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Permalink
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Journal
Circulation: Genomic and Precision Medicine, 16(1)

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Publication Date
2023-02-01

DOI
10.1161/CIRCGEN.121.003676

Peer reviewed

Machine Learning to Understand Genetic and Clinical Factors Associated with the Pulse Waveform Dicrotic Notch

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Abstract

Background: Absence of a dicrotic notch on finger photoplethysmography (PPG) is an easily ascertainable and inexpensive trait that has been associated with age and prevalent cardiovascular disease (CVD). However, the trait exists along a continuum, and little is known about its genetic underpinnings or prognostic value for incident CVD.

Methods: In 169,787 participants in the UK Biobank, we identified absent dicrotic notch on PPG and created a novel continuous trait reflecting notch smoothness using machine learning. Next, we determined the heritability, genetic basis, polygenic risk, and clinical relations for the binary absent notch trait and the newly derived continuous notch smoothness trait.

Results: Heritability of the continuous notch smoothness trait was 7.5%, compared with 5.6% for the binary absent notch trait. A genome-wide association study of notch smoothness identified 15 significant loci, implicating genes including *NT5C2* (P=1.2×10^{-26}), *IGFBP3* (P=4.8×10^{-18}),

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and *PHACTR1* (P=1.4×10^{-13}), compared with 6 loci for the binary absent notch trait. Notch smoothness stratified risk of incident myocardial infarction or coronary artery disease, stroke, heart failure, and aortic stenosis. A polygenic risk score for notch smoothness was associated with incident CVD and all-cause death in UK Biobank participants without available PPG data.

Conclusion: We found that a machine learning derived continuous trait reflecting dicrotic notch smoothness on PPG was heritable and associated with genes involved in vascular stiffness. Greater notch smoothness was associated with greater risk of incident CVD. Raw digital phenotyping may identify individuals at risk for disease via specific genetic pathways.

Introduction

Finger photoplethysmography (PPG), the measurement of pulse volume waveforms using infrared light, is an inexpensive, non-invasive, and scalable test similar to pulse oximetry that may provide insight into a patient's cardiovascular physiology.[1,2] Arterial stiffness index (ASI), the most commonly used PPG metric, is associated with elevated blood pressure and incident cardiovascular disease (CVD).[3,4] Another PPG phenotype, absence of the dicrotic notch, has been recognized as a marker of age and prevalent coronary artery disease since the 1970s. Dawber and colleagues in the Framingham Heart Study classified dicrotic notch morphology in 4 groups; class IV (absent notch) was associated with a 4-fold greater prevalence of myocardial infarction compared with class I (distinct notch).[1,5] Absent notch has been associated with risk factors for atherosclerotic heart disease, and has been considered an extreme phenotype of arterial stiffness.[6] However, the biological mechanisms driving absent notch, and its prognostic value for CVD events, are unknown. Examining the genetic basis of observed phenotypes like absent notch has been an effective strategy for identifying biological mechanisms underlying CVD.[3,7,8]

We investigated absent notch on the PPG waveform in 169,787 participants in the UK Biobank. First, to maximize power, we produced a machine learning-based predictor of absent notch using PPG waveforms that yielded a continuous trait representing the likelihood of notch absence (Figure 1). Waveforms with absent or small notches were assigned higher values of this notch smoothness trait, whereas waveforms with large notches were assigned lower values. Second, we performed a genome-wide association study of this continuous trait to elucidate genetic mechanisms underlying notch smoothness. Third, we characterized associations of notch smoothness with incident cardiovascular disease.

Methods

Analysis of UK Biobank data was performed under application 17488 and approved by the Mass General Brigham institutional review board in accordance with institutional guidelines. Informed consent was obtained from all participants by the UK Biobank. Individual-level data are available by application from the UK Biobank. A full description of the methods are available in the Supplemental Material.

Results

Baseline characteristics

Among the 169,787 participants who underwent PPG at the first visit, dicrotic notch was absent in 25,286 (14%). Baseline characteristics of participants with and without a dicrotic notch are shown in Supplemental Figure I and Supplemental Table I. Patients with absent notch were older (61.5 vs 56.5 years), more commonly female (66% vs 52%), and had a higher heart rate (70.1 vs 68.6 beats per minute), body mass index (BMI) (28.1 vs 27.4 kg/m^2), and systolic blood pressure (SBP) (147.5 vs 139.3 mm Hg), but similar diastolic blood pressure (DBP). Prevalent cardiovascular diseases were rare but more common in patients with an absent notch, such as myocardial infarction or coronary artery disease (MI/CAD) (6.4% vs 3.9%).

The distribution of the notch smoothness trait and a sample of waveforms representing the spectrum notch smoothness are shown in Figure 1. Notch smoothness discriminated binary absent notch with area under the receiver operator curve of 0.997. In an independent set of PPG tracings from the imaging visit not used in model training, the average of the five models that generated the notch smoothness trait discriminated the binary absent notch label very accurately (area under receiver operator characteristic curve 0.997). The notch smoothness trait was not calibrated to reflect numerical probability of absent notch, as this probability was near zero in patients without binary absent notch and near 100% in patients with absent notch, due to the high discrimination of the model (Supplemental Figure II).

