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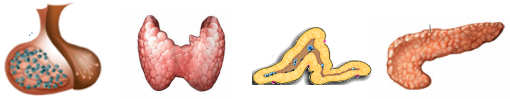
Skin autofluorescence predicts incident type 2 diabetes, cardiovascular disease and mortality in the general population



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ARTICLE

Skin autofluorescence predicts incident type 2 diabetes, cardiovascular disease and mortality in the general population

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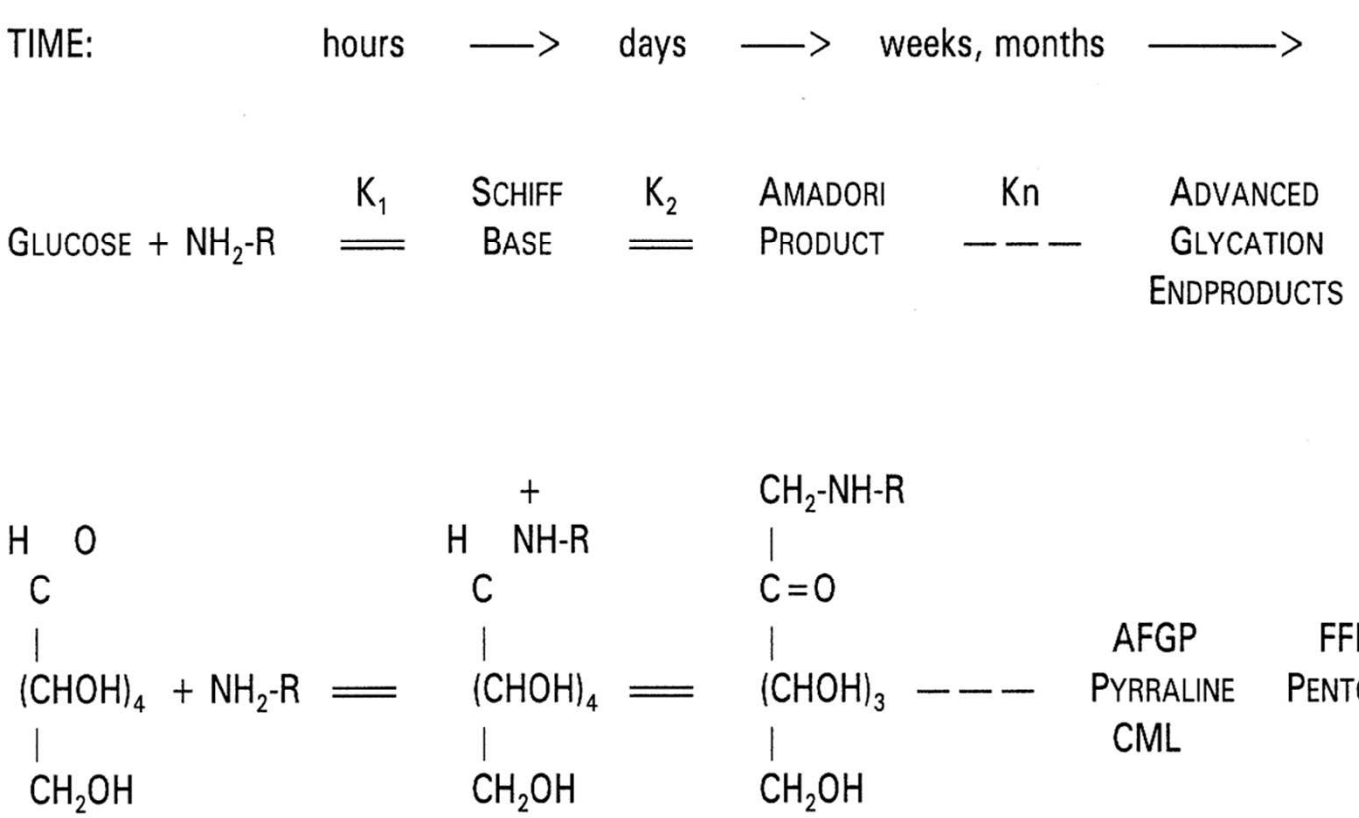
Advanced glycation endproducts (AGEs) are chemical compounds, formed in our body. The main drivers are glucose and ageing.



