Amsterdam UMC Doctoral School - Science & Awards Day - 6 March2026

Amsterdam UMC
Universitair Medische Centra

Contractility measurements combined with single cell perfusion reveal kinetics and variability of Isoprenaline response in mouse cardiomyocytes

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Introduction

To develop new therapies for cardiovascular diseases, contractility measurements in isolated mouse cardiomyocytes (CMs) are often used. Even though this provides valuable insights and allows for screening of compounds, a large degree of variation is observed in contractility and relaxation between individual cells. This requires a large number of cells to be measured for significant results. The reasons for this variability in contractile behavior between cells is not known.

Aim & hypothesis

- Developing a stable and reproducible methodology to measure single cell drug response.
- And gain insights into mechanisms underlying variation in drug response.

Basal differences in molecular signaling pathway determine the response to drugs.

Methods

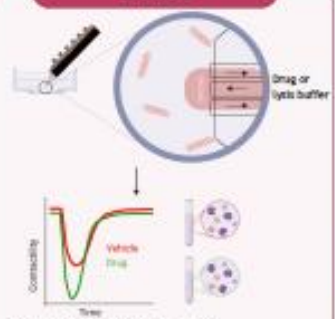

Figure 1: Overview of CADENCE project.

Results

Figure 2: Mass spectrometry analysis of 40 single lysed mouse cardiomyocytes (CMs), pooled to increase protein detectability, revealed two main clusters.
Forty individual mouse CMs were lysed using a urea buffer (8M) containing phosphatase inhibitors and were pooled. Mass spectrometry analysis revealed a total of 1858 proteins, of which the 100 most abundant proteins are plotted. These 100 proteins cluster into two main groups: 1) 60 mitochondrial proteins, 2) 17 Contractile proteins.

- Mitochondrial proteins (Generation of precursor metabolites and energy)
- Contraction proteins (Striated muscle contraction)

Results

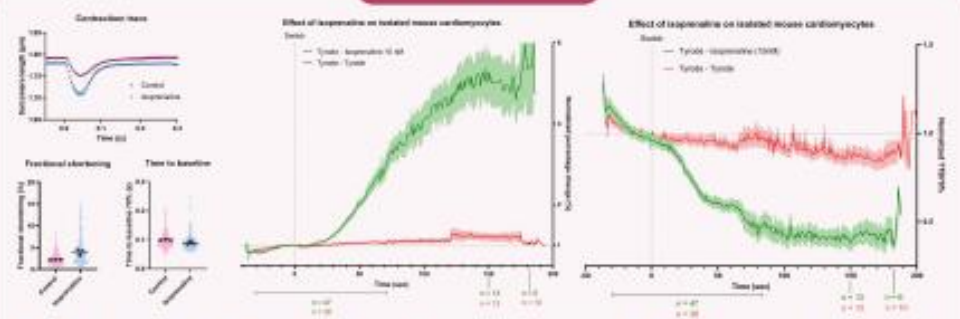

Figure 3: Effect of isoproterenol (Iso) on contractility in isolated adult mouse CMs after applying the drug directly in the dish. Variation was observed both in CT group (n=253, N=3) and in drug response (n=276, N=3) between isolated adult mouse CMs.

Figure 4. Increased contractility and accelerated relaxation in individual adult mouse cardiomyocytes after perfusion with ß-adrenergic agonist isoprenaline. Each transient was normalized by mean of first 5 transients before switching solution. A). Increased percentage change (%) was seen in individual adult mouse cardiomyocytes (n=47 at t=0, N=3) perfused with isoprenaline (15nM) compared to individual adult mouse cardiomyocytes perfused with tyrode (n=38 at t=0, N=3). B) Decreased TTB70% was detected in individual adult mouse cardiomyocytes (n=47 at t=0, N=3) after isoprenaline treatment (15nM) relative to individual adult mouse cardiomyocytes (n=38 at t=0, N=3) perfused with tyrode.

Conclusion and future research

Variation in drug response was still detectable between CMs, but these effects appeared smaller than in traditional measurements where the drug is applied directly to the dish. Therefore, we conclude that kinetics measurements of drug response can be obtained, and this single-cell perfusion method can also be used to lyse cells and perform proteomic analysis in groups of similarly behaving cells. In the future, we will accelerate cardiac drug discovery by reducing compounds usage and providing single-cell drug response insights across different models.

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100-plus Study
Amsterdam UMC

Genetic variants of *HLA* class II genes associated with longevity and Alzheimer's disease: what are their functional effects?

D. Álvarez Sirvent[1], N. Tesi[1,2], M. Hulsman[1], A.N. Salazar[1], N.M. van Schoor[3,4], M. Huisman[3,4], Y. Pijnenburg[5], W.M. van der Flier[5,6], E.M.M. Strijbis[7], S. van der Lee[1,6] and H. Holstege[1,2,5,6]

Background: Human Leukocyte Antigens

Key immune proteins are encoded in the *HLA* class II region, where genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) as markers of genetic risk modifiers of longevity and Alzheimer's disease (AD).

Study cohort

- 100-plus Study Amsterdam UMC: Cognitively healthy centenarians, age>100 N=443
- Longitudinal Aging Study Amsterdam: Middle-aged healthy Individuals, age≈62 N=3,219
- Alzheimercentrum Amsterdam UMC: Alzheimer's disease patients, age≈68 N=2,391

Methods

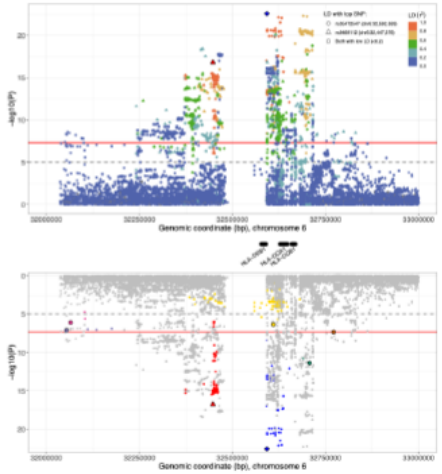
SNP array data, LD structure

HLA class II region

Imputed *HLA* alleles: DRB1, DQA1, DQB1

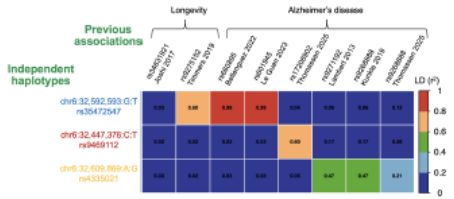
AD-GWAS stats: Bellenguez et al. (*under review*)

AD-GWAS reports two top SNPs, but are there additional signals?

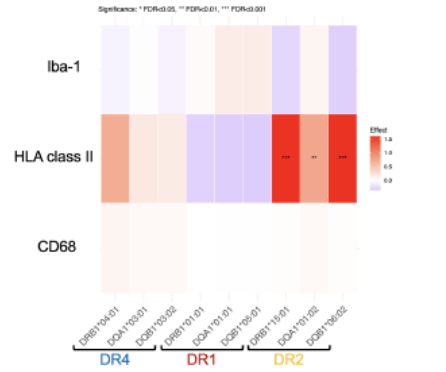


SNP clumping at r^2>0.8 and COJO analysis reveal additional haplotypes, including AD-GWAS top signals (*blue* diamond and *red* triangle haplotypes)

Blue, red and yellow haplotypes partially overlap with AD and longevity, and HLA class II alleles that belong to ancestral major HLA-DR structures



Do these *HLA* class II alleles impact the immunopositivity of microglia markers in brain tissue from 47 CHCs? Iba-1 (pan-microglia), *HLA* class II (antigen presentation) and CD68 (lysosomal phagocytic)



Carriers of alleles in the *yellow* haplotype had increased *HLA* class II activity in the brain, proposing a functional link with AD etiology

Amsterdam Neuroscience
Amsterdam UMC

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D. Álvarez Sirvent

Cell-cell interactions dictate the success of GSK-3/BCL-XL combination therapy in CRC

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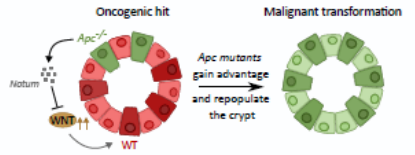
Oncode Institute · Amsterdam UMC · Disease Models & Mechanisms · The Company of Biologists

Abstract

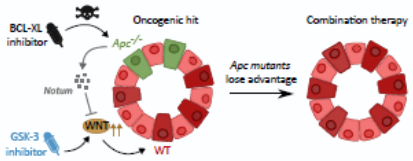
Apc mutations confer a competitive advantage over wild-type cells in a WNT-dependent manner. Combining GSK-3 and BCL-XL inhibitors boosts wild-type fitness while targeting *Apc*-mutants. In monocultures, *Apc*-mutants show reduced viability but retain resistant clones, whereas in co-cultures, wild-type cells outcompete mutants. *In vivo*, the combination reduces lesion burden, highlighting that therapeutic efficacy arises from wild-type/mutant interactions that co-culture models capture and monocultures can underestimate.

Introduction

Apc mutations in intestinal stem cells (ISCs) are often the initiating event in the development of CRC. Cancer stem cells (CSCs) that arise from these mutations rely heavily on the anti-apoptotic protein BCL-XL for survival after transformation. *Apc*-mutant cells also gain a competitive advantage by secreting WNT inhibitors, such as *Notum*, which suppress proliferation in neighboring wild-type ISCs.



Targeting BCL-XL with BH3 mimetics kills CRC cells but is limited by platelet toxicity. Adding GSK-3 inhibitors boosts wild-type intestinal stem cell fitness, countering the competitive advantage of *Apc*-mutant cancer stem cells and protecting normal tissue.



Aim: Test how GSK-3 and BCL-XL inhibitor combination affects early-stage CRC and how wild-type/*Apc*-mutant cell interactions influence therapy response.

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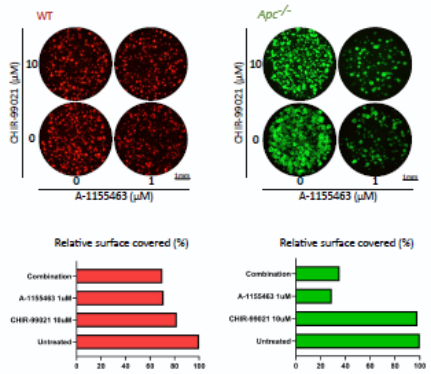
Scan this

Effect in monoculture

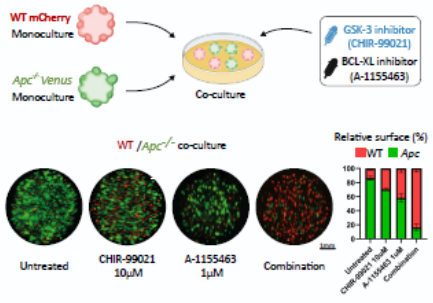
WT and *Apc*-mutant organoids were tested in mono cultures to assess their individual responses to the combination treatment.

WT organoids remained largely unaffected by the treatment, while *Apc*-mutant organoids showed reduced viability, with a subset of resistant clones persisting.



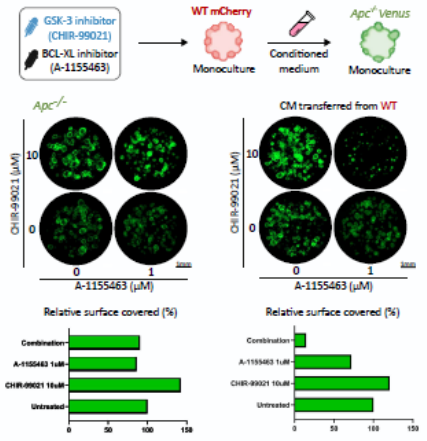
Effect in co-culture

In co-cultures of WT and *Apc*-mutant organoids, treatment with the combination eliminated the competitive advantage of *Apc*-mutants, allowing WT cells to dominate the culture.