The continuous notch smoothness trait was associated with similar differences in baseline characteristics as binary absent notch (Table 1). Most participants with binary absent notch (99.8%) had notch smoothness in the highest quartile. Notch smoothness was associated with other PPG traits: later position of the shoulder and peak of the waveform, greater arterial stiffness index, and greater wave reflection index (ratio of notch height to peak height). After adjustment for age, sex, heart rate, body mass index, systolic blood pressure, and diastolic blood pressure, smoking, diabetes mellitus, and hypercholesterolemia, greater notch smoothness was associated with greater prevalent cardiovascular conditions such as hypertension (adj. OR 1.07 [95% CI 1.06–1.08] per standard deviation [SD]), MI/CAD (adj. OR 1.10 [95% CI 1.07–1.13] per SD, stroke (adj. OR 1.18 [95% CI 1.13–1.23] per SD), aortic stenosis (adj. OR 1.16 [95% CI 1.03–1.30] per SD) and atrial fibrillation (adj. OR 1.17 [95% CI 1.13–1.21] per SD, but not cancer (adj. OR 0.97 [95% CI 0.95–0.98]) (Supplemental Table II).

Genome wide association study of notch smoothness reveals 15 significant loci

We examined the SNP heritability of continuous notch smoothness compared with binary absent notch. Notch smoothness had a greater heritability at 7.5% (95% CI 6.8%−8.3%) versus 5.6% (95% CI 4.9%−6.4%) for the binary absent notch.

We then performed a GWAS of notch smoothness in 148,310 unrelated participants with PPG data, which revealed 15 loci at genome-wide significance ($p < 5 \times 10^{-8}$) (Figure 2A, Table 2). Inflation (LD score regression intercept 1.013) was acceptable (Supplemental Figure III). The strongest associations were identified at chromosome 10 near *NT5C2* and

CNNM2 (p=1.2×10^{-26}), chromosome 7 near *IGFBP3* (p=4.8×10^{-18}), chromosome 6 near *PHACTR1* (p=1.4×10^{-13}), chromosome 14 near *SMOC1* (p=7.2×10^{-12}), and chromosome 11 near *MYBPC3* (p=6.2×10^{-10}) (Supplemental Figure 4). A similar GWAS using the binary absent notch phenotype identified only 6 genome-wide significant associations (Figure 2B, Supplemental Table III), all at loci also identified for the continuous trait: chromosome 2 near *TEX41*, chromosome 3 near *ATP1B3*, chromosome 7 near *IGFBP3*, chromosome 10 near *NT5C2* and *CNNM2*, chromosome 11 near *MYBPC3*, and chromosome 14 near *SMOC1*. In a sensitivity analysis including only participants of European ancestry (n=123,644) 13 out of 15 loci significantly associated with notch smoothness remained associated (Supplemental Table IV). In a sensitivity analysis in which we performed a GWAS of notch smoothness after inverse rank normalization, 11 of the 15 genome-wide significant loci remained significant, and the remaining 4 had p-values <5×10^{-7} (Supplemental Table V and Supplemental Figure V). Of the 15 genome-wide significant loci in the primary GWAS, two were in close linkage disequilibrium (r^2>0.8) with top loci for coronary artery disease identified in a published meta-analysis of the Million Veteran Program, UK Biobank, and CARDIoGRAMplusC4D cohorts:[9] rs11977526 on chromosome 9 near *CDKN2B-AS1* (r^2 0.88) and rs6224 on chromosome 15 near *FURIN* (r^2 0.94).

Finally, we performed a transcriptome wide association study to identify genes for which predicted expression is associated with notch smoothness (Table 3). We found 11 significant associations with genes in aortic tissue and 3 with genes in left ventricular tissue. The strongest associations were with *NT5C2*, *PHACTR1, SMOC1*, and *ATP1B3* in aortic tissue, and *IGFBP3*, *MFSD13A*, and *BORCS7* in left ventricle.

Association of Notch Smoothness with Incident Cardiovascular Disease

Greater notch smoothness was associated with incident CVD and all-cause death in patients free of cardiovascular disease at the time of assessment (Figure 3, Figure 4 & Supplemental Table VI). In a minimally adjusted model including age and sex, notch smoothness was associated with greater risk of hypertension, heart failure, MI/CAD, stroke, aortic stenosis and death, but not a negative control, incident cancer. All of these associations remained statistically significant after further adjustment BMI, heart rate, SBP, DBP, diabetes, hypercholesterolemia, and ever smoking. Adjusted Kaplan-Meier curves demonstrated that continuous notch smoothness stratified by quartiles added only modest risk discrimination to these covariates (Supplemental Figure VI). Risk discrimination of MI/CAD, heart failure, aortic stenosis, and stroke was stronger using notch smoothness compared to binary absent notch in univariable but not multivariable analyses (Supplemental Tables VII and VIII). Possible non-linear relationships were assessed by restricted cubic splines. The null hypothesis of a linear association was rejected by a likelihood ratio test for only 2 of the 8 outcomes: hypertension (p=0.002) and death (p=0.03) (Supplemental Table IX). Nevertheless, for these two outcomes, the association between continuous notch smoothness and adjusted risk was nearly linear by visual inspection of the spline (Supplemental Figure VII) and improvements in Akaike information criterion were modest. The linear model was therefore retained as the primary analysis.

