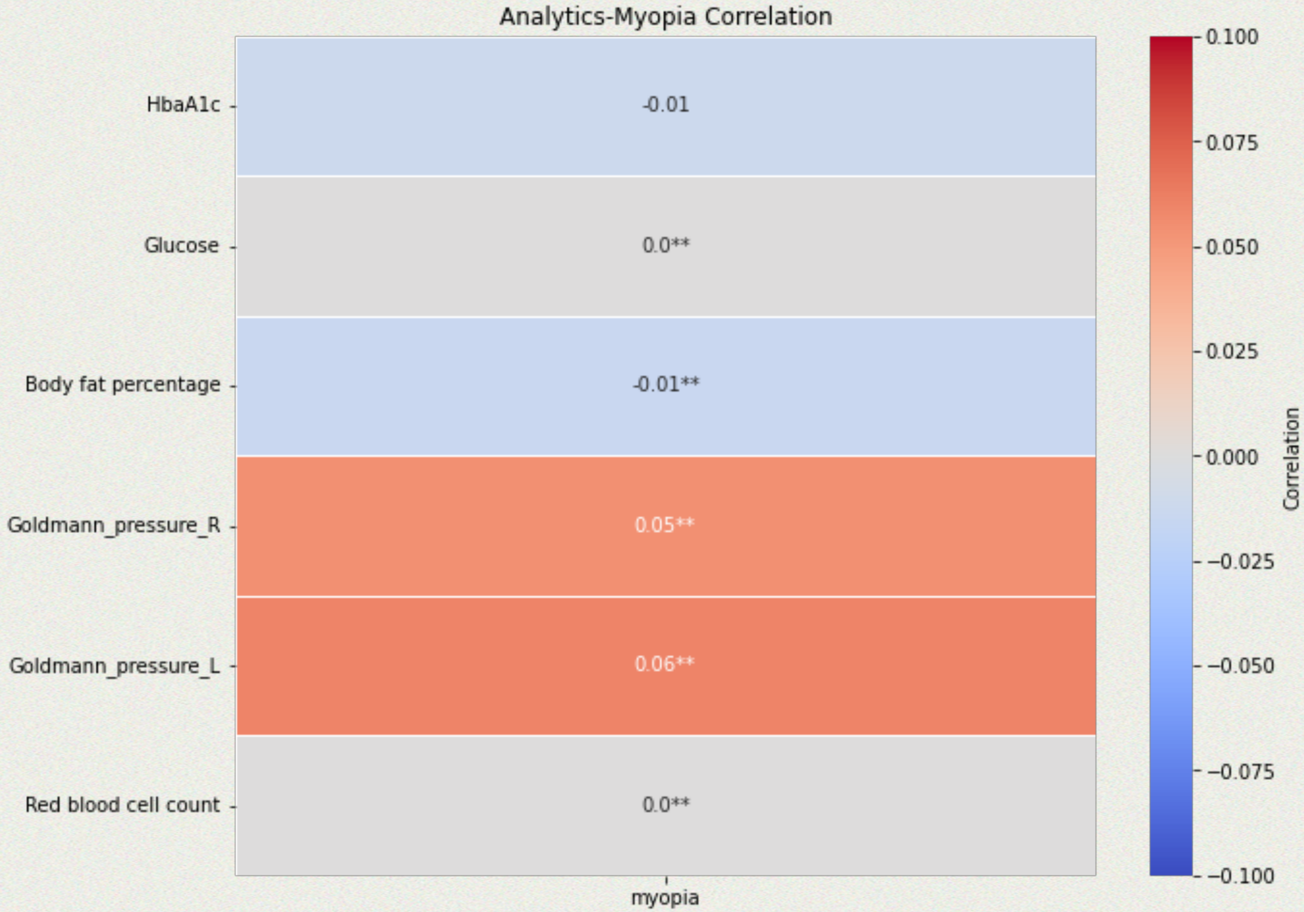
Myopia (24.6k)
*
**
**
**
**
**
**
**
A temporal angle
V temporal angle
V tortuosity
A tortuosity
ratio tortuosity
A central retinal eq
ratio central retinal eq
A std diameter
V std diameter
V central retinal eq
ratio vascular density
A vascular density
bifurcations
V vascular density
A median diameter
V median diameter
ratio median diameter
0.2
0.0
−0.2
Standardised β