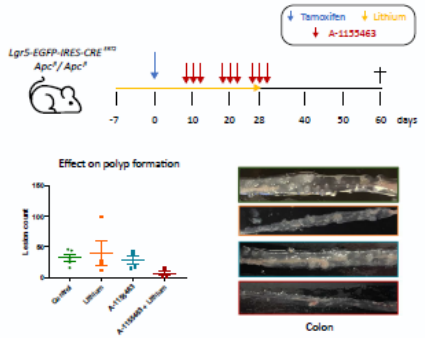
WT conditioned medium

Conditioned medium from WT organoids treated with the combination was transferred to *Apc*-mutant organoids, almost completely eliminating them.



Co-cultures recapitulate *in vivo* effect

In vivo, mice treated with the combination therapy (using Lithium as GSK-3 inhibitor) showed fewer lesions and reduced polyp formation, mirroring co-culture results and highlighting their translational value.



Conclusion

The GSK-3/BCL-XL combination's efficacy depends on wild-type/*Apc*-mutant interactions, including WT-derived secreted factors that help therapy eliminate mutants. This effect is missed in monocultures, making co-cultures a more accurate *in vivo*-predictive model.

L. Atencia Taboada

Amsterdam UMC

Amsterdam Cardiovascular Sciences

Prevalence and Early Outcomes of Pulmonary Hypertension in Thoracic Aortic Surgery: A retrospective Analysis using Dutch National Registry Data

Y. Aouragh BSc [1,2], R.T. Thijsse BSc [1], H. Heinsius, MD, PhD [2], S. Eisel, MD, PhD [2], M. Groenink, MD, PhD [2], A.R.H. Groenwold, MD, PhD [3,4], A.M. Beulens [5], A.M. Klasis MD, PhD [5], Saba Wunderink R.O., N. Grewal, MD, PhD [6,7] on behalf of the Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration

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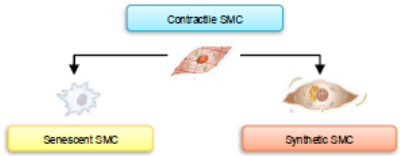
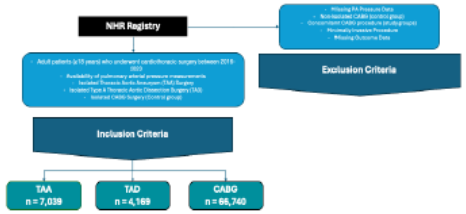
Background



- Thoracic aortopathy and PH are progressive vascular diseases with shared remodeling features
- Both conditions show VSMC phenotypic switching, ECM accumulation, and inflammation
- Pulmonary artery and ascending aorta share a neural crest origin --> possible developmental link
- PH is defined as mPAP ≥20 mmHg (WHO Groups 1-5)
- In aortic disease, it is unclear whether PH reflects Group 1, Group 2, or a mixed mechanism
- PH worsens postoperative outcomes in cardiac surgery, but its role in thoracic aortic aneurysm/dissection is unknown

Methods

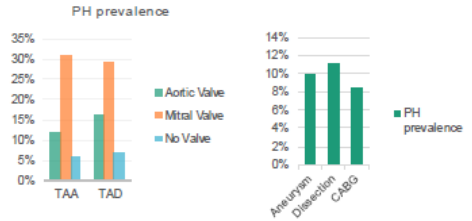


Conclusion

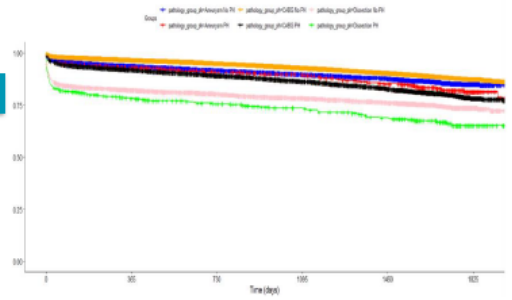
- PH is common in patients undergoing surgery for TAAD
- PH also occurs without valvular involvement
- PH without valvular disease may reflect broader vascular vulnerability
- PH is associated with worse postoperative outcomes.
- Preoperative PH assessment may improve risk stratification and perioperative management.

Results

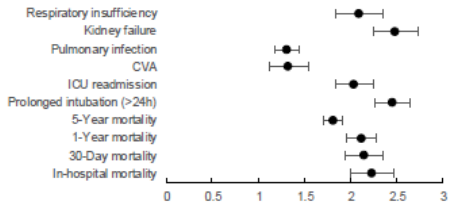
Pulmonary Hypertension Prevalence



5-Year Survival Curve



Forest Plot Pulmonary Hypertension in TAAD (OR)



University of Amsterdam

VU University Amsterdam

Y. Aouragh

University of Amsterdam | Amsterdam UMC | Amsterdam Public Health Quality of Care

Enhancing Quality of Care Assessments: Managing Atypical Patients in ICU Benchmarking in The Netherlands

Mohammad Azizmalayeri, Sylvia Brinkman, Nicolette de Keizer, Fabian Termorshuizen, Dave A. Dongelmans, Ameen Abu-Hanna, Giovanni Cina

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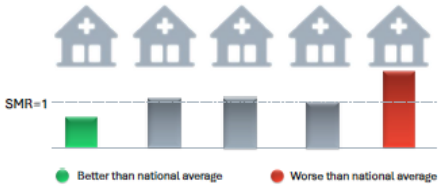
Published in ***Critical Care Medicine***, November 2025.

Benchmarking ICU Performance

ICU performance is evaluated based on standardized mortality ratio (SMR), calculated as **observed** versus **predicted** number of deaths.



The Challenge

Hey! Maybe our ICU looks worse simply because our patients are different.

If we admit more **atypical** patients, can we actually **trust** the **predictions** for our population?

Seen or Unseen? The Challenge of Atypical Patients

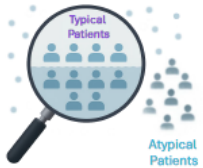
Clinical models are developed for already seen patients.

Real-world data includes unseen (atypical) patients.

Atypical patients, those whose characteristics deviate from the typical ICU population, can occur in every **ICU dataset** and consistently affect **prediction accuracy** and **fairness**.

Typical ICU Patients
- Accurate predictions
- Stable SMR

Atypical ICU Patients
- Unreliable predictions
- Distorted SMR



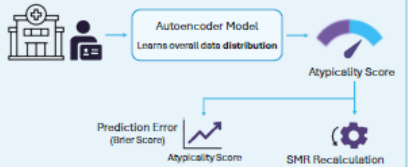
Quantifying Atypicality and Its Effects in Dutch ICU Benchmarking

National Intensive Care Evaluation (NICE) Data for ICU Benchmarking

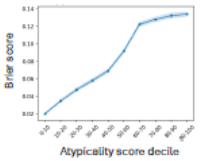
- 2018–2023
- 344,452 **patients** across **75 ICUs**
- **SMR** used as ICU performance measure
- **APACHE-IV** model for mortality prediction

Are APACHE-IV predictions robust to atypical patients?

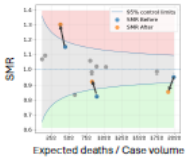
Framework to assess robustness



Prediction Error vs. Atypicality Score Across All Patients



Changes in SMR Before and After Exclusion of Atypical Patients



- Prediction **error** and **mortality** rate **increased** with higher **atypicality scores**.
- **Excluding** the top atypical patients from analysis **altered conclusions for 13 ICUs** over the full study period.
- ICUs with many atypical patients are often academic or cardiac centers.

Full Article | Editorial Commentary on This Study | Letter and Response Discussing This Study

Mohammad Azizmalayeri

NIVEL

Category: Quality of Care - Safety

Amsterdam UMC · VU · Amsterdam Public Health

Exploring the Hazards of Medical Devices: A Qualitative Study in Hospital Care and Hospital-Care-at-Home

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1 Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands; 2 Amsterdam UMC, Department of Public and Occupational Health, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

Background

Medical devices, such as implants, surgical instruments and endoscopes, are essential for patient care. These devices pose risks to patient safety and may contribute to (preventable) adverse events, including infections, internal bleedings and intestinal perforations.

Aim

Exploring medical device-related hazards in hospital care and hospital-care-at-home from the perspective of hospital-based experts on medical devices.

Methods

11 semi-structured interviews with 14 hospital-based experts on medical devices:

- Medical physicists and managers of department medical technology

Interview guide including:

- Policies for safe application of devices
- (Potential) patient safety issues related to devices
- Hospitals and hospital-care-at-home

Thematic and inductive analysis was conducted.

Results

Hospital Care

Medical device shortages have led to increased use of (expensive) alternatives, causing device unfamiliarity

Medical staff developments increase device unfamiliarity and skill gaps (with little time for training)

Complex device networks impact **interoperability and integration** of medical devices

Due to the high number of alarms from **surveillance systems** critical alarms can be missed, settings may be the solution

Sharing patient safety information, including (intrinsic) risks, can be used for trend analysis and risk-based action

Artificial intelligence can improve care, but safe development, implementation and application are essential

Hospital-Care-at-Home

Devices used in **alternative (non-clinical) context** can bring unforeseen risks and alter (user) responsibilities

Ensuring the **competence of non-professional users** is challenging; various training methods are used

Transferring **data** from homes to hospitals poses technical, privacy, and data quality challenges

Conclusions

This study enhances understanding of hazards associated with medical devices in hospitals and hospital-care-at-home. The identified hazards inform policy development, user competence and data sharing, and guide research into hazards and preventive interventions.

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Funding / Conflict of interest: Funded, as part of the Monitor on Adverse Events in Dutch hospitals was provided by the Dutch Ministry of Health, Welfare and Sport

LinkedIn of Monitor Patient Safety – collaboration Nivel & Amsterdam UMC

K.E. van Beekum

NIVEL

Amsterdam Public Health, Quality of Care
Quality of Care - safety - Auditing

A new tool for measuring Team Resilience in healthcare

The ADAPTER-Health questionnaire

Ilja Brugman, Caroline Schlinkert, Linda van Eikenhorst & Cordula Wagner

The Medical Ethics Review Board of the Amsterdam University Medical Center, location VUmc waived the need for a full ethics review (2023.0829).

Background

We used an existing questionnaire on resilience in high-risk work environments based on theory from the Resilience Analysis Grid (RAG) as a foundation[1].

Aim

We wanted to gain insight in the factors contributing to resilient team performance in Dutch hospitals. Therefore, we validated the newly developed **ADAPTER-Health questionnaire** in the healthcare setting and investigated relevant moderating factors.

Methods

The ADAPTER-Health questionnaire measures team resilience through 7 dimensions: the 4 RAG principles and 3 dimensions on teamwork.

Data were analyzed using confirmatory factor analysis (CFA) and analysis of variance (ANOVA). Several moderators were examined:

- Hospital type
- Medical specialty
- Profession
- Patient interaction
- Work experience

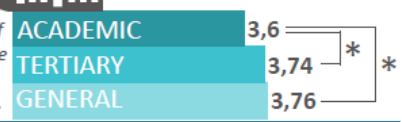
Conclusion

The ADAPTER-Health questionnaire can be used for monitoring and strengthening team resilience. The subscales can be used as starting points for learning about and improving a teams' resilient performance.

Results

The ADAPTER-Health was administered on 42 wards across 15 Dutch hospitals, resulting in 622 responses. The (sub)scores are reported on a scale from 1 to 5.

Comparison of team resilience scores across hospital types.



© 2025 Nivel, PO Box 1568, 3500 BN Utrecht, The Netherlands Contact: Ilja Brugman, i.brugman@nivel.nl

1. van der Beek, D. and J.M. Schraagen, ADAPTER: Analysing and developing adaptability and performance in teams to enhance resilience. Reliability Engineering & System Safety, 2015. 141: p. 33-44. Image spiral, created by zaenulyahya from Noun Project.