The prognostic value of notch smoothness was independent of, and superseded, the most commonly used PPG metric, arterial stiffness index (ASI), measured on the same PPG for all outcomes except hypertension (Supplemental Table VI). When notch smoothness and ASI were included in the same adjusted Cox regression, ASI was not associated with heart failure, aortic stenosis, or stroke whereas notch smoothness remained associated with these outcomes. However, ASI (HR 1.09 [95% CI 1.07–1.11] per SD, p=6.3×10^{-16}) was more strongly associated with incident hypertension than notch smoothness (HR 1.03 [95% CI 1.01–1.05] per SD, p=0.01).

Absent notch is associated with smaller left ventricular cavity size and higher left ventricular ejection fraction by cardiac magnetic resonance imaging

PPG and cardiac magnetic resonance imaging data were obtained simultaneously in 30,999 participants at the imaging visit. Participants with greater notch smoothness had smaller indexed left ventricular end diastolic volume (mean difference −1.8 ml/m^2 [95% CI −1.7, −2.0] per SD notch smoothness) and left ventricular end systolic volume (mean difference −1.1 ml/m^2 [95% CI −1.0, −1.1] per SD) and higher ejection fraction (mean difference 0.6% [95% CI 0.5%, 0.7%] per SD) (all p<10^{-28}). After adjustment for age, sex, SBP, DBP, heart rate, and BMI, notch smoothness remained associated with smaller end diastolic volume (mean difference −0.5 ml/m^2 [95% CI −0.3, −0.6] per SD), end systolic volume (mean difference −0.4 ml/m^2 [95% CI −0.3, −0.5] per SD) and higher ejection fraction (mean difference +0.3% [95% CI 0.3, 0.4%] per SD) (all p<10^{-12}). Similar associations were observed for binary absent notch (Supplemental Table X).

Polygenic risk score

The best polygenic risk score for the notch smoothness (linkage disequilibrium r^2<0.6 and p<0.05; 183,888 variants) was selected based on most accurate prediction of observed notch smoothness in an independent validation cohort including 25% of participants with available PPG data (Supplemental Table XI). Among participants without PPG data, one standard deviation greater polygenic risk score for notch smoothness was associated with greater risk of incident hypertension (HR 1.06 [95% CI 1.04–1.07], p=2.5×10^{-14}), MI/CAD (HR 1.05 [95% CI 1.03–1.07], p=1.8×10^{-8}), stroke (HR 1.06 [95% CI 1.01–1.12], p=0.01) and death (HR 1.02 [95% CI 1.00–1.04], p=0.02) after adjustment for age, sex, genotyping array and the first 12 principal components and exclusion of participants with prevalent cardiovascular disease (Figure 4). These associations were linear by restricted cubic spline analysis except for a suggestion of curvilinear relationship with 4 or 5 knots for the MI or CAD outcome which was not biologically plausible (Supplemental Table XII and Supplemental Figure VIII). The polygenic risk score was not significantly associated with incident heart failure (HR 1.02 [95% CI 0.99–1.05] per SD) or aortic stenosis (HR 1.04 [95% 1.00–1.08] per SD), though both point estimates exceeded 1.00. The polygenic risk score was not significantly associated with the negative control outcome, incident cancer (HR 1.00 [95% CI 0.98–1.01], p=0.48).

Discussion

Absent dicrotic notch on finger PPG is a marker of age and prevalent cardiovascular disease. In 169,787 UK Biobank participants, we derived a continuous trait reflecting a spectrum of dicrotic notch smoothness using machine learning interpretation of the raw pulse volume waveforms. A genome wide association of this continuous measure of dicrotic notch smoothness identified 15 loci, implicating genes including *NT5C2, ATP1B3, IGFBP3*, and *MYBPC3* and pathways of vascular stiffness, compared with 6 loci for binary absent notch. A polygenic risk score for notch smoothness was associated with incident hypertension, coronary artery disease, stroke and death in UK Biobank participants without available PPG data. Notch smoothness was associated with incident cardiovascular disease independent of clinical risk factors and even arterial stiffness index measured on the same PPG. These results suggest that raw digital phenotyping may identify individuals at risk for disease through specific genetic pathways.

The primary innovation of this study is the creation of a novel continuous trait reflecting the dicrotic notch smoothness using machine learning. This trait represented our ResNet model's prediction of the likelihood of absent notch based on the participant's raw PPG waveform. For example, the model assigned low scores to participants with large dicrotic notches, intermediate scores to those with small but present notches, and high scores to those with absent notch. This notch smoothness trait was more heritable than binary absent notch, and a genome wide association study identified 15 rather genome wide significant associations compared with 6 for binary absent notch. These results illustrate that analysis of high-dimensional raw physiological data using machine learning can provide richer traits for genetic discovery.