Background of skin autofluorescence

- Skin autofluorescence (SAF) can be measured with a so-called AGE-reader, it estimates accumulation of AGEs in the skin
- SAF increases with ageing, and is higher in people with the metabolic syndrome (a cluster of cardiovascular risk factors) and in type 2 diabetes as a consequence of higher blood glucose levels
- Smoking, impaired renal function and coffee consumption also increase SAF
- SAF predicts the development of vascular complications in people with diabetes
- No data on the measurement of SAF in the general population were available until now

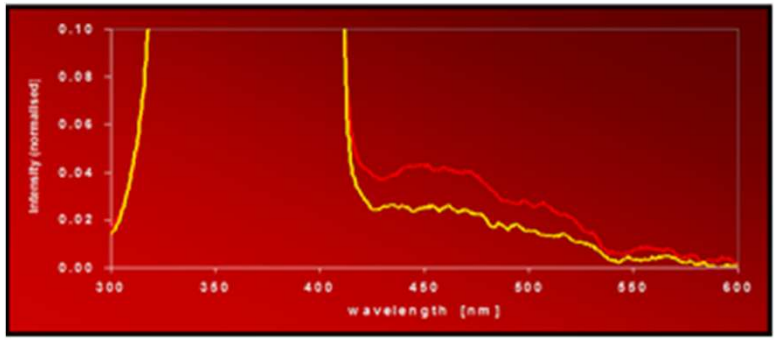
The AGE-Reader is a device which non-invasively measures the amount of AGE in the body

2010

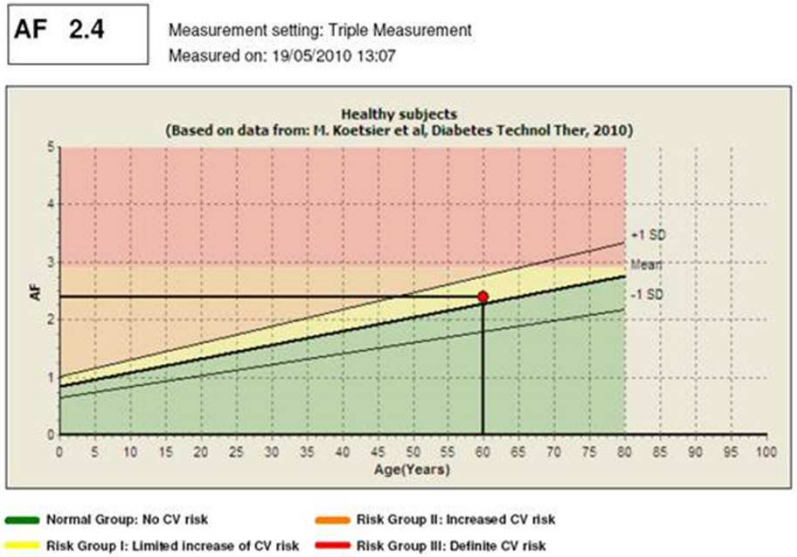
2015

2018

The 'raw' machine measurement



The actual measurement put into context



SAF is increased in people with metabolic syndrome (pre-diabetes), and increases with the number of metabolic syndrome criteria

Skin autofluorescence, a non-invasive biomarker for advanced glycation end products, is associated with the metabolic syndrome and its individual components

Robert P. van Waateringe ✉, Sandra N. Slagter, Andre P. van Beek, Melanie M. van der Klauw, Jana V. van Vliet-Ostaptchouk, Reindert Graaff, Andrew D. Paterson, Helen L. Lutgers and Bruce H. R. Wolffenbuttel