Ilja Brugman

Peroxisomes: the forgotten organelle

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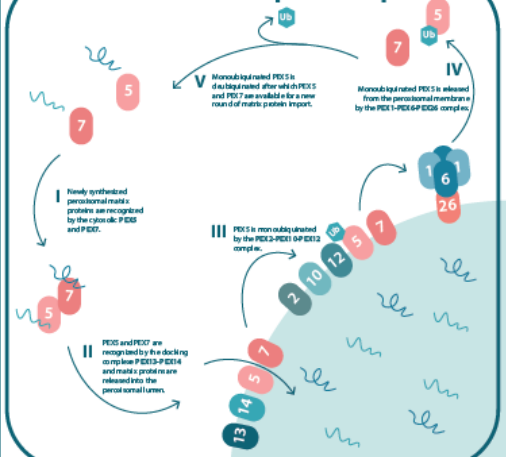
Introduction

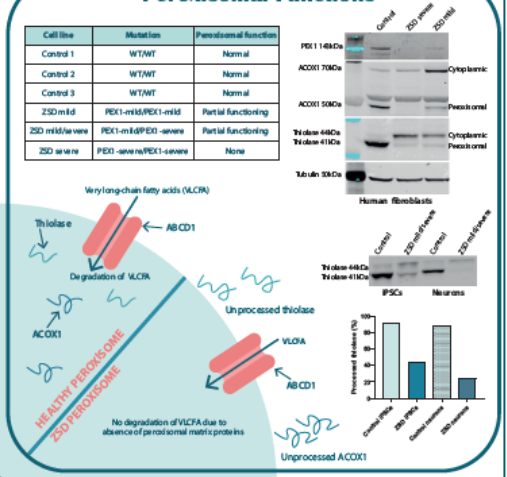
Peroxisomes are essential organelles found in every cell type. They play a key role in lipid metabolism including synthesis of plasmalogens and breakdown of very long-chain fatty acids (VLCFA). Peroxisome biogenesis occurs through the transport/import of peroxisomal membrane and matrix proteins by PEX proteins. Mutations in any of the 13 PEX genes involved in peroxisome biogenesis causes Zellweger Spectrum Disorder (ZSD), a rare autosomal recessive disorder. Most ZSD mutations impair the import of peroxisomal matrix proteins, leading to dysfunctional peroxisomes, which in turn causes plasmalogen deficiency and accumulation of VLCFA. We generated iPSC-derived NGN2-neurons and astrocytes from ZSD patients and assessed whether these new cellular models recapitulate patient phenotypes such as altered thiolase processing and mislocalization of the peroxisomal matrix protein catalase. Since there is an important crosstalk between mitochondria and peroxisomes, we also investigated whether ZSD astrocytes show a mitochondrial phenotype.

Peroxisomal matrix protein import



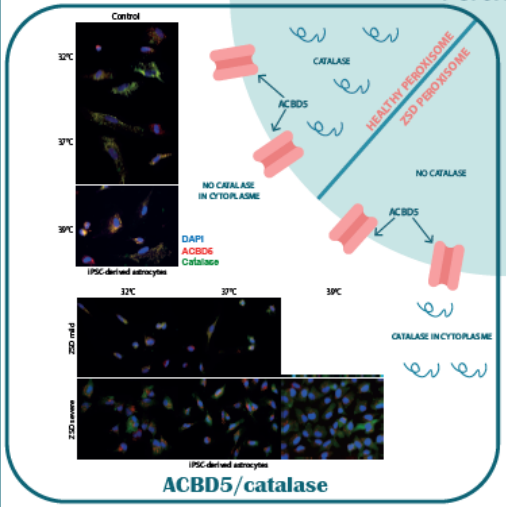
Peroxisomal Functions

Cell line	Mutation	Peroxisomal function
Control 1	WT/WT	Normal
Control 2	WT/WT	Normal
Control 3	WT/WT	Normal
ZSD mild	PEX1-mild/PEX1-mild	Partial functioning
ZSD mild/severe	PEX1-mild/PEX1 -severe	Partial functioning
ZSD severe	PEX1 -severe/PEX1-severe	None

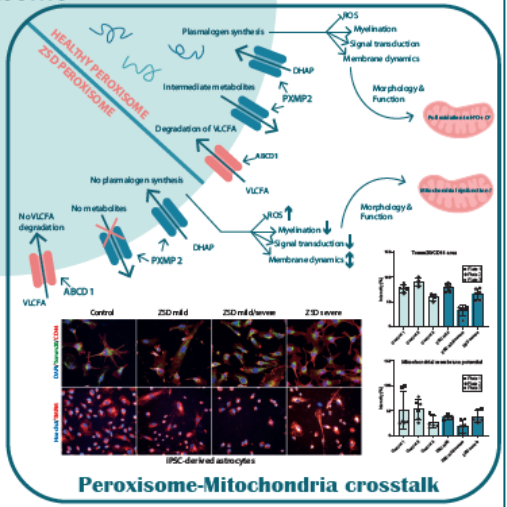


Peroxisome

ACBD5/catalase



Peroxisome-Mitochondria crosstalk



Conclusions

iPSC-derived NGN2-neurons from ZSD patients show altered thiolase processing. At 37°C, iPSC-derived astrocytes from mild ZSD patients show a mosaic pattern with cells displaying peroxisomal catalase next to cells with cytoplasmic catalase. At 32°C, all astrocytes show normal peroxisomal catalase, while at 39°C, all astrocytes show abnormal cytoplasmic catalase. Under the different temperatures, control astrocytes always show peroxisomal catalase and astrocytes from severe ZSD patients always show cytoplasmic catalase. These findings confirm the relevance of these new cellular models for studying ZSD. Although there is crosstalk between peroxisomes and mitochondria, we did not observe any differences in mitochondrial number or mitochondrial membrane potential between control and ZSD astrocytes. In order to determine whether mitochondria are affected in ZSD, further experiments need to be performed.

Amsterdam Neuroscience · VU · Amsterdam UMC Universitair Medische Centra · SIMPATHIC · HORIZON 101080249

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Clinical & Epidemiological Surveys

Cardiovascular Disease Risk in Adult Patients with Hematological Malignancies: A Population-Based Cohort Study Using Linked Databases

Jesse Geels MD, Anna van Rhenen PhD, Clara Gomes MD, Avinash G. Dinmohamed PhD, Prof Folkert W. Asselbergs MD, Marijke Linschoten MD

Background

Survival rates for hematological malignancies have substantially improved over recent decades, prompting growing attention to **treatment-related side effects** and **long-term health complications**, including **cardiovascular disease** (CVD). These complications may limit treatment tolerability and contribute to increased morbidity and mortality. However, the **short- and long-term incidence of CVD** across different **hematological malignancies** remains unclear.

Methods

For this **population-based cohort study**, all adult patients (≥18 years) registered in **the Netherlands Cancer Registry** from **1995** to **2023** with a diagnosis of one of the **12 most common hematological malignancies** were matched to **general population controls**. Data was subsequently linked to **national hospitalization and cause of death registries** to ascertain **11 cardiovascular outcomes**. Poisson regression and Fine & Gray competing risks models were used to evaluate **absolute and relative CVD risk** for each hematological malignancy subtype.

Conclusion

Patients and survivors of hematological malignancies face **substantially elevated short- and long-term risk of CVD compared to the general population, varying markedly by malignancy subtype**. Identifying **patient-, disease, and treatment-specific drivers** of this risk is essential to **develop targeted prevention** and **management strategies** and improve outcomes.

Table 1: Baseline characteristics

Variable	Cancer (n=174,984)	Controls (n=855,085)	SMD
Age, years	68 (58-77)	68 (58-76)	<0.01
Sex, female	77,152 (44)	374,464 (44)	0.01
CV risk factors/comorbidities			
Diabetes	15,939 (12)	77,095 (12)	0.01
Dyslipidemia	38,309 (30)	191,864 (30)	<0.01
Heart failure	6,207 (4)	24,615 (3)	0.04
Stroke	5,545 (3)	25,942 (3)	0.01
Coronary artery disease	18,267 (10)	85,022 (10)	0.02
Peripheral artery disease	3,736 (2)	15,084 (2)	0.03
Arrhythmia	15,079 (9)	65,213 (8)	0.04
COPD/asthma	21,316 (17)	95,535 (15)	0.05
Cancer history	22,293 (13)	-	
Prior chemotherapy	2,939 (2)	-	
Prior radiotherapy	7,162 (4)	-	
Current cancer treatment			
Chemotherapy	98,217 (56)	-	
Radiotherapy	18,388 (11)	-	
Stem cell transplantation	10,790 (6)	-	

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Results

Among **174,984** patients with **hematological malignancies** matched to **855,085 controls, heart failure incidence was elevated across all malignancy subtypes**, with the highest excess rates per 1,000 person-years in myelodysplastic syndromes (37-75; 95%CI 35-60-39-90), multiple myeloma (24-68; 95%CI 23-46-25-90), and acute myeloid leukemia (20-67; 95%CI 18-72-22-62). **Venous thromboembolism risk peaked within the first year after diagnosis and remained elevated up to five years across all malignancies** except indolent non-Hodgkin lymphoma. First year hazard ratios (HRs) for deep venous thrombosis ranged from 3-52 (95%CI 2-58-4-80) in chronic lymphocytic leukemia to 34-04 (95%CI 19-83-58-44) in Hodgkin lymphoma.

Figure 1: Absolute heart failure/cardiomyopathy risk

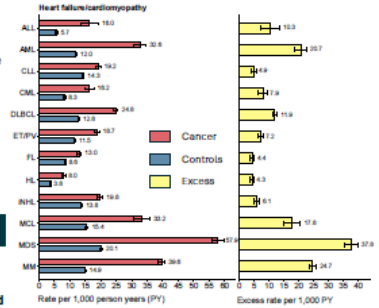
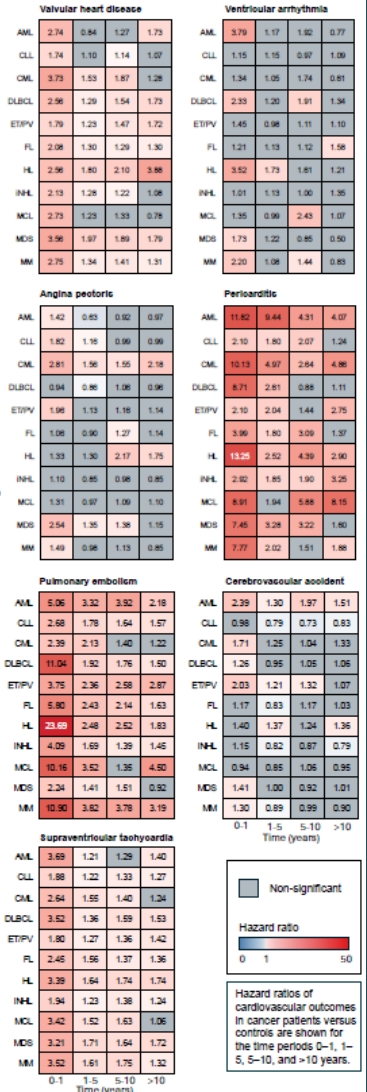


Figure 2: Relative cardiovascular risk over time



Amsterdam UMC

Rigid rocker soles improved both pressure and comfort. Most other components didn't.

Footwear effects on **biomechanical** and user-related outcomes, in individuals with diabetes at moderate-to-high risk of foot ulceration and other populations: a systematic review

MS Isabella Gigante
Dr. Jaap van Netten
Prof. dr. Sicco Bus

Insole

16 studies

Risk of Bias
- 0 High
- 13 Moderate
- 3 Low

Metatarsal Dome
- Decreased pressure at MTH up to 57% if placed 10.6mm prox. to MTH 2 (p<0.0001)
- No user-related data

Material Top Cover
- 6 mm top cover decreases pressure at forefoot up to 8% (p<0.001)
- No effect on comfort and fit (p>0.05)

Material Hardness
- 35 shore custom-made insoles decreased overall plantar pressure with 15% compared to 35 shore prefab. insoles, while harder custom-made decreased it with 10%
- No user-related data

Outsole

9 studies

Risk of Bias
- 0 High
- 6 Moderate
- 3 Low

Rocker Sole
- Decreased forefoot pressure up to 50%, and heel pressure up to 23% (p<0.05)
- Comfort: Rigid rockers increased comfort compared to semi-rigid rockers

Outsole Stiffness

With carbon-fiber reinforced outsole
- Decreased pressure at forefoot and hallux pressure up to 17% (p<0.01)
- No difference in comfort (p=0.87)

Aim & Background

Diabetes impacts 537 million people, with approximately 19 to 34% developing a foot ulcer during their life. Foot ulcers have a high risk of recurrence and subsequent lower limb amputations, creating a global health issue. To prevent foot ulcers, international guidelines recommend therapeutic footwear for people with diabetes at moderate-to-high ulceration risk.