Genome-wide and transcriptome wide association studies of notch smoothness identified loci known to be associated with cardiovascular disease, particularly hypertension (Supplemental Table XIII). The strongest locus in our GWAS, chromosome 10 near *CNNM2* and *NT5C2*, has been associated with systolic blood pressure. Knockdown of these 2 genes (but not other genes in the locus such as *AS3MT*, *BORCS7* or *CP17A1*) causes increased renin expression and arterial pulse in zebrafish.[10,11] *IGFBP3* inhibits IGF-1, which exerts pleiotropic effects including dilation of the peripheral vasculature through a nitric oxide dependent effect on vascular smooth muscle and endothelial cells.[12] Higher circulating IGFBP3 is associated with greater mean arterial pressure.[13] *FURIN* is an upstream regulator of natriuretic peptides that is associated with blood pressure and coronary artery disease.[14,15] *SMOC1* has been associated with hypertension, though with marginal significance in a large GWAS;[16] our findings further nominate this gene in cardiovascular disease. *TEX41* has been associated with systolic blood pressure, aortic stenosis and arterial stiffness index by PPG.[3,16,17] Variants near *ATP1B3*,[14] *FGD5*,[16,7] *AFAP1L2*,[18] and *MYBPC3*[7] have also been associated with blood pressure traits, and *COL4A2* with coronary artery disease.[15] Identification of *MYBPC3*, a top susceptibility gene for hypertrophic cardiomyopathy, raises the possibility that cardiac hypertrophy or dysfunction may affect dicrotic notch shape.

One genome-wide significant variant, rs9349379 near *PHACTR1*, offers a window into dicrotic notch physiology because the G allele is known to confer higher risk of coronary artery disease but lower risk of hypertension. In our study, the G allele was associated with lower values of notch smoothness, suggesting that hypertension rather than atherosclerosis is the primary driver of notch smoothness. This variant has been shown to affect vascular disease risk through expression of *EDN1*, which encodes the protein ET-1, a potent vasoconstrictor.[19]

A polygenic risk score for notch smoothness was associated with cardiovascular diseases in UK Biobank participants without PPG data. This result indicates that inherited predisposition to smoother dicrotic notch modestly reflects predisposition to cardiovascular diseases. Future studies may examine whether raw digital health data such as PPG can define genetically mediated forms of disease with distinct physiology and potentially differential treatment response.

Smoother dicrotic notch by PPG is a meaningful cardiovascular trait associated with prevalent and incident disease independent of clinical risk factors and arterial stiffness index. In the 1970s, Dawber and colleagues demonstrated that absent notch was more common in older Framingham Heart Study participants with history of myocardial infarction.[5] We extend these findings to incident CV events, independent of clinical risk factors, in a much larger cohort. The null association between notch smoothness and non-CV negative control, incident cancer, after minimal adjustment for age and sex suggests that notch smoothness is a specific marker of CV risk. Continuous notch smoothness was strongly prognostic of events in minimally adjusted models but only modestly improved risk prediction after adjustment for cardiovascular risk factors. While absent notch has been considered to reflect extreme arterial stiffness, the prognostic value of notch smoothness in our study was independent of arterial stiffness index for most clinical cardiovascular outcomes. PPG may be particularly useful in CV risk prediction because it is easily obtained, including from wearable devices.

These results must be interpreted in the context of the study design. Prevalent and incident cardiovascular disease events in the UK Biobank are derived from hospitalization records and self-report, and may be subject to misclassification. The UK Biobank is predominantly composed of individuals of European ancestry who were healthy at enrollment, and generalization of findings to other ancestral groups and individuals is unclear. The PPG signal was acquired over 15 seconds at a single encounter; averaged repeated measures may improve the precision of the phenotype. These results depend on the adjudication of binary absent notch, which was generated by the PulseTrace PCA2 software and provided by the UK Biobank.

Conclusion

In 169,787 UK Biobank participants, we leveraged raw PPG data and supervised machine learning to develop a continuous trait reflecting smoothness of the dicrotic notch. A GWAS of continuous notch smoothness identified 15 loci, many with known association with cardiovascular disease, particularly hypertension. A polygenic risk score for notch

smoothness was associated with hypertension, coronary artery disease, stroke and all-cause death, suggesting that this phenotype shares underlying pathophysiology with multiple cardiovascular diseases. Measured notch smoothness was independently associated with risk of incident cardiovascular disease. These results provide a proof of concept that raw digital phenotyping may identify individuals at risk for disease through specific genetic pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding:

Disclosures:

Nonstandard Abbreviations and Acronyms

ASI	aortic stiffness index
BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
DBP	diastolic blood pressure
GWAS	genome-wide association study
HR	hazard ratio
MI/CAD	myocardial infarction or coronary artery disease
OR	odds ratio
PPG	photoplethysmography