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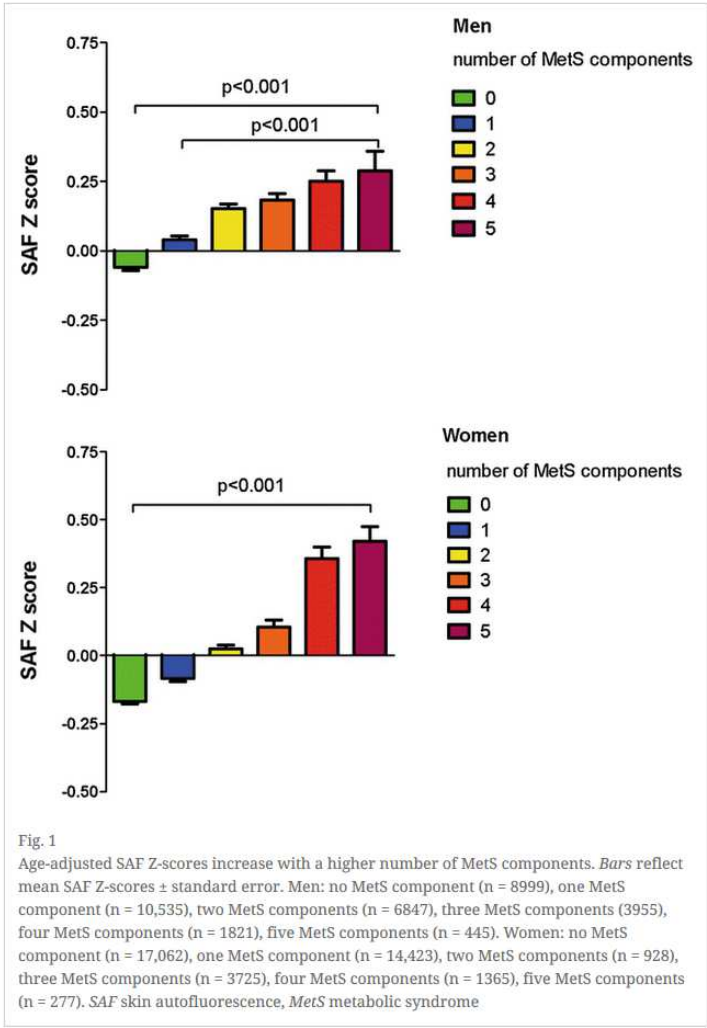
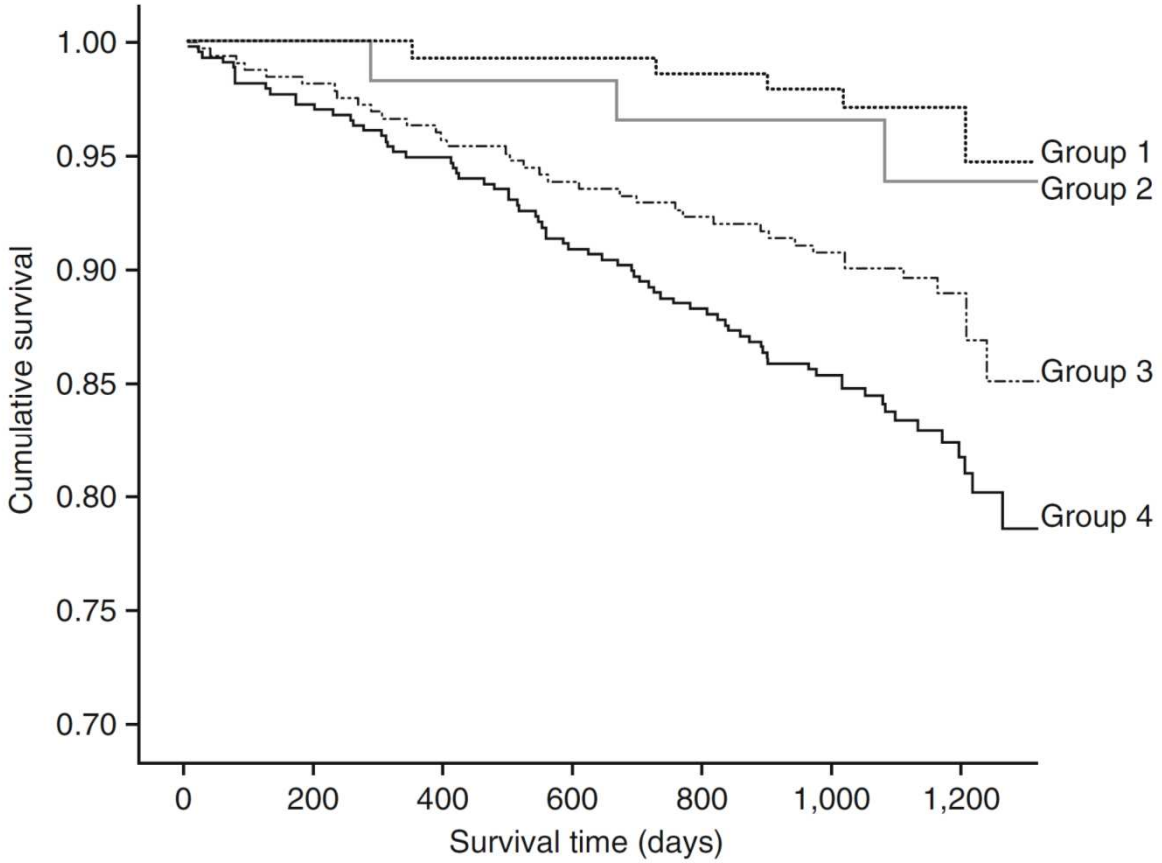


Fig. 1
Age-adjusted SAF Z-scores increase with a higher number of MetS components. *Bars* reflect mean SAF Z-scores ± standard error. Men: no MetS component (n = 8999), one MetS component (n = 10,535), two MetS components (n = 6847), three MetS components (3955), four MetS components (n = 1821), five MetS components (n = 445). Women: no MetS component (n = 17,062), one MetS component (n = 14,423), two MetS components (n = 928), three MetS components (n = 3725), four MetS components (n = 1365), five MetS components (n = 277). *SAF* skin autofluorescence, *MetS* metabolic syndrome

Skin autofluorescence adds to the UKPDS risk score for the prediction of CVD * in people with type 2 diabetes