We aimed to systematically review biomechanical and user-related effects of footwear in people with diabetes at moderate-to-high ulceration risk (i.e. target population) and other populations.

Method

We did a systematic literature search in PubMed and EMBASE using search terms related to interventions (footwear) and outcomes (biomechanical and user-related), including only experimental studies in English. Two reviewers screened paper eligibility. Included publications were categorized into subject groups: 5 interventions and 7 outcomes. We conducted a PRISMA-guided systematic review in PubMed and Embase. Included studies were categorized by population, footwear type and components, and outcomes: pressure, shear stress, stability, adherence, usability, and quality of life. Studies involving the target population were classified as 'direct evidence', others as 'indirect evidence.' Risk of bias was assessed using the Critical Appraisal Skills Programme.

Conclusions

This review provides a comprehensive overview of how footwear (components) influences biomechanical and user-related outcomes in populations with and without moderate-to-high ulceration risk. Rocker outsoles effectively reduce forefoot pressure but may compromise stability. Insoles, the most studied component, show positive effects on pressure redistribution and comfort. User-related outcomes, shoe uppers, and shear stress are underexplored despite their clinical relevance. Overall, study quality was moderate. The outcomes of this systematic review guide clinicians and technicians in selecting appropriate footwear (features) for the target population.

DIALECT
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Isabella Gigante

Trends in Mental Health Care Use Among Children and Adolescents: A 9-Year overview of the DREAMS Cohort (N = 90,558)

Haveman, Y.R.A., Van der Mheen, M., Zijlmans, J., Wildschut, M., De Vries, Y.A., Tieskens, J.M. Broek, E.M., Bird, J.K., Visser, I., Klip, H., Van der Doelen, D., Hoekstra, P.J., Nauta-Jansen, L., Staal, W., Vermeiren, R.R.J.M., DREAMS consortium, Lindauer, R.J.L. & Polderman, T.J.C.

INTRODUCTION

- Childhood mental health disorders are increasing, but research on long-term mental health care use is limited.
- Studies suggest that older girls with internalizing problems, a high level of impairment and comorbidity receive the most care [1-4].
- This study examines mental health care use and its relations to diagnosis over a 9-year period in Dutch children

RESULTS

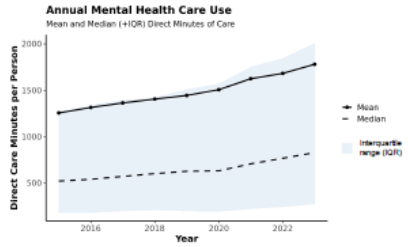

Fig 1: Temporal trends of mean and median minutes of direct care per person per year.

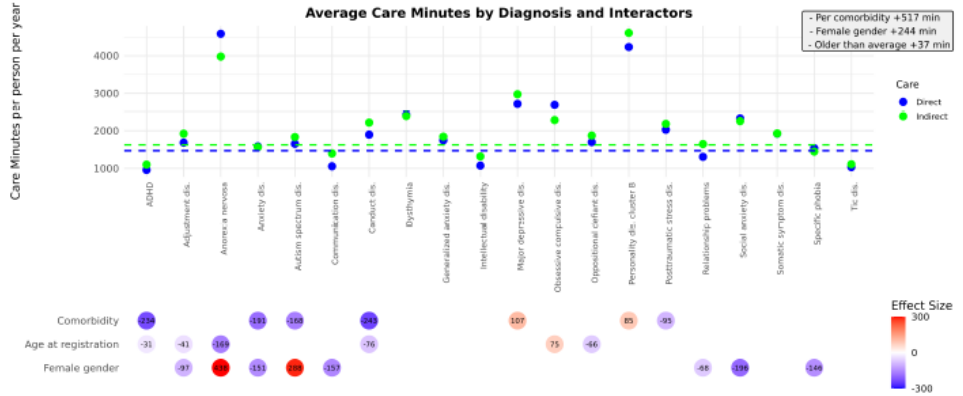

Fig 2: Results of the lasso-regularized GLM predicting annual direct care minutes. Top: average annual care minutes for the 20 most common DSM-5 diagnoses; Grey square: main effects of comorbidity, gender and age on direct care minutes per person per year; Bottom: stable interactions between diagnoses and comorbidity, age or gender on direct care minutes. Circles are color-coded relative to their reference.

CONCLUSION

- Median care use per person per year increases over time
- Girls with comorbid diagnoses are at risk for more care
- The diagnoses anorexia nervosa and personality disorders - cluster B receive most minutes of care, neurodevelopmental disorders relatively few.

METHODS

Sample: Children aged 0.5–18.0 years who received care at a DREAMS center between 2015 and 2023.

Measures:
- DSM-5 diagnoses labeled as primary or comorbid disorder
- Direct care (patient contact)
- Indirect care (administration, family contact, consultation)

Statistical analysis:
Generalized linear model (GLM) with lasso regularization and cross-validation to model direct care use. Stability selection by 100-fold bootstrapping. References are males at mean age (10.7), no comorbidities.

- 90,558 children (mean age = 10.7 years, SD = 4.28; 57% male) received care between 2015-2023.
- The average direct care minutes per child per year increased by 41.8% (Fig 1).
- Anorexia nervosa and cluster B personality disorders receive most minutes of care, followed by MDD and OCD; neurodevelopmental disorders receive less care.
- Higher care use is generally linked to female gender, older age, and comorbidities.

DREAMS CENTERS

DISCUSSION

The increase in annual care use in recent years suggests that children with more complex problems are being treated, underscoring the need to identify children at risk of extended care.

- Only primary diagnoses and comorbidity counts are included, not their specific types or complexity.
- Data from other tiers of mental health care and clinical practice patterns could clarify the rise in care minutes.

Our findings help guide healthcare policy, and optimization of resource allocation for vulnerable youth.

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Conflicts of Interest: No potential conflicts of interest
Funding by: Association of Netherlands Municipalities

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Y.R.A. Haveman

Evaluating the potential of quantitative assessment of intraoperative fasciocutaneous flap perfusion using microscope-integrated indocyanine green fluorescence angiography

Lasse W.P. van 't Hof, David J. Nijssen, Richard M. van den Elzen, Joost R. van der Vorst, Roel Hompes, Mark-Bram Bouman, Mark I. van Berge Henegouwen, Matthijs Botman, Caroline Driessen

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The problem
- Perfusion-related complications remain a major cause of fasciocutaneous flap morbidity
- Current intraoperative assessment using ICG-FA is largely subjective

The limitation
- Interpretation varies between observers
- Subtle perfusion disturbances go unnoticed

The gap
- Can quantitative ICG-FA detect fasciocutaneous flaps compromise intraoperatively?

Methods
- Patients undergoing fasciocutaneous flap reconstruction
- Intraoperative microscope-intregrated ICG-FA
- Postoperative quantitative analysis
- 3 predefined regions of interest (reference, proximal flap tissue, distal flap tissue)
- Fluorescence-time curve analysis
- Compared flaps with vs. without perfusion-related complications

Results
- 7/20 patients developed perfusion-related complications
- Venous congestion most common complication
- FTCs of compromised flaps showed delayed fluorescence peak and plateau phase
- Time-to-peak was significantly prolonged in compromised flaps
- Inflow and outflow slopes were significantly reduced in compromised flaps
- Intraoperative clinical assessment did not identify these compromised flaps

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BAPRAS EURAPS

What the Eye Misses, Quantitative Fluorescence Imaging Reveals: Early Perfusion Failure in Reconstructive Flap Surgery

Take a picture to download the full paper

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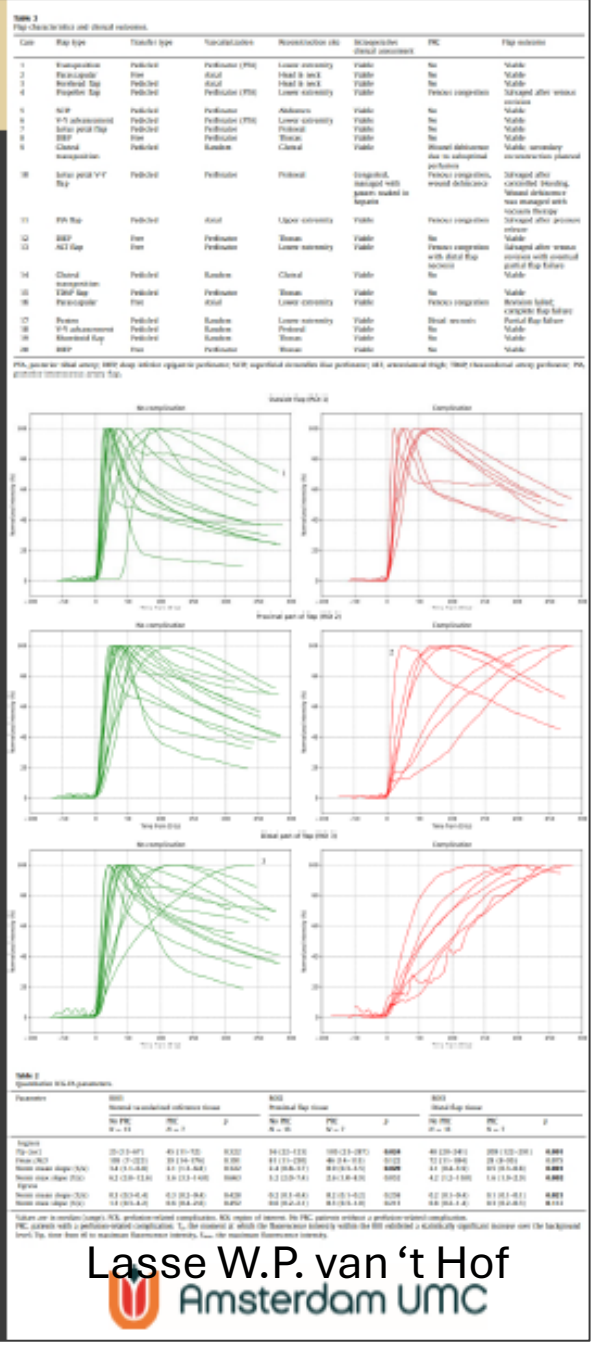

Lasse W.P. van 't Hof

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Amsterdam Cardiovascular Sciences

Integrative Genomics Identifies Putative Causal Genes and Therapeutic Targets in Thoracic Aortic Disease

Julia Horjus[1,2], Sean J. Jurgens[1], Connie R. Bezzina[1], Nimrat Grewal[2]

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[2] Department of Cardiothoracic Surgery, Amsterdam UMC, Amsterdam, The Netherlands

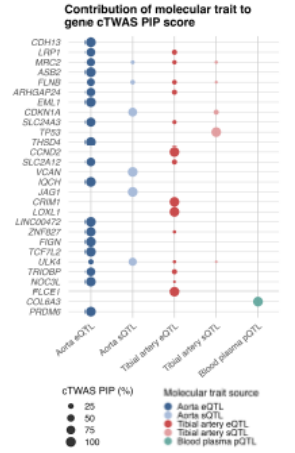
Background

Thoracic aortic dissection (TAD) is a life-threatening condition with high mortality. Current clinical guidelines solely rely on prophylactic surgery once a critical aortic diameter is reached, as thoracic aortic aneurysm (TAA) is a key risk factor for TAD. To improve risk prediction and enable therapeutic development, a deeper understanding of genetic and molecular mechanisms underlying both TAD and TAA (TAA/D) is required.