SBP   systolic blood pressure

SD   standard deviation

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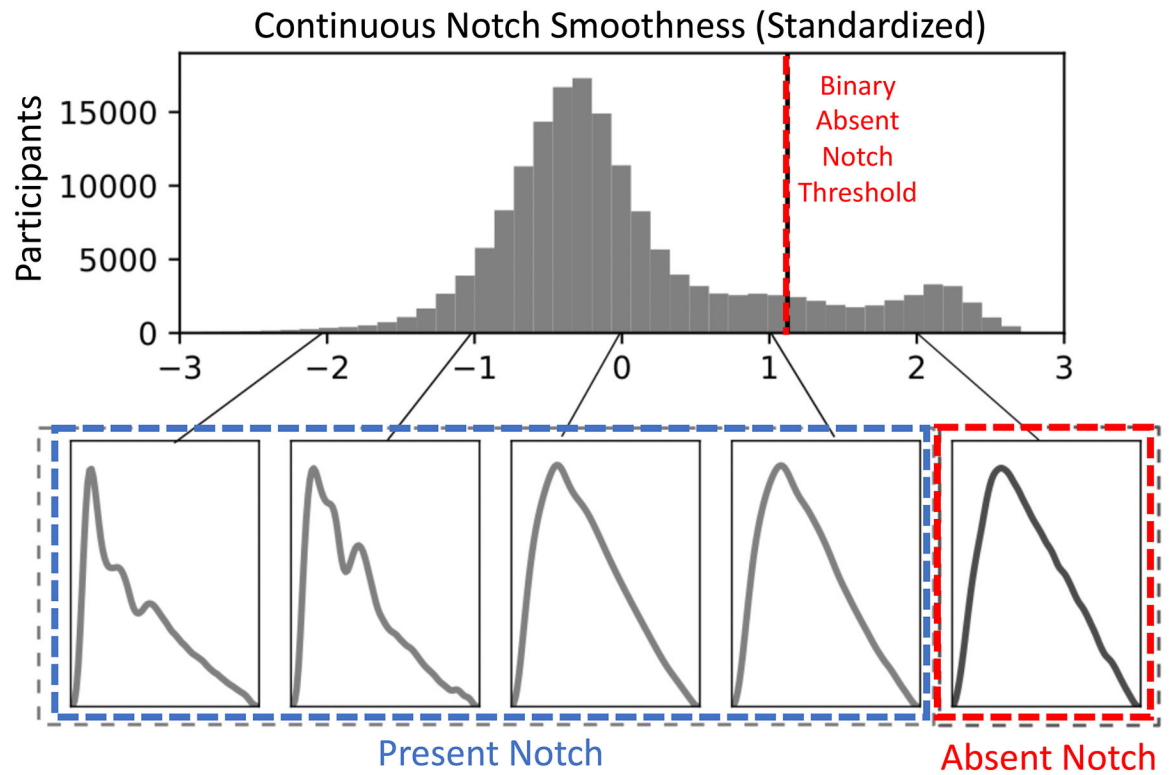
Figure 1:
Transformation of Absent Notch to Continuous Notch Smoothness Using Supervised Machine Learning. The continuous notch smoothness trait reflects the likelihood of absent notch determined by the Resnet supervised machine learning model from interpretation of the raw PPG waveform. The distribution of the standardized notch smoothness is shown on top and sample PPG waveforms at each integer value are shown on bottom. The threshold for absence of a notch is illustrated in red.