AF<median
UKPDS risk score <10%
AF>median

AF<median
UKPDS risk score >10%
AF>median

* CVD=cardiovascular disease

Lutgers HL, et al. Diabetologia 2009; 52:789

Goal of the present study

- To assess whether SAF was able to predict the development of type 2 diabetes, CVD and mortality **in the general population**

Methods and participants

- Participants from the **Lifelines Cohort Study**, a large population-based study in the northern region of the Netherlands
- Physical and laboratory examination and extensive questionnaire data at baseline, incl. measurement of skin autofluorescence, between 2007 and 2013
- 4-year follow-up (median)

- Incidence of type 2 diabetes, CVD and mortality was calculated separately and as a composite outcome for all age-decade groups (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80 years)
- Uni- and multivariate logistic regression analyses using different models for composite and separate outcomes

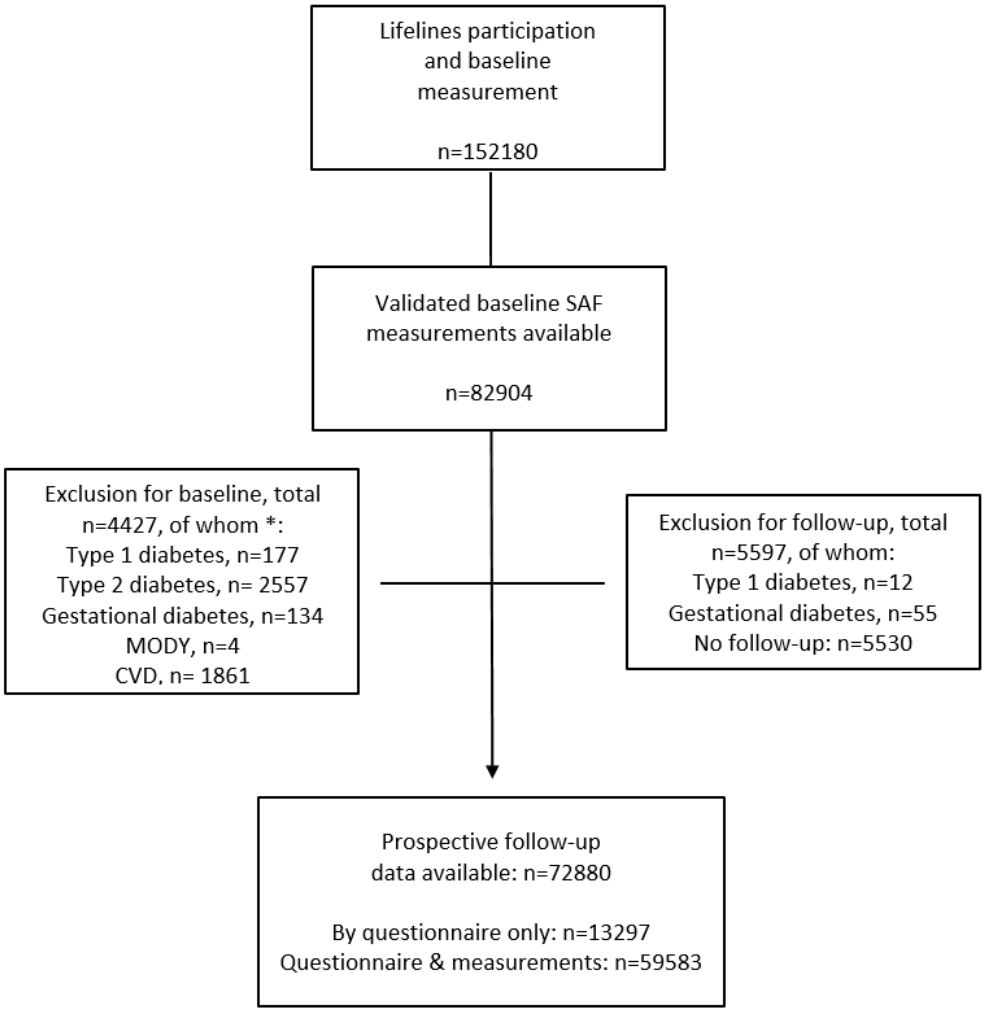
Definition of events /outcomes

- **Incident Type 2 Diabetes**
  - self-reported
  - fasting blood glucose ≥ 7.0 mmol/l and/or HbA1c ≥ 6.5% at follow-up

- **Incident Cardiovascular Disease**
  - self-reported myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), stent positioning, coronary artery bypass grafting (CABG)
  - transient ischaemic attack (TIA), cerebrovascular accident (CVA)
  - intermittent claudication or peripheral artery vascular surgery