Myopia-Biomarkers

Biomarkers values have a very little association on myopia

Possible explanation:

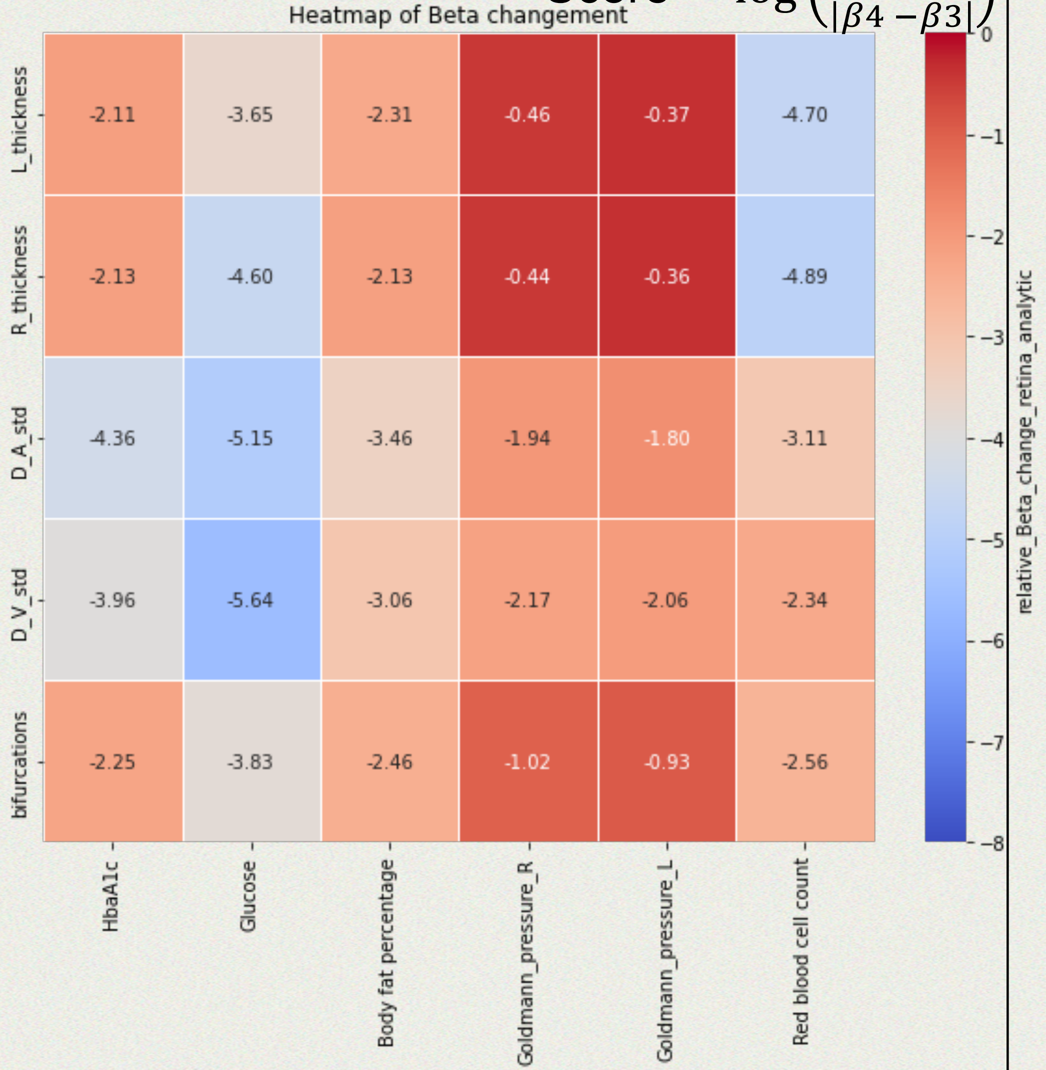
- Myopia→eyes diasease
- Genetic influence
- Myopia datas are binary