Figure 2:
Genome Wide Association Study of Notch Smoothness and Binary Absent Notch. Genome-wide association study in 148,310 unrelated participants identifies 15 loci (green) associated w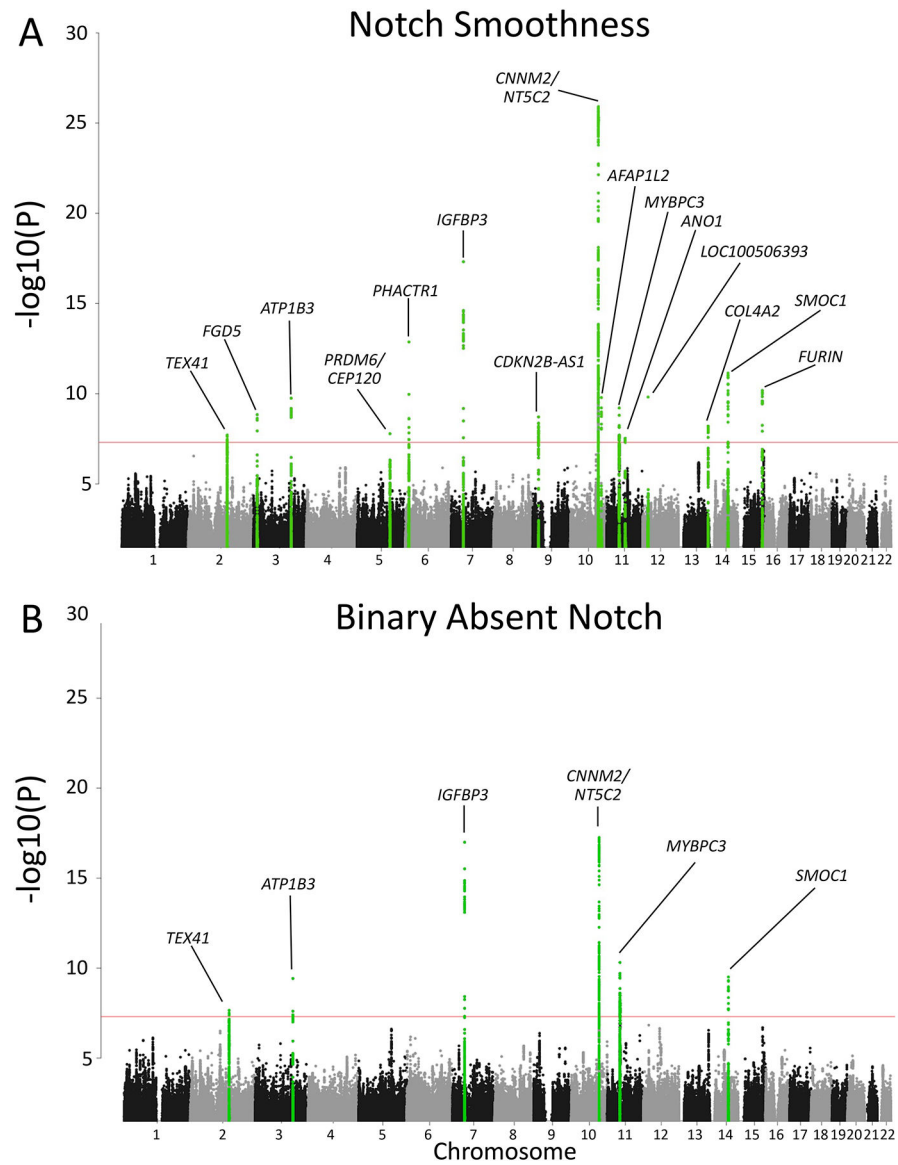ith continuous notch smoothness (Panel A) and 6 loci associated with binary absent notch (Panel B). The significance threshold of a p-value less than 5×10^{-8} is indicated in red.
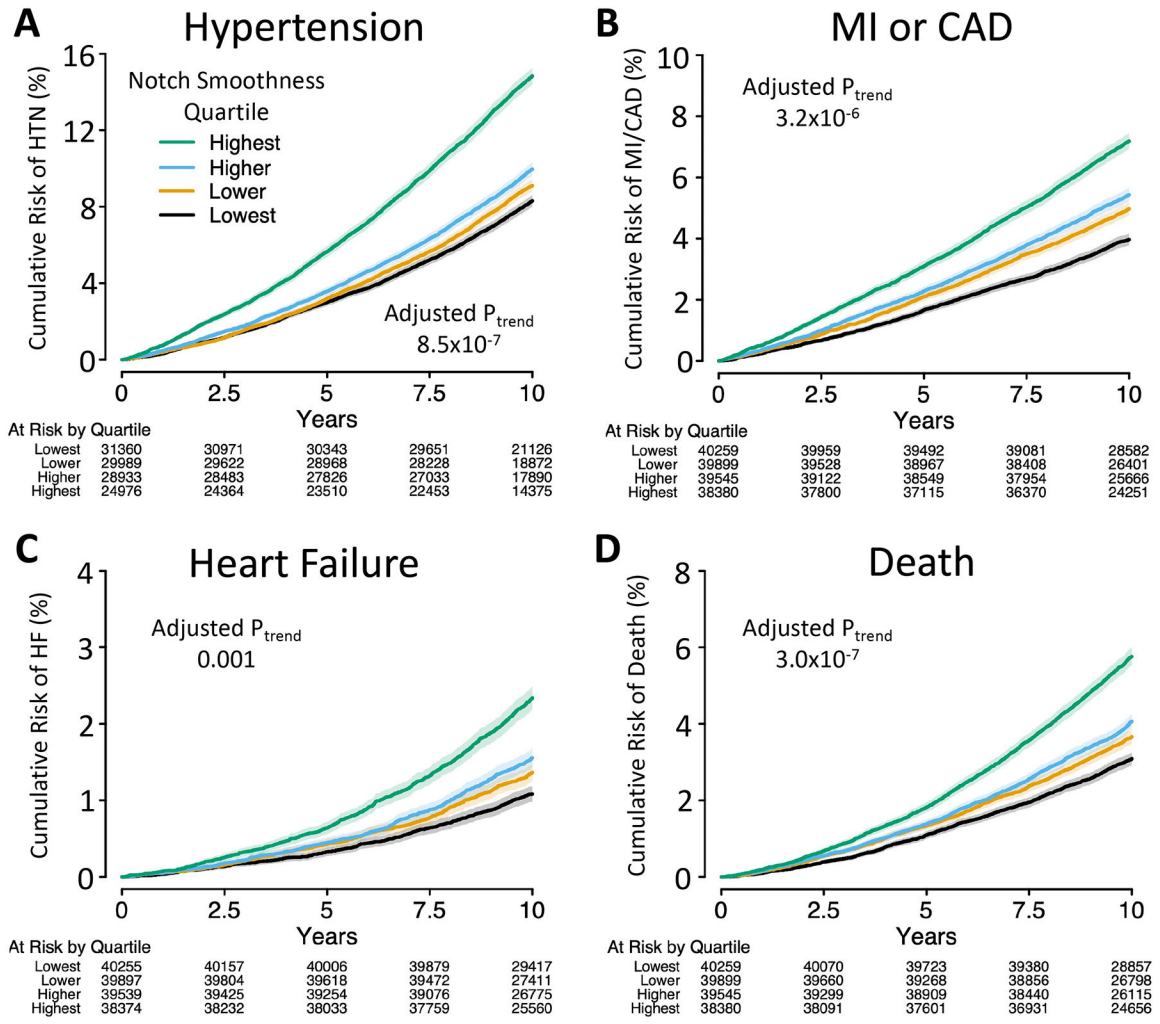
Figure 3:

Cumulative Incidence of Cardiovascular Disease by Notch Smoothness Quartile. Higher notch smoothness quartile was associated with greater risk of incident hypertension, MI/CAD, heart failure, and all-cause death. Adjusted p-value for trend refers to a Cox proportional hazards regression model with notch smoothness quartile as continuous predictor variable, adjusted for age, sex, body mass index, heart rate, systolic and diastolic blood pressure, smoking, diabetes mellitus, and hypercholesterolemia. Participants with prevalent CVD (myocardial infarction or coronary artery disease, heart failure, stroke, aortic stenosis, or atrial fibrillation) at baseline were excluded. Participants with prevalent hypertension were excluded from analysis of incident hypertension only (Panel A).
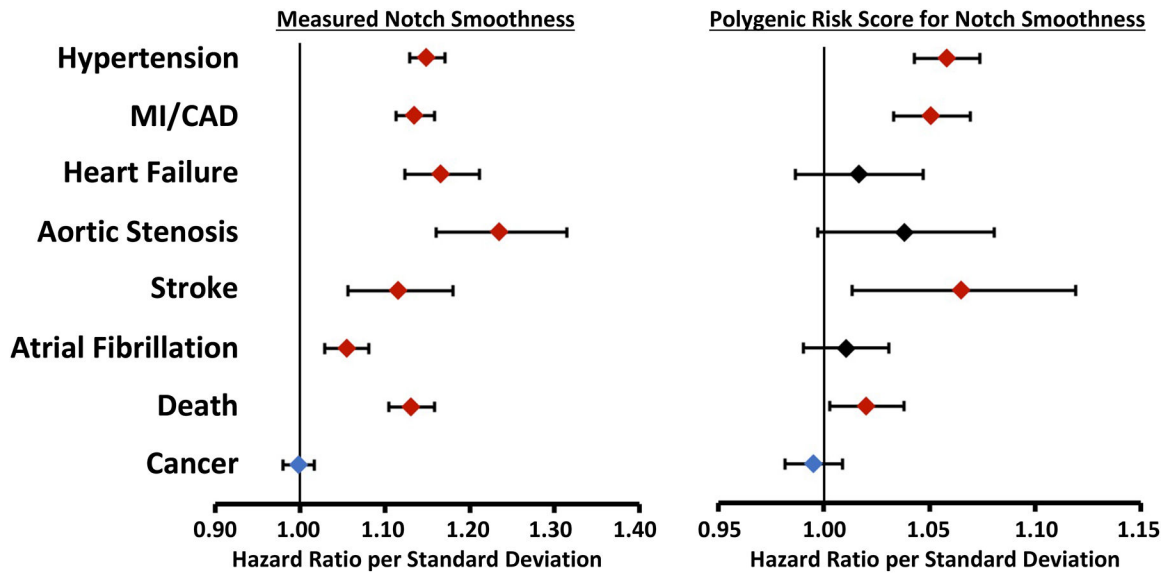
Figure 4:

Prediction of Incident Cardiovascular Disease by Measured Notch Smoothness or Polygenic Risk Score for Notch Smoothness. Measured notch smoothness and polygenic risk score for notch smoothness predict incident cardiovascular disease, but not incident cancer. Left panel: Hazard ratio for incident disease per standard deviation of measured notch smoothness adjusted for age and sex, in participants with available PPG data. Right panel: Hazard ratio for incident disease per standard deviation of notch smoothness polygenic risk score, adjusted for age, sex, genotyping array, and the first 12 principal components of ancestry, in participants without available PPG data. Participants with prevalent CVD (myocardial infarction or coronary artery disease, heart failure, stroke, aortic stenosis, or atrial fibrillation) or the outcome of interest at baseline were excluded.

Table 1:

Baseline Characteristics by Quartile of Notch Smoothness

	Quartile 1	Quartile. 2	Quartile 3	Quartile 4	p-value
n	42447	42447	42447	42446	
Absent notch on PPG waveform	2 (0.0)	4 (0.0)	41 (0.1)	25239 (59.5)	<0.001
Age, years	55.3 (8.3)	55.9 (8.1)	57.1 (8.1)	60.8 (6.8)	<0.001
Male sex	17870 (42.1)	22571 (53.2)	21508 (50.7)	15812 (37.3)	<0.001
Heart rate, beats per minute	67.4 (10.8)	69.3 (10.8)	68.9 (11.3)	69.7 (13.1)	<0.001
Body mass index, kg/m^2	26.8 (4.6)	27.6 (4.8)	27.6 (4.8)	28.0 (5.0)	<0.001
Systolic blood pressure, mm Hg	137.7 (19.5)	138.0 (18.7)	139.91 (19.3)	146.26 (20.4)	<0.001
Diastolic blood pressure, mm Hg	81.7 (10.8)	82.3 (10.6)	82.2 (10.6)	82.8 (10.8)	<0.001
Ever smoking	24166 (57.2)	25055 (59.3)	25273 (59.9)	26186 (62.2)	<0.001
Hypercholesterolemia	5321 (12.5)	6145 (14.5)	6932 (16.3)	9044 (21.3)	<0.001
Diabetes mellitus	937 (2.2)	1117 (2.6)	1333 (3.1)	1806 (4.3)	<0.001
Heart failure	201 (0.5)	232 (0.5)	245 (0.6)	327 (0.8)	<0.001
Myocardial infarction or coronary artery disease	1309 (3.1)	1536 (3.6)	1836 (4.3)	2534 (6.0)	<0.001
Aortic stenosis	49 (0.1)	54 (0.1)	59 (0.1)	118 (0.3)	<0.001
Stroke	471 (1.1)	558 (1.3)	608 (1.4)	909 (2.1)	<0.001
Atrial fibrillation	539 (1.3)	634 (1.5)	726 (1.7)	1056 (2.5)	<0.001
Cancer	3586 (8.4)	3482 (8.2)	3671 (8.6)	4495 (10.6)	<0.001
Position of shoulder, % of R-R cycle	16.8 (5.2)	20.5 (5.0)	22.0 (4.6)	25.3 (3.8)	<0.001
Position of peak, % of R-R cycle	18.8 (6.0)	21.7 (5.0)	22.9 (4.3)	25.8 (3.5)	<0.001
Position of notch, % of R-R cycle	43.5 (6.5)	43.1 (5.8)	43.4 (6.0)	44.2 (7.0)	<0.001
Wave reflection index	61.4 (27.7)	67.7 (24.1)	69.2 (27.0)	72.5 (44.6)	<0.001
Arterial stiffness index, m/s	7.5 (2.6)	9.2 (2.9)	9.7 (4.5)	10.9 (4.9)	<0.001