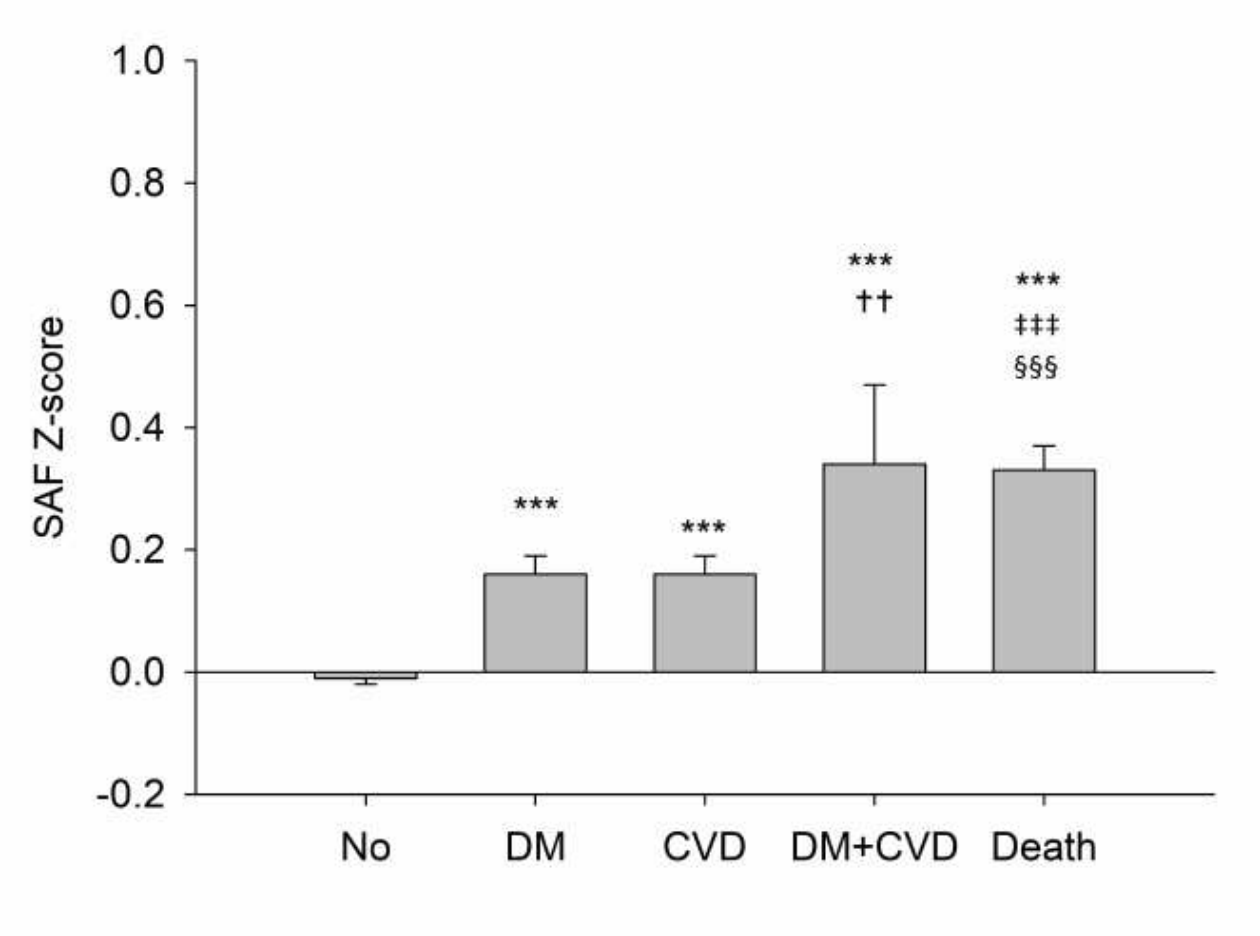
- **Mortality**
  - Vital status ascertained with the Municipal Personal Records Database (GBA)

Disposition of participants in the study



* multiple reasons for exclusion may apply

Baseline skin autofluorescence (Z-score) and future events



DM, type 2 diabetes; CVD, cardiovascular disease
Z-score is measure how much participant deviates from the normal value for his/her age
For explanation of symbols, see the original paper