Aim

To identify putative causal genes for TAA/D through a novel integrative statistical framework that combines multi-tissue molecular traits with the largest TAA/D GWAS meta-analysis to date (14,409 cases and 1,210,227 controls).

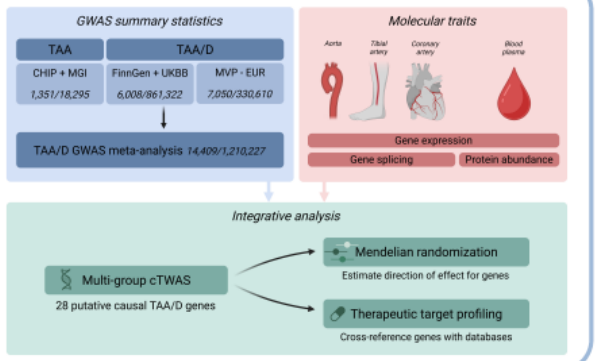
Majority of genes is identified through aortic tissue



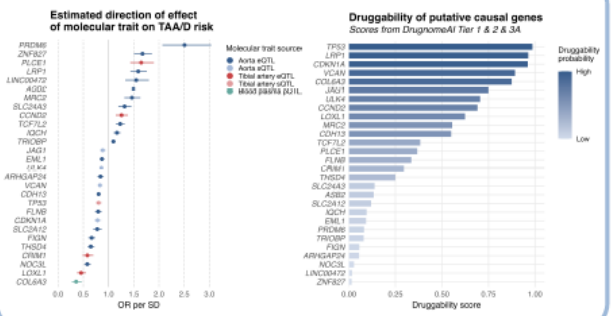
Conclusion

Integration of TAA/D GWAS data and multi-tissue molecular traits identified both established and novel TAA/D candidate genes. These results highlight promising therapeutic targets and provide a framework for future functional studies.

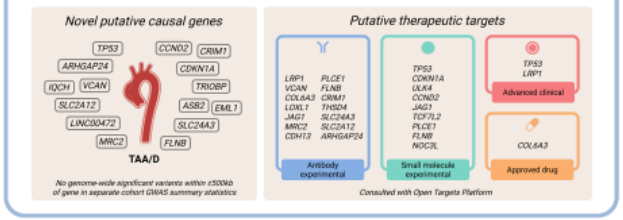
Combining GWAS and molecular trait data for integrative analysis



Direction of effect and druggability of putative causal genes



Identification of novel candidate genes and therapeutic targets



University of Amsterdam
VU Vrije Universiteit Amsterdam
Financed by Hartstichting
Research Institute: Amsterdam Cardiovascular Sciences
Category: Other

Julia Horjus

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Universitair Medische Centra

How clinicians perceive and manage cancer patients' decision-making burden.

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Take home message

Clinicians' responses to perceived decision-making burden in patients were variable. Discussions about how to navigate tensions between autonomy and avoiding harm could foster greater unity among clinicians on addressing patients' burden in SDM.

Background
Clinicians are increasingly expected to involve patients in treatment decision making. Some patients may feel burdened by such involvement. It is unclear how clinicians recognize and respond to patient burden in shared decision making (SDM).

Objective
We aimed to gain more insight into experiences of clinical oncologists regarding patients' burden of involvement in decision making.

Method
Semi-structured interviews (N=20) with clinicians who discussed treatment options with patients diagnosed with early-stage breast or prostate cancer.

Analysis
Thematic analysis (inductive approach).

Main results

How clinicians detect burden

Patients…
… tell directly they find it hard
… ask for advice or *"What would you do doctor?"*
… take a long time before deciding
… look confused or 'go blank'
… exchange doubts or considerations with companions
… ask very few or a lot of questions

How clinicians respond to burden

- Offering more information or more time
- Acknowledging the burden
- Stressing importance of patient preferences

How clinicians respond to 'What would you do, doctor?'

Providing a treatment recommendation ⟷ **Refraining from giving explicit advice**, believing that SDM entails patients should make their own choice.

'In those cases, they [patients] need support. So, I will take the decision - and they are completely at ease with that.'

'Then I say: I <u>am not allowed</u> to make that choice for you'

Discussion

- **Clinicians intuitively assess whether a patient feels burdened.**
- **Clinicians vary in how they balance the two ethical principles 'avoiding harm' and 'respecting patient autonomy' when giving patients decisional responsibility, leading to unwanted practice variation.**

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PARADOX
Reducing the burden of SDM

Topic
Quality of Care

F.L. Huijgens

Amsterdam UMC

Tegaderm Stickover Technique for Nipple Grafting in DIFNG Mastectomy

M.M.F. Jorna, D.A. Young-Afat, T.C. Van de Grift, J.M. Smit, T.S. Schäfer, M.B. Bouman, M.G. Mullender, W.B. Van der Sluis

BACKGROUND

Top-surgery is the most commonly performed GAS in transmasculine and non-binary assigned-female-at-birth (AFAB) persons.
The double insicion with free nipple grafting (DIFNG) technique is the most performed.

Traditional tie-over dressings can be time consuming, uncomfortable, and may leave scars.

AIM

To evaluate the surgical and patient-reported outcomes, and provide a detailed description of the Tegaderm stickover technique for free nipple-areola complex graft (FNACG) fixation in gender-affirming double incision mastectomy.

METHODS

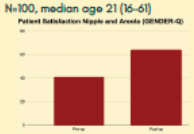
Retrospective cohort, 01/2024 - 01/2025
All patients undergoing DIFNG mastectomy using the Tegaderm stickover technique.

Outcomes:
- Graft survival
  - 6 week postoperative
  - Using photographs
  - Two independent reviewers
- Patient-reported satisfaction
  - Preoperative, and 6 month postoperative
  - GENDER-Q
- Reoperations nipple-areola-complex (NAC)

RESULTS

Graft survival (6 weeks)
N=447, median age 21 (16-61)

Satisfaction nipple and areola complex (6 months)
N=100, median age 21 (16-61)



Complications / Reoperations:
- 7 secondary corrections NAC
- 1 case of NAC infection

DISCUSSION

The Tegaderm stickover technique offers a simple, reproducible and patient-friendly method for FNACG fixation in gender-affirming double incision mastectomy with 1) high graft survival (higher or comparable compared to existing literature), and 2) an increase in satisfaction of the nipple and areola (GENDER-Q).

Our strengths include our large cohort and the use of the GENDER-Q. Our limitations include reliance on six-week photographs only, the absense of a control group, and the limited response rate for the GENDER-Q outcomes.

CONCLUSION

**The suture-free Tegaderm stickover technique is easy, reproducible, and patient-friendly.
It achieves excellent graft survival, high patient satisfaction, low material use, and painless removal.**

Making it a strong alternative to traditional fixation.

SURGICAL TECHNIQUE

FNACGs were fixated using the Tegaderm Stickover Technique, in which compressive dressings are secured solely with a Tegaderm dressing, eliminating the need for traditional non-absorbable sutures or skin staples.

Get in touch:
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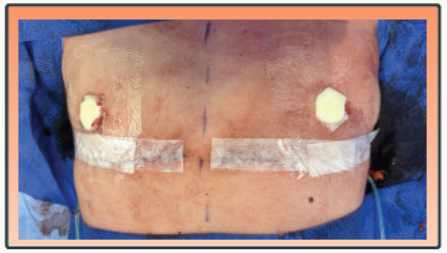

M.M.F. Jorna

A multi-center cohort study: inflammatory markers, smoking and body mass index are associated with electroconvulsive therapy response in depression

Dominika M Karaszewska, Tim J van der Putten, Anja Lok, Dominique S Scheepens, Karel WF Scheepstra, Guido A van Wingen, Jentien M Vermeulen, Rob Kok, Esmée Verwijk, Johanna M. Hegeman, Karen van den Berg, Dore Loef, Mardien L Oudega, Eric van Exel, Frank L Gerritse, Hanneke van Welie, Dieneke Bloemkolk, Sjoerd M. van Belkum, Maurice Vischjager, Bartholomeus CM Haarman, Willemijn Heijnen, Tom Birkenhager, Esther Pluijms, Birit Broekman, Thomas Zoon, Anton Vergouwen, Indira Tendolkar, Jordy Rovers, Metten Somers, Bart PF Rutten, Philip van Eijndhoven, Annemiek Dols, Damiaan Denys, Roel JT Mocking

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Biomarkers: Clinical

Amsterdam Neuroscience

INTRODUCTION

- **Electroconvulsive therapy (ECT)** is an effective treatment for **treatment-resistant depression** with response rates varying between 58% and 70%.
- However, interindividual variability in treatment outcomes remains substantial.
- **Inflammation** has emerged as a potential biological correlate of both depression and ECT efficacy.
- **Smoking and high body mass index** (BMI) contribute to a state of **low-grade systemic inflammation** and have both been associated with depression. However, their relationship to ECT response remains unclear.

AIM

- This study investigates the association between CRP, leukocytes, ESR, smoking status, BMI, and ECT response in patients with unipolar and bipolar depression.

METHODS

- Dutch ECT Consortium (DEC), 11 centers in the Netherlands.
- 1836 patients with depression treated with ECT.
- Linear mixed model analysis: investigating the relationship between change in Hamilton Depression Rating Scale (HAM-D) or Montgomery–Åsberg Depression Rating Scale (MADRS) scores over time, and inflammation/BMI/smoking status.

RESULTS

- Non-smokers and former smokers showed greater reduction in depressive symptoms compared to current smokers (ß=-2.29; 95% CI, -4.13 to .44; F=7.82, p<.001, N=1526).
- Patients with BMI below 25 improved more than those with higher BMI (ß= 0.24; 95% CI, .1 to .37; F=11.6, p<.001, N=1103).
- Higher baseline CRP levels, but not leukocytes and ESR, were associated with higher post-ECT HAM-D scores, but only after adjusting for smoking (F=4.28, p<.05), suggesting a confounding effect.

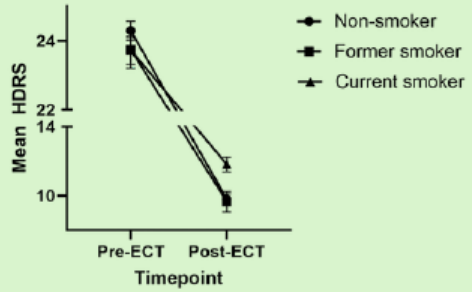

Figure 1. Current smoking was associated with higher HAM-D scores after ECT (ß=-2.29; 95% CI, -4.13 to .44 ; P<.001).

DISCUSSION

- Smoking and obesity, both potentially modifiable risk factors, are associated with reduced efficacy of ECT, possibly through inflammation-related pathways.
- CRP may serve as a clinically relevant biomarker when interpreted alongside smoking status.
- Smoking cessation and weight management could be implemented into pre-ECT care in research settings to improve response rates in the future.

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PI-NL Trial: Metformin for the treatment of early-onset preeclampsia

Maryam Khelil[1], Wessel Ganzevoort[1], Rebecca Painter[2], and *the PI-NL study team*

Clinical Intervention

Background

Preeclampsia (PE) = high blood pressure in pregnancy due to placental dysfunction.

- 1-3% of pregnancies
- ~1% early-onset PE (<32 weeks)
- Often leads to prematurity and fetal growth restriction (FGR)

No treatment except delivery.
Prolongation of pregnancy, when safe, can reduce child complications.

Objective

To assess if metformin could be used to safely prolong pregnancy in early-onset PE.

Methods

8 Perinatal centers with NICU in the Netherlands

180 singleton pregnant individuals with early PE and no imminent delivery

Metformin 3000 mg/day or placebo till delivery

Inclusion: 2025-2028

Outcomes

- Primary: prolongation of pregnancy
- Secondary/exploratory: adverse maternal, fetal, and neonatal outcomes till 90 days after birth

Impact

If effective, metformin would be the first treatment to safely extend pregnancy in early-onset PE.

By extending pregnancy, it may reduce the risk of prematurity-related morbidity, mortality, and costs.

Metformin is a registered treatment for diabetes in pregnancy, which would facilitate implementation.