Values are expressed as mean (standard deviation) for continuous variables and number (percentage of total) for categorical variables.

Table 2:

Variants Associated with Notch Smoothness at Genome-Wide Significance Threshold

rsID	Chr	Position (hg18)	Nearest Gene	Effect Allele	Allele Frequency (%)	Beta (95% CI)	P Value	Binary Notch GWAS Association
Variants Robust to Non-Normality								
rs7652774	3	141579311	ATP1B3	C	38%	0.023 (0.016,0.03)	1.77×10^{-10}	Yes
rs744892	3	14871766	FGD5	A	12%	0.033 (0.022,0.044)	1.45×10^{-09}	No
rs6890990	5	122599707	PRDM6 / CEP120	G	18%	−0.026 (−0.035,−0.017)	1.66×10^{-08}	No
rs9349379	6	12903957	PHACTR1	G	40%	−0.027 (−0.034,−0.02)	1.35×10^{-13}	No
rs11977526	7	46008110	IGFBP3	A	41%	−0.031 (−0.038,−0.024)	4.82×10^{-18}	Yes
rs1537370	9	22084310	CDKN2B-AS1	T	50%	0.021 (0.014,0.028)	1.93×10^{-09}	No
rs1926034	10	104829102	CNNM2 / NT5C2	A	38%	−0.039 (−0.046,−0.032)	1.21×10^{-26}	Yes
rs4751648	10	116132246	AFAP1L2	C	46%	0.023 (0.016,0.03)	1.64×10^{-10}	No
rs10770612	12	20230639	LOC100506393	G	20%	−0.028 (−0.037,−0.02)	1.54×10^{-10}	No
rs227424	14	70456804	SMOC1	A	43%	−0.025 (−0.032,−0.018)	7.18×10^{-12}	Yes
rs6224	15	91423543	FURIN	T	48%	0.023 (0.016,0.03)	6.63×10^{-11}	No
Variants With Suggestive Sub Genome-Wide Significance after Inverse Rank Normalization								
rs763944709	2	145700572	TEX41	C	24%	0.024 (0.015,0.032)	1.94×10^{-08}	Yes
rs2269434	11	47360412	MYBPC3	C	36%	−0.023 (−0.03,−0.016)	6.20×10^{-10}	Yes
rs28691743	11	69797119	ANO1	T	16%	−0.027 (−0.036,−0.017)	2.96×10^{-08}	No
rs9521719	13	111017784	COL4A2	A	41%	−0.021 (−0.028,−0.014)	6.28×10^{-09}	No

Beta coefficient indicates expected increase in standardized continuous trait per allele. Binary notch GWAS association indicates loci which are associated with binary absent notch at genome-wide significance level in the same population. The 11 variants robust to non-normality were defined as those with p-values less than 5×10^{-8} in the sensitivity analysis GWAS in which continuous notch smoothness was inverse rank normalized (Supplemental Table 5) and are shown in the top section of the table. Variants with p-values less than 5×10^{-8} in the primary GWAS but greater than not the inverse rank normalized GWAS are shown at the bottom section of the table.

Abbreviations: Chr, chromosome; CI, confidence interval

Table 3:

Transcriptome Wide Association Study of Notch Smoothness

Tissue	Gene	Standardized Effect Size	Z score	P value	Variants used
Aorta	NT5C2	0.40	9.2	3.7×10^{-20}	12
	PHACTR1	0.16	6.9	5.7×10^{-12}	8
	SMOC1	−0.11	−6.6	5.2×10^{-11}	10
	ATP1B3	0.49	6.4	1.5×10^{-10}	6
	AS3MT	0.03	6.2	5.1×10^{-10}	24
	BORCS7	0.05	6.1	1.1×10^{-09}	24
	ZEB2	0.28	5.7	1.1×10^{-08}	15
	FES	−0.13	−5.3	1.0×10^{-07}	7
	MFSD13A	0.05	5.1	3.3×10^{-07}	33
	MRPS25	0.86	4.9	1.0×10^{-06}	1
	PACSIN3	−0.19	−4.7	3.1×10^{-06}	24
Left Ventricle	IGFBP3	0.31	8.1	6.3×10^{-16}	8
	MFSD13A	0.09	7.2	5.9×10^{-13}	54
	BORCS7	0.08	6.7	1.8×10^{-11}	17

Only associations with p value less than Bonferroni-corrected significance threshold are shown.