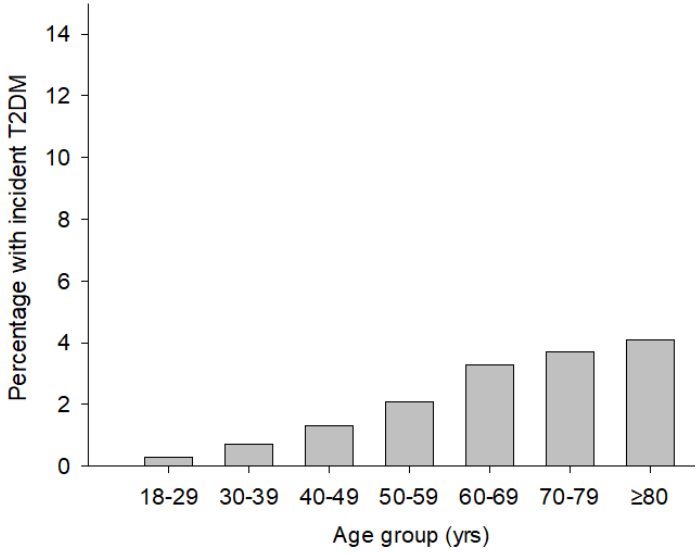
Incidence of events during a 4-year follow-up period

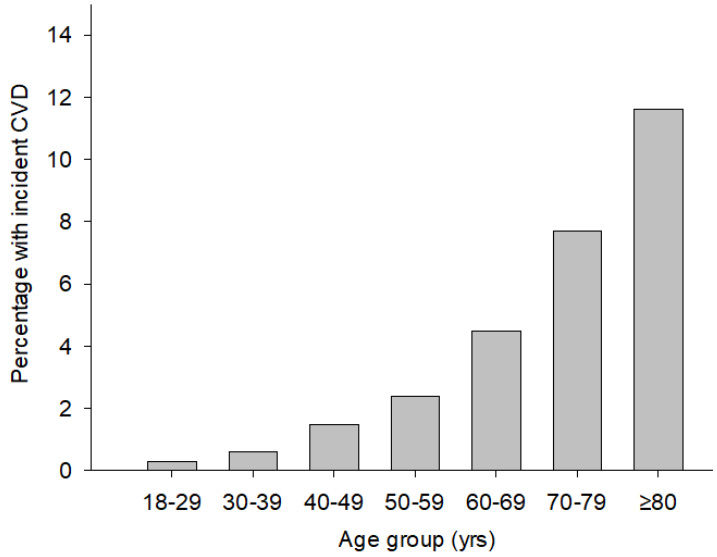
Clinical endpoint	number
No type 2 diabetes, CVD or death	69749
Incident type 2 diabetes only	977
Incident CVD only	1171
Death [a]	874
Incident type 2 diabetes and CVD	55
Type 2 diabetes and death	22
CVD and death	30
Type 2 diabetes, CVD and death	2

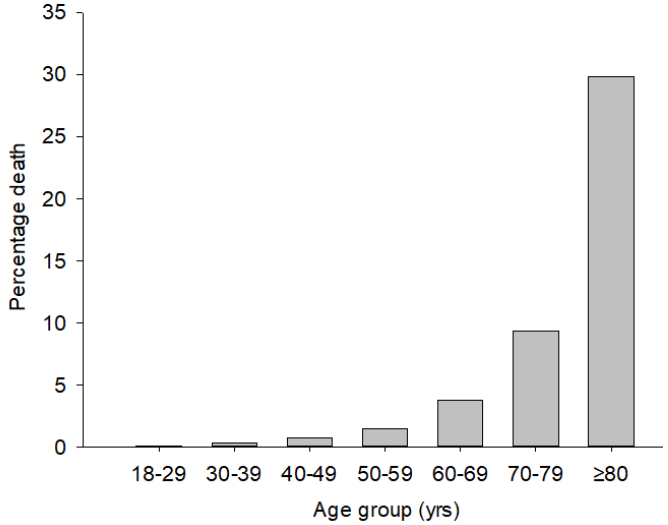
72880 participants in total

[a] without/before ascertainment of diabetes or CVD status

Incidence of type 2 diabetes, cardiovascular disease and death according to age group







Skin autofluorescence

Regression analysis of SAF and age to predict the 3 major outcomes and their combined outcome

Outcome	Parameter	OR (95% CI)	P-value
Composite outcome *	SAF (AU)	3.84 (3.57, 4.11)	1.5×10^{-307}
	Age (yrs)	1.07 (1.07, 1.08)	$<1.0\times10^{-350}$
Type 2 diabetes	SAF (AU)	2.74 (2.44, 3.07)	1.0×10^{-68}
	Age (yrs)	1.05 (1.05, 1.06)	1.5×10^{-91}
Cardiovascular disease	SAF (AU)	3.25 (2.93, 3.60)	2.5×10^{-111}
	Age (yrs)	1.07 (1.06, 1.07)	3.1×10^{-184}
Mortality	SAF (AU)	5.10 (4.56, 5.70)	4.1×10^{-181}
	Age (yrs)	1.10 (1.09, 1.10)	3.4×10^{-239}