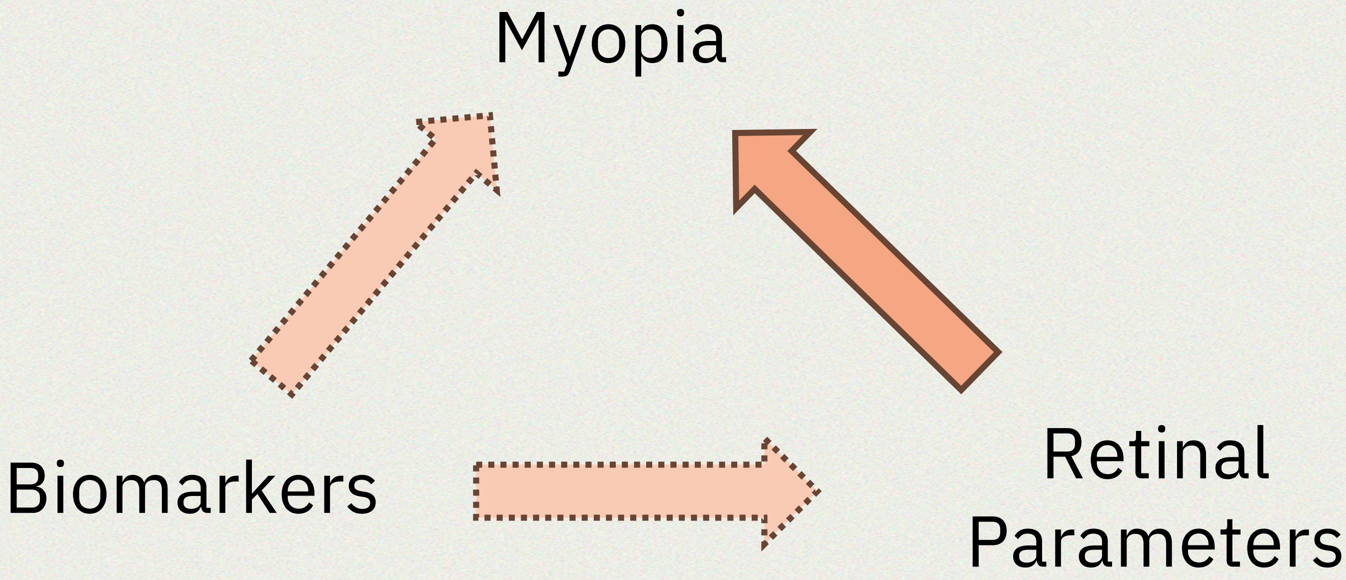
Retina - Biomarkers

- Always negative
- The intraocular pressure has the highest variation

$$\text{Score} = \log\left(\frac{|\beta 2 - \beta 1|}{|\beta 4 - \beta 3|}\right)$$



Conclusion



General Conclusion

General correletion between the disease and the retinal parameter:

- Myopia→ eyes disease→high correletion of retinal parameter
- Diabetes and Hypertension → General disease→ biomarkers predominant

General disease:
- Biomarkers have infleunction on retinal parameters
- Biomarkers have stronger association with disease than retinal parameters

Retinal parametes → another source of information to predict the disease

What could we do

- Add more retinal parameters to see if it can increase the influece on the disease
- Add some genetic parameter as covariance/ retinal parameters to reduce the influence on the retinal and Biomarkers datas
- Have more data from other nation and not only UK

Future application

- Use the retinals parameters as source to detect some desease
- Implement early detection and intervention strategies
- Enhance diagnostic accuracy using combined retinal and analytical data
- Explore the potential for non-invasive disease monitoring

Feedback

- Intressing to work with some real data but sometimes it takes too long to have access to it
- Have some projects focus more on algoritm thinking and other to statistics application was a good proposition
- The UK databank has data only from people over 37 year so we miss all the adolescent period so maybe use other databanks

THANKS!

DO YOU HAVE ANY QUESTIONS?