Questions? Feel free to reach out
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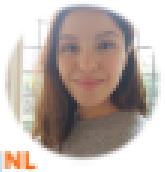

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University Medical Centers

Cancer Center Amsterdam

Establishment and Characterization of Patient-Derived Lung Normal Airway and Non-Small Cell Lung Cancer Organoids for Evaluating Novel Therapies

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Introduction

Non-small-cell lung cancer (NSCLC) remains the most commonly diagnosed cancer and a major cause of cancer-related mortality worldwide. There is an urgent need for more effective therapeutic strategies. To enable studies into the efficacy and toxicity of novel therapies, we established patient-derived NSCLC and Normal airway organoids cultures.

Method

Results

We established Normal airway and NSCLC tumor organoids cultures from eight different lung tumor resections with a success rate ≥85%, NSCLC and Normal airway organoids displayed distinct morphologies (Fig.1). Gene expression analysis confirmed that Normal Airway organoids contained alveolar type 1 and 2 cells, basal epithelial cells, club cells, goblet cells and ciliated cells (Fig.2). NSCLC organoids were characterized on the basis of subtype-specific gene expression (Fig.3). In contrast to lentiviral vectors, adenoviral vectors were highly efficient (>90%) for gene delivery into established NSCLC and Normal airway organoids (Fig.4).

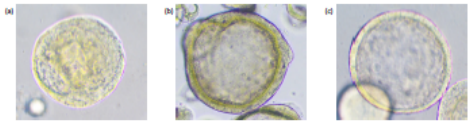

Figure 1. Morphology of NSCLC and Normal airway organoids. (a) Squamous carcinoma organoid, (b) Adenocarcinoma organoid, (c) Normal airway organoid.

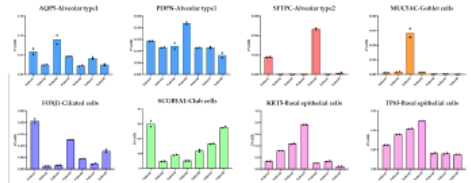

Figure 2. RT-qPCR detection in Normal airway organoids to evaluate the gene expression of human lung epithelial cell markers.

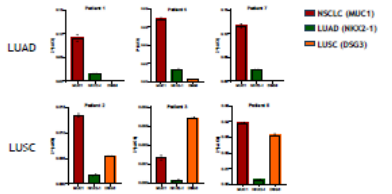

Figure 3. RT-qPCR detection of cancer-related gene expression in patient-derived tumor organoids to characterize the subtype of non-small cell lung cancer (NSCLC).

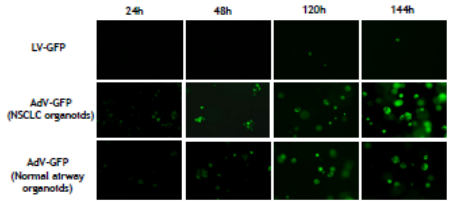

Figure 4. Comparison of transduction efficiency between lentiviral vector-GFP and adenoviral vector-GFP in established NSCLC organoids and Normal airway organoids.

Conclusion

Establishment, long-term culture and biobanking of NSCLC and Normal airway organoids are effective. Normal airway organoids present all cellular components of human lung epithelium. Adenoviral vectors are highly efficient for gene delivery to organoids.

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ZonMw

Development of a Core PRO(M) set in Pediatric Physiotherapy

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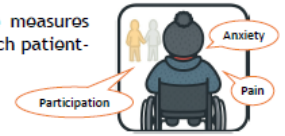
Find this poster online

Background

Physical impairments affect children's wellbeing. Patient-reported outcome measures (PROMs) reveal patient perspectives on their health. Consensus is lacking on which patient-reported outcomes (PROs) and PROMs best suit pediatric physiotherapy (PPT).

This study aims to develop a core PRO(M) set for PPT.



Methods

This multimethod study consists of five steps:

1. Relevant PROs were identified with a scoping review and qualitative study
   Focus groups with:
   - Adolescents (12-18y, n=17)
   - Parents (4-18y, n=16)
   - Pediatric physiotherapists (n=10)
2. PROs were operationalized with an expert panel of researchers in PPT and PRO(M)s
3. PROs were prioritized
   - Online survey
   - 96 pediatric physiotherapists
4. An expert panel incorporated PROs into a national model for generic PROs →
5. Valid, reliable and practical PROMs were selected by an expert panel

Results

Core PRO set		Core PROM set
Participation	Participation	No PROM found
	Social functioning	PROMIS Pediatric Peer Relations*
Physical functioning/ activity		PROMIS Pediatric Mobility* and/or PROMIS Pediatric Upper Extremity*
Fatigue	Intensity	NRS Fatigue
	Interference	PROMIS Pediatric Fatigue^
Pain	Intensity	NRS Pain
	Interference	PROMIS Pediatric Pain Interference^
Quality of life		NRS Quality of life
Perceived health		NRS Perceived health

* Computer adaptive tests recommended
^ Shortform 4 items recommended

Optional PROs
- Mental functioning
  - Anxiety
  - Depression
  - Anger
- Sleep
- Cognitive functioning

Completion time core PROM set 10 MIN

Discussion

- Core PRO(M) set for: **daily practice** (www.klik-fysio.nl), **research**, **quality assessments**
- The core PRO(M) set can aid in **early identification of health-related problems**, **facilitate communication**, and **ensure comparability** of outcomes.

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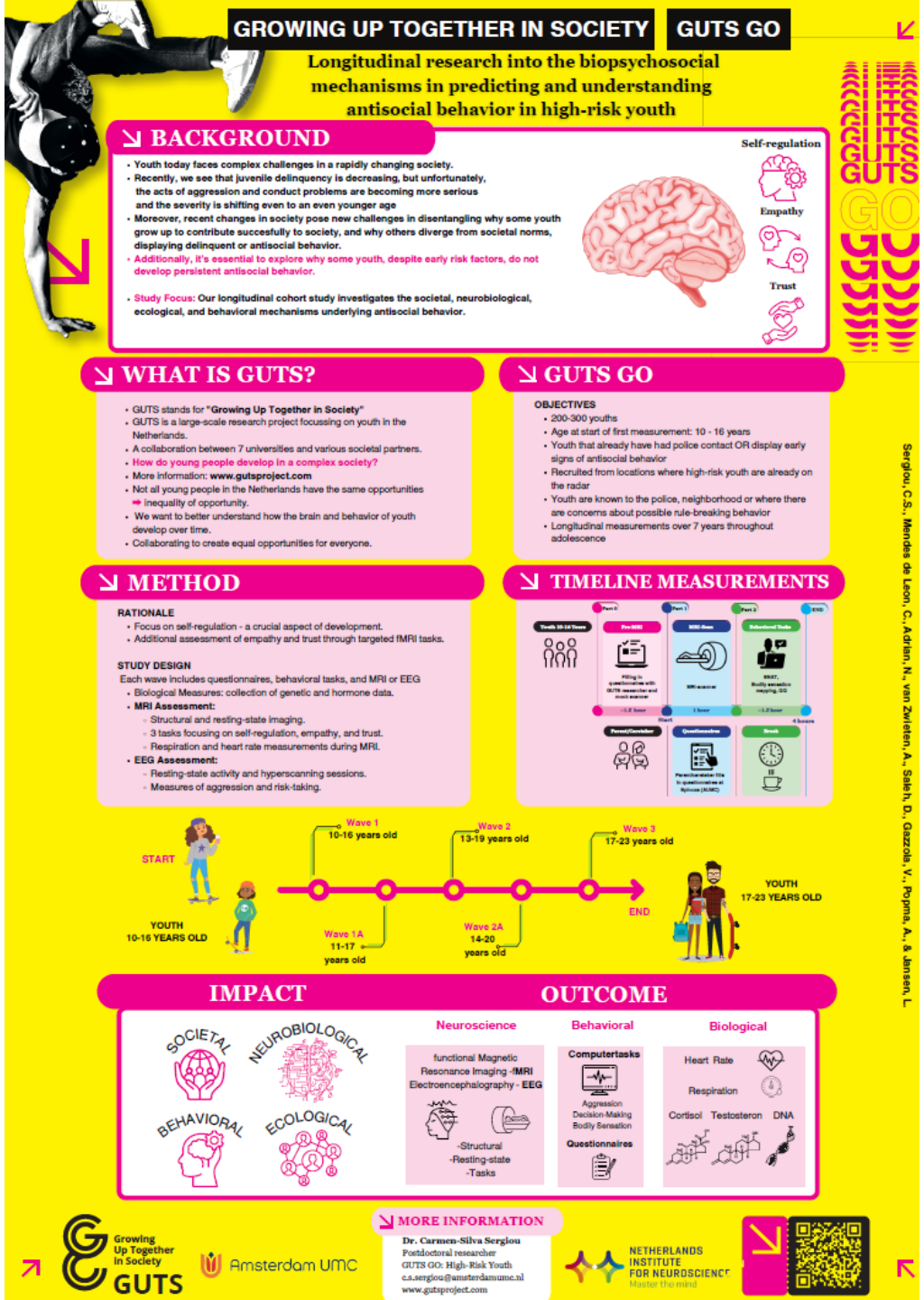
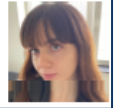


C.S. Mendes de Leon

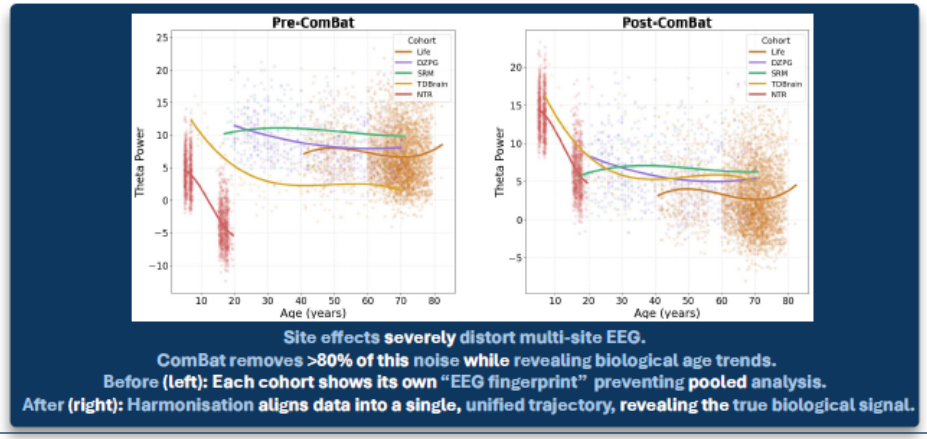
Amsterdam Neuroscience

Compulsivity, Impulsivity & Attention (CIA)
Biomarkers: Experimental and Methods



Site Noise Out, Brain Signal In: ComBat Harmonisation for Multi-Site EEG

Danae Mitsea[1], Philippe Jawinski[2], Dirk Smit[1] — [1]Amsterdam UMC, Dept. Psychiatry, NL; [2]HU Berlin, Dept. Psychology, DE



Site effects severely distort multi-site EEG.
ComBat removes >80% of this noise while revealing biological age trends.
Before (left): Each cohort shows its own "EEG fingerprint" preventing pooled analysis.
After (right): Harmonisation aligns data into a single, unified trajectory, revealing the true biological signal.

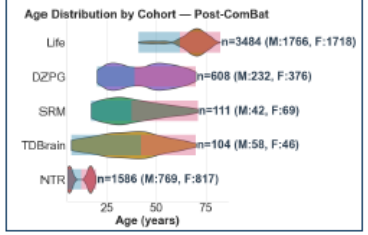
Introduction

- **Mental health is in crisis (WHO, 2025)** with neuropsychiatric disorders on the rise. Detection of early biomarkers and benchmarking normative development is crucial.
- **EEG should be our scalable solution**—fast, cheap, portable, and tied to brain function.
- But **multi-site EEG** remains a **challenge.** Different machines, labs, and montages warp the signal, **hiding meaningful neurodevelopmental patterns**. Without harmonisation, **normative EEG is impossible**.
- **ComBat might fix this** (successful in genomics/MRI) but **has not been systematically tested for EEG**.