SAF, skin autofluorescence; AU, arbitrary units, OR, odds ratio, CI, confidence interval
* Combination of type 2 diabetes, cardiovascular disease and mortality

Multivariate logistic regression analysis for the composite primary outcome (T2D, CVD & death) during a 4-year follow-up period

Multivariate model 5[e]	n=70612	OR	95%CI	P-value
SAF (AU)		1.54	1.40, 1.70	3.9×10^{-18}
Age (years)		1.06	1.05, 1.06	1.4×10^{-107}
Glucose (mmol/l)		2.37	2.20, 2.55	1.3×10^{-112}
Current smoker (yes/no)		1.61	1.46, 1.77	8.3×10^{-23}
Waist circumference (cm)		1.02	1.02, 1.02	2.6×10^{-26}
Male sex (yes/no)		0.93	0.86, 1.02	0.108
SBP (mmHg)		1.01	1.01, 1.01	3.6×10^{-10}
Cholesterol (mmol/l)		0.93	0.89, 0.97	0.001
Triacylglycerol (mmol/l)		1.15	1.10, 1.19	5.4×10^{-13}
eGFR (ml/min)		1.00	1.00, 1.01	0.176
Coffee consumption (cups/day)		0.99	0.97, 1.00	0.135

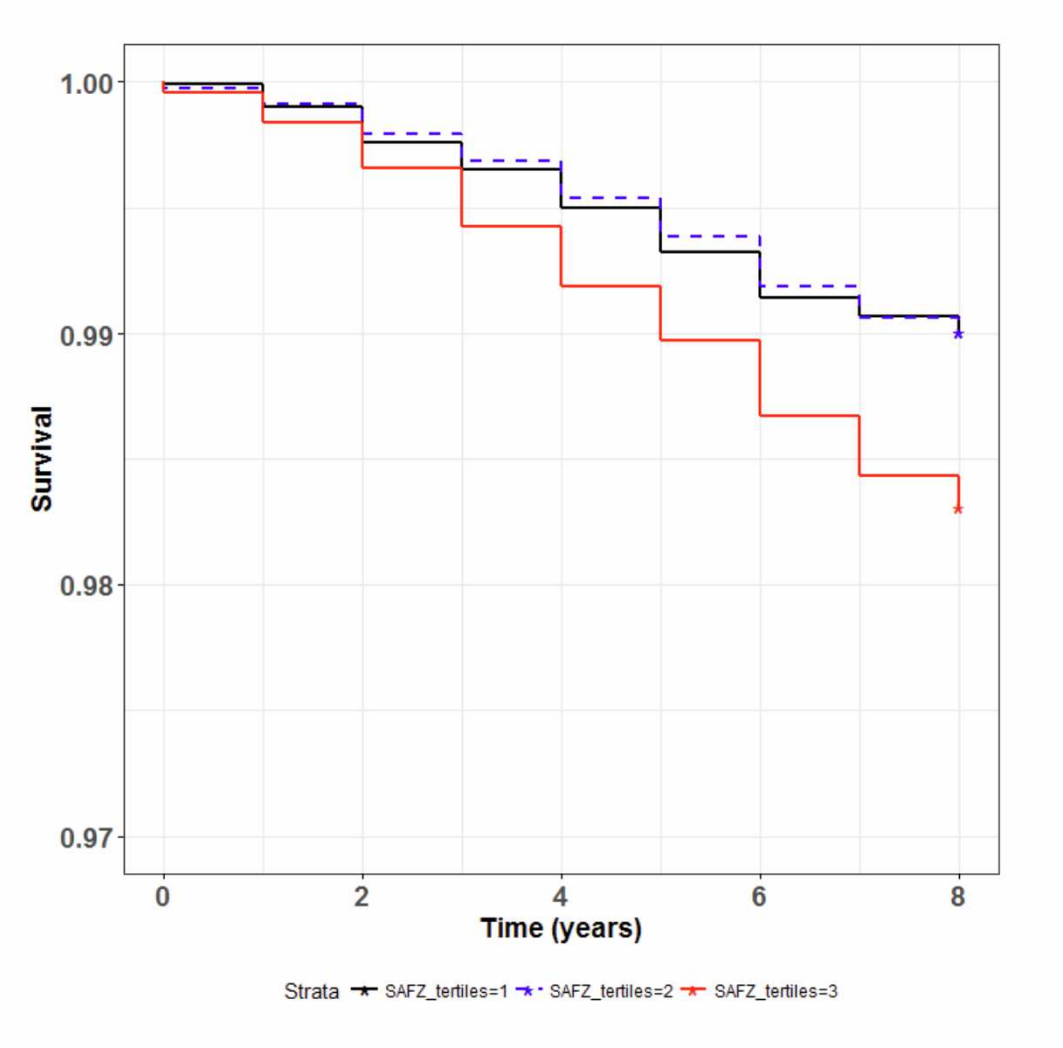
SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate (kidney function)

Multivariate logistic regression analyses for the separate primary outcomes (T2D, CVD, death) during a 4-year follow-up period

	New type 2 diabetes		New cardiovascular disease		Death	
Multivariate model 5	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
SAF (AU)	1.26 (1.06, 1.48)	0.008	1.33 (1.16, 1.54)	6.0×10^{-5}	1.96 (1.69, 2.28)	6.7×10^{-19}
Age (years)	1.02 (1.02, 1.03)	3.8×10^{-8}	1.06 (1.05, 1.06)	3.4×10^{-58}	1.08 (1.08, 1.09)	9.1×10^{-84}
Male sex (yes/no)	0.65 (0.57, 0.75)	6.4×10^{-10}	1.16 (1.03, 1.31)	0.019	1.25 (1.08, 1.44)	0.003
Waist (cm)	1.03 (1.02, 1.04)	1.2×10^{-26}	1.02 (1.01, 1.02)	2.4×10^{-9}	1.01 (1.00, 1.02)	0.009
Glucose (mmol/l)	8.9 (8.0, 10.0)	2.0×10^{-302}	0.96 (0.85, 1.08)	0.458	1.10 (0.96, 1.26)	0.172
SBP (mmHg)	1.00 (1.00, 1.01)	0.175	1.01 (1.01, 1.01)	2.7×10^{-7}	1.01 (1.00, 1.01)	4.5×10^{-4}
Cholesterol (mmol/l)	0.84 (0.78, 0.90)	9.4×10^{-7}	1.05 (0.99, 1.11)	0.149	0.91 (0.85, 0.98)	0.014
Triacylglycerol (mmol/l)	1.24 (1.18, 1.30)	9.9×10^{-19}	1.06 (0.99, 1.13)	0.088	1.05 (0.96, 1.14)	0.275
eGFR (ml/min)	1.00 (1.00, 1.01)	0.120	1.00 (0.99, 1.00)	0.706	1.00 (1.00, 1.01)	0.641
Current smoker (yes/no)	1.22 (1.04, 1.44)	0.017	1.69 (1.47, 1.94)	7.7×10^{-14}	1.96 (1.67, 2.30)	1.5×10^{-16}

SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate (kidney function)

Cox regression analysis depicting the effect of SAF Z-score (divided into tertiles) on mortality



Summary of the results

- SAF is significantly associated with new-onset type 2 diabetes, CVD and mortality during a median follow-up of 4 years in people from the general population
- SAF predicted these outcomes, **independent** of several traditional risk factors, such as the metabolic syndrome, glucose, HbA1c, blood pressure, smoking status
- A longer follow-up of Lifelines participants and detailed information on causes of death will allow further validation and expand the present findings

Strengths and limitations

- Data from a prospective population-based study that included almost 73000 participants within a broad range of age and cardiovascular risk
- Very large study performed in people of Western European descent
- The first prospective study to examine SAF as a predictor for type 2 diabetes, CVD and mortality in the general population

- No data yet on the use of new medications or changes in medications, to validate self-reported diagnosis of 2 diabetes
- Data regarding the exact time of diabetes diagnosis and CVD events not collected

Acknowledgements and data availability

Acknowledgements

- The authors acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants

Data availability

- The manuscript is based on data from the Lifelines Cohort Study. Lifelines adheres to standards for data availability. The data catalogue of Lifelines is publicly accessible at www.lifelines.nl. All international researchers can obtain data at the Lifelines research office (research@lifelines.nl), for which a fee is required. The Lifelines system allows access for reproducibility of the study results.

Executive summary - research in context

What is already known about this subject?

- Skin autofluorescence, measured with an AGE reader, estimates AGE accumulation in the skin
- Skin autofluorescence increases with ageing, and is associated with the metabolic syndrome and type 2 diabetes
- Skin autofluorescence predicts the development of diabetes-related complications

What is the key question?

- Can the measurement of skin autofluorescence predict 4 year risk of incident type 2 diabetes, cardiovascular disease and mortality in the general population?

What are the new findings?

- Baseline skin autofluorescence was elevated in participants with incident type 2 diabetes and/or cardiovascular disease and in those who had died (all $p<0.0001$), compared with individuals who survived and remained free of the two diseases
- Skin autofluorescence predicted the development of type 2 diabetes, cardiovascular disease and mortality, independent of several traditional risk factors, such as the metabolic syndrome, glucose, HbA1c, smoking status

How might this impact on clinical practice in the foreseeable future?

- Non-invasive measurement of skin autofluorescence can be used in the general population to estimate the risk of type 2 diabetes, cardiovascular disease and mortality