We ask: **Can ComBat remove site distortion while keeping real age effects in attempt to model normative development?**

Methods

1. **Data**
   5 cohorts, N ≈ **5,000 healthy participants**, ages 5–82.
2. **Preprocessing**
   Automated pipeline (EEGLAB-based):
   - Channel cleaning, re-referencing to average reference, ICA artefact removal.
   - Standardised power-spectral extraction (**alpha & theta power** per channel).
3. **Harmonisation**
   ComBat model: **Power ~ Age + Sex + Site**
4. **Validation**
   - Site-explained variance (R^2),
   - PCA clustering,
   - Random forest site prediction,
   - Cohort-specific lifespan curves (cubic models).

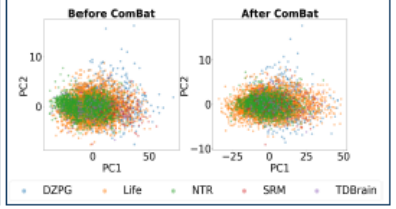


Results

1. Site noise sharply reduced
- Site-explained R^2 drops (α: 0.35→0.13; θ: 0.40→0.29).
- Mean power ranges compress across sites.
- PCA clusters dissolve (shown below after covariate adjustment).
- RF site classification decreases toward chance (e.g., 0.45→0.31 α; 0.49→0.39 θ).

2. Biological signals preserved or strengthened
- Age–alpha correlation stable (|r| ≈ 0.40). Age–theta correlation increases (|r|= 0.43→0.58).
- Age regression coefficients preserved (r = 0.99 α; r = 0.95 θ).

3. Lifespan curves align across cohorts
- Alpha: declines with age.
- Theta: early-life decline, mid-life fluctuations and late-life increase.



Conclusions

- ComBat removes site-driven artefacts in multi-site EEG while **revealing neurobiological age trends**.
- Reported trends for α and θ were in accordance with existing studies → biology maintained.
- **Cross-study comparability** for translational neuroscience can be **achieved**.

Next Steps

- Expand database: 5k → 30k participants.
- **Launch clinical platform**: EEG upload + normative comparison.
- Enable personalised medicine: **harmonised EEG biomarkers for clinical translation.**

Scan here for **more info!**

Danae Mitsea

Parental Mental Health Following Very Preterm Birth up to Term Age: Contributing Factors

Clinical & Epidemiological Surveys

HIPPO

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Background

Preterm infants admitted to the Neonatal Intensive Care Unit (NICU) are exposed to stressful procedures and events, not only stressing the infant but also affecting parental mental health. Understanding key contributors to maternal and paternal mental health at various stages is crucial for targeted early interventions and optimal child development. This study aims to examine the contributing factors of parental mental health after very preterm birth up to term age.

Methods

Mothers and fathers of preterm infants completed self-report questionnaires assessing posttraumatic stress (PCL-5) and depressive symptoms (PROMIS Depression) 1-2 weeks after birth, 1 month after birth, and around term equivalent age using the KLIK PROM Portal.

Additional questionnaires (including the LEC-5 and PSS:NICU) captured prenatal psychosocial history, birth-related and family factors, postnatal stressors, and protective factors.

Conclusions

The findings highlight the impact of preterm birth and NICU admission on parental mental health. As expected, there were indeed different contributors to the mental health of fathers and mothers. More neonatal stress exposure, having fewer children, and perceived social support were additional factors for fathers only.
However, there was also considerable overlap. For both parents, prenatal psychosocial history and stress related to the NICU environment were significant contributors to parental mental health.
Further research should focus on prevention and early intervention, and explore long-term effects to better support families.

The Happiness for Improvement of Premature and Parental Outcome (HIPPO) study is a national multicenter prospective cohort study that examines the amount and impact of neonatal and parental stress during NICU admission in preterm infants. 446 preterm infants born <29 weeks from the 10 NICUs located in The Netherlands were included.

Results

Table 1. Results on Posttraumatic Stress and Depressive Symptoms for Mothers and Fathers

	Posttraumatic stress symptoms				Depressive symptoms			
	Mothers		Fathers		Mothers		Fathers	
	b	p-value	b	p-value	b	p-value	b	p-value
Past life events	0.54	.019*	0.37	.049*	0.23	.038*	0.13	.284
Received prior support	3.66	.006**	4.06	.005**	1.10	.087	0.70	.443
Stress during pregnancy	0.30	.003**	0.30	.001**	0.14	.002**	0.15	.010*
Birth weight	0.0015	.633	-0.0029	.338	0.0019	.211	0.0016	.376
Birth location	0.48	.891	3.45	.246	0.08	.959	0.73	.701
Twin/triplet	-0.08	1.000	1.97	.250	-0.14	.867	1.56	.148
Education (2)	-0.52	.769	1.22	.648	0.28	.808	0.57	.735
Education (3)	-1.31	.577	1.06	.689	0.72	.535	1.18	.483
Number of children	-1.31	.068	-1.37	.037*	-0.32	.358	-0.64	.120
NICU-related parental stress	6.63	< .001***	6.99	< .001***	3.87	< .001***	5.04	< .001***
Neonatal stress exposure	0.0014	.173	0.0032	< .001**	0.0007	.144	0.0018	.015*
Skin-to-skin contact	-0.006	.792	-0.003	.891	0.009	.450	0.023	.148
Perceived support	-0.64	.824	6.01	.008**	-0.84	.553	1.32	.353

Note. Significance: *** $p < .001$, ** $p < .01$, * $p < .05$. Data from 217 families (259/446 children) were analyzed using generalized least squares.

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PETRA

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Best Segmentation Methods for Baseline 18F-FDG PET-CT in Follicular Lymphoma Patients

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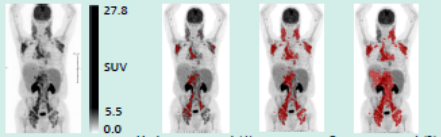
Introduction

- Follicular Lymphoma (FL)
  - 18%-26% relapses within 24 months
  - Need for more prognostic information
- Quantitative ^{18}F-FDG PET/CT has shown some prognostic value.
  - e.g. metabolic tumor volume (MTV) and distance (Dmax)
- Tumor delineation method needed for quantitative PET



Aim

Compare different single and multi threshold **delineation methods** for **follicular lymphoma** ^{18}F-FDG PET/CT on segmentation quality, interobserver variability and ease-of-use

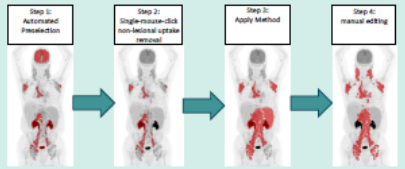
Methods

Patients

- 25 second-line FL patients (HOVON110) [4]
- 12 first-line FL patients (PETAL) [5]

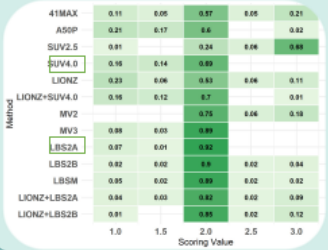
13 delineation methods by 2 observers

Single threshold methods	Multi-threshold methods
SUV threshold *(SUV4.0, SUV2.5)* [1]	Majority vote *(MV2, MV3)* [1]
SUVmax threshold *(41MAX)*	Lesion-based *(LBS2A, LBS2B, LBSM)* [3]
SUVpeak threshold *(A50P)*	LIONZ AI preselection + LBS2A
LIONZ AI [3]	LIONZ AI preselection + LBS2B
LIONZ AI preselection + SUV4.0	



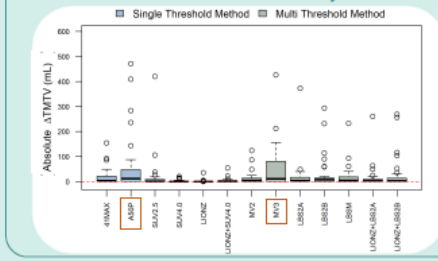
Results

Delineation Quality

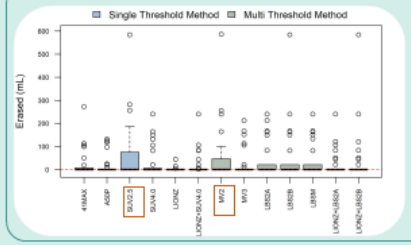


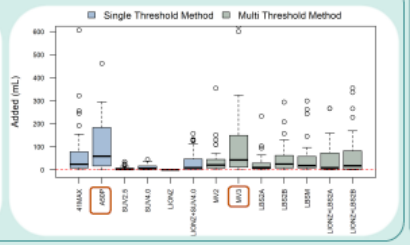
- Weighted score
- Mean square deviation from 2

Interobserver variability



Ease-of-use





- SUV2.5 consistent oversegmentation
- Addition of LIONZ AI did not improve outcome
- Good correlation between observers for all methods (ICC>0.9)

Conclusion

- Best single threshold method: **SUV4.0**
- Best multi-threshold method: **Lesion-based (LBS)**
- Single threshold methods better on: **+ Interobserver variability + Ease of implementation**
- Multi-threshold methods better on: **+ Segmentation quality**

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KWF HOVON SAKK

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Amsterdam UMC

Detection of recurrent endometrial cancer via DNA methylation analysis of cervicovaginal self-samples and urine

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Cancer Center Amsterdam - Biomarkers: Clinical

Introduction

Endometrial cancer patients undergo frequent follow-up monitoring for five years after treatment, causing a substantial burden on both patients and healthcare. However, less than 20% develop a recurrence and its detection often relies on symptoms. Previous research demonstrated that DNA methylation analysis accurately detects endometrial cancer in cervicovaginal self-samples and urine. (1)

Here, we explore the potential of DNA methylation analysis of cervicovaginal self-samples and urine for the detection of recurrent endometrial cancer.

Methods

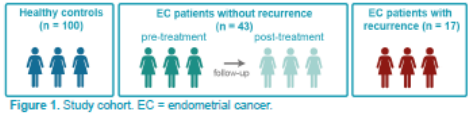

Figure 1. Study cohort. EC = endometrial cancer.

Participants collected cervicovaginal self-samples and urine. DNA was isolated, bisulfite-converted and analysed for nine markers by quantitative methylation-specific PCR (qMSP). DNA methylation positivity was assessed using logistic regression.

Results

- DNA methylation levels decreased post-treatment in patients without recurrence compared to pre-treatment (Fig. 2).
- In patients with recurrence, most DNA methylation levels were similar to, or just below the levels at primary diagnosis (pre-treatment) (Fig. 2).
- Based on previously established logistic regression models, the detection rate for recurrence was 62.5% in cervicovaginal self-samples and 58.8% in urine (Fig. 3).
- The diagnostic performance was highest for local recurrence specifically, reaching 100% DNA methylation positivity in cervicovaginal self-samples and 90% in urine (Fig. 3).

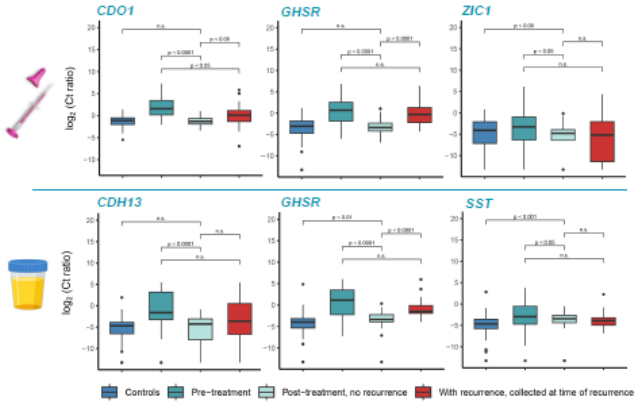

Figure 2. DNA methylation levels in cervicovaginal self-samples and urine. Only markers used in the logistic regression models are shown.

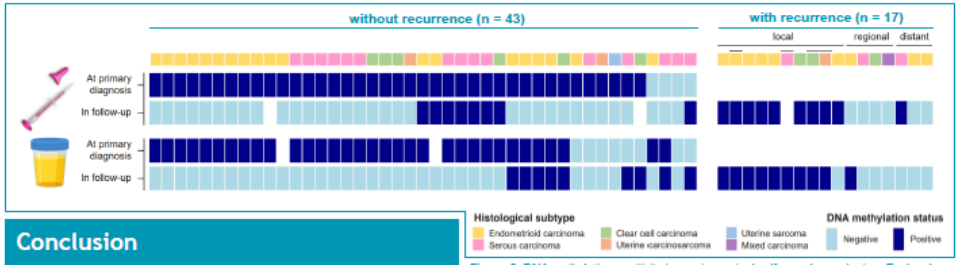

Figure 3. DNA methylation positivity in cervicovaginal self-samples and urine. Each column represents a patient. Black lines indicate local recurrence combined with regional or distant recurrence.

Conclusion

DNA methylation analysis of self-collected samples offers a promising method for remote monitoring of endometrial cancer patients after treatment. This approach could potentially reduce follow-up burden on both patients and healthcare.

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A.J. Nouwens

The use of systems archetypes in

Local obesity prevention: how the system behaves and how to change it

Well-intended health interventions can reinforce the problem.

1 THE PROBLEM

Methodologies for changing complex systems driving public health problems lack.

Participatory system dynamics approaches have gained traction in public health. However, methods to move from understanding the *beahviour* of the system to leveraging change are still lacking.

2 WHAT WE DID

We developed a novel approach using systems archetypes, common patterns of system behaviour that drive unwanted outcomes.

We applied this method to data from the LIKE project – a participatory system dynamics project on childhood obesity in Amsterdam.

3 WHAT WE FOUND

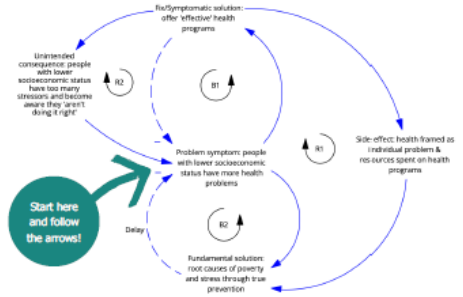
We found 6 archetypes. The most common was 'fixes that fail' e.g. that health interventions can produce unintended consequences that reinforce the problem.

Systems archetypes can help hypothesize about a system's behaviour and lead to novel and more refined insights into how it could be changed.

Fixes that fail

The story: People with lower SES face more health issues, but current health programmes only address symptoms. These programmes often make individuals feel like they're "doing it wrong," raising stress and worsening the problem. As a side-effect these programmes frame health as an individual issue, diverting attention and funds from addressing the root causes, such as poverty and stress.

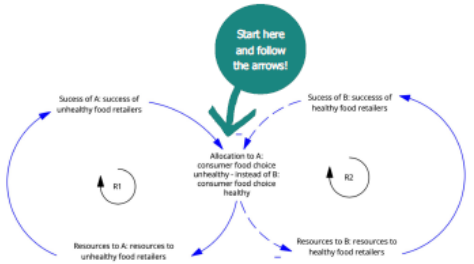
Solution? Restructure to focus resources away from individual health programmes towards root causes of poverty and stress



Success to the successful

The story: The food environment is dominated by unhealthy foods, heavily marketed to consumers. This leads people to choose unhealthy options, boosting demand and making production cheaper. As a result, unhealthy foods receive more resources, while small local healthy food producers struggle with higher costs and lower demand.

Solution? Break up concentrations of power and resources by exposing retail tactics or implementing antitrust measures



Jillian O'Mara (j.r.omara@amsterdamumc.nl)

Using systems archetypes to understand system behaviour and identify leverage points for change in local obesity prevention in the Netherlands
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Jillian O'Mara

Personalized versus standard cognitive behavioral therapy for fear of cancer recurrence, depressive symptoms or cancer-related fatigue in cancer survivors

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MATCH

1 Introduction

Fear of cancer recurrence, depressive symptoms, and cancer-related fatigue are common among cancer survivors, negatively impacting their quality of life and everyday functioning. Cognitive behavioral therapy (CBT) targeting these factors typically show small to medium effects, with limited long-term benefits, high dropout rates, and other influences on treatment outcomes. Therefore, personalization of treatment may offer a potential solution.

Aims: Compare the efficacy of personalized CBT versus standard CBT in cancer survivors with moderate to severe fear of cancer recurrence, depressive symptoms, and/or cancer-related fatigue.

2 Methods

Randomized Controlled Trial
Standard CBT vs Personalized CBT

Standard CBT	Personalized CBT
Fixed protocol	Patients' need
Standard (blended) delivery	EMA-based modules^
Fixed duration	Self-chosen delivery
	Flexible duration

^Ecological Momentary Assessment

Outcomes

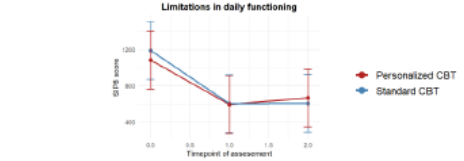
- Primary: limitations in daily functioning
- Secondary: fatigue severity, depressive symptoms, fear of cancer recurrence, quality of life, therapist time, dropouts

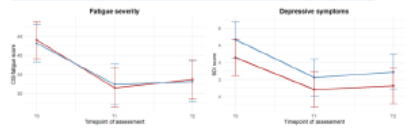
Analysis: A linear mixed model (LMM)

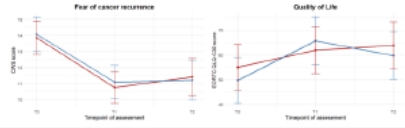
3 Results

There were 76 patients in the group of standard CBT with an average age of 50.8 years; 60 (79%) were female. The personalized CBT group consisted of 78 patients with an average age of 52.1 years; 57 (73%) were female.

- Significant reduction in limitations in daily functioning, fatigue severity, depressive symptoms, fear of cancer recurrence and an improvement of quality of life for both groups.
- No significance differences between the two groups.
- Treatment time: personalized significant more efficient for fatigue, depressive symptoms and fear of recurrence treatment.
- Dropouts: significantly lower in the personalized group (p = 0.024).







4 Discussion

- No differences in clinical outcomes between personalized and standard CBT.
- This may be due to the effectiveness of the standard protocol.
- Also, standard CBT may already include elements of personalization in routine practice.

- Despite similar outcomes, personalized CBT was associated with shorter treatment duration and lower dropout rates.
- These findings support our hypothesis that personalized CBT may enhance treatment efficiency (rather than effectiveness).

Reference: study protocol
*Including all coauthors

Reference study website

5 Conclusion

- Both personalized and standard CBT led to significant improvement across all outcomes.
- No significant outcome differences observed between the two groups.
- Significant less treatment time and dropouts for personalized group.

- Personalized CBT did not lead to better outcomes but seems to be more efficient.

MATCH

Amsterdam UMC

Hannah van der Pas

Amsterdam UMC

DOSE MATTERS: HAPLOINSUFFICIENCY IN OSTEOGENESIS IMPERFECTA

Category: Other

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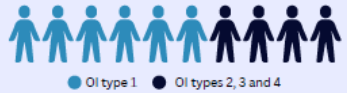
BACKGROUND

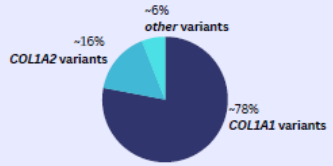
Osteogenesis imperfecta (OI) type 1, the most common OI form, has historically been labelled "*mild*," despite being a **lifelong multisystemic disorder** [1].
This misclassification has contributed to delayed diagnosis, unmet patient needs, and limited research attention.

OI type 1 is the most prevalent type of OI

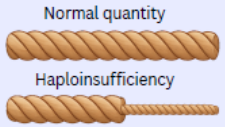


It accounts for **50-70%** of all OI cases

Predominant genetic driver



Haploinsufficiency mechanism



Structurally normal collagen but **quantitatively reduced**.

CONCLUSION

Our literature review emphasizes that **OI type 1 is not a mild disorder**, but a distinct multisystem disease. Patients need personalized clinical approaches and dedicated research. We urge the attention of the OI community to HI OI so that this significant patient group can also benefit from adequate research and care.

CLINICAL MANIFESTATIONS

In OI type 1, disease burden evolves over time, shifting from childhood **bone fragility** towards **extraskeletal complications**, chronic pain, fatigue, and **mental challenges** in adulthood, together profoundly **impacting quality of life** [1, 2].

Skeletal manifestations

Bone fragility and frequent fractures | Short stature | Scoliosis

Extraskeletal manifestations (systemic disease)

Blue sclerae | Dentinogenesis imperfecta | Hearing, joints, muscles, lungs, heart and GI tract

Quality of life and Mental health

Chronic pain and fatigue | Anxiety and PTSD-like symptoms | Invisible disability stigma

MODELS AND THERAPIES

Despite its prevalence, very few models for HI OI exist, hindering research and therapy development [3].

Haploinsufficient disease models

Mouse models: Mov13, Col1a1+/-365, hiOI | **Zebrafish model** col1a1a$_{+/-}$;col1a1b$_{+/-}$ | **Cell models**: Fibroblasts, MSCs, iMSCs, iPSCs

Therapies

- **Bisphosphonates** (off-label)

Emerging:

- Anabolic agents: **Teriparatide**
- Anti-sclerostin antibodies: **romosozumab**, **setrusumab**
- Anti-resorptives: **denosumab**
- TGF-B modulation: **fresolimumab**, **SAR439459**, **losartan**

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Amsterdam UMC Science & Awards Day 2026 6 March 2026, Amsterdam UMC

Anastasia Sclocco

Amsterdam UMC
Universitair Medische Centra

Lipidomic Signatures of Aging and Alzheimer's Disease Across Key Brain Regions in Humans

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Background

- Brain lipids are central to membrane function, signaling, and metabolism, and are strongly linked to aging and neurodegeneration.
- Tau pathology in Alzheimer's disease (AD) initiates in the entorhinal cortex and spreads to the hippocampus and prefrontal cortex (van der Kant *et al., Nat Rev Neurosci*, 2020).
- Bis(monoacylglycero)phosphates (BMPs) accumulate with aging in peripheral tissues (Janssens *et al., Nat Aging*, 2024); whether this extends to the brain is unknown.

Aim

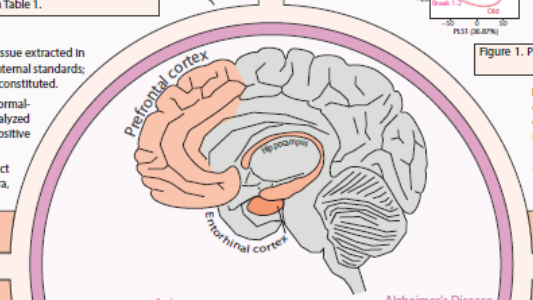
To profile lipidomic changes in aging and AD across the entorhinal cortex, hippocampus, and prefrontal cortex, highlighting region-specific alterations in brain samples, as detailed in Table 1.

Methods

Sample Preparation: 2 mg freeze-dried tissue extracted in methanol:chloroform with class-specific internal standards; apolar phase dried under nitrogen and reconstituted.

LC–MS Analysis: Lipids separated by normal- and reversed-phase UHPLC and analyzed on a Q Exactive Plus Orbitrap MS in positive and negative ESI modes.

Data Processing: Lipids annotated by exact mass, retention time, MS/MS spectra, and reference standards.



	Aging			Alzheimer's Disease		
	Young	Middle Age	Old	Braak 1-2	Braak 3-4	Braak 5-6
Sample Size	7, 9	8, 9	19	12	19, 20	20
Age Range	18-40	47-58	63-100	71-96	78-103	61-92
% Male	67%, 71%	44%, 50%	47%	33%	63%, 65%	45%
PMD (h)	40.8	37.5	41.8	43.5	49.4	35
APOE 3/4 Count	0	0	4	4	5	9
APOE 4/4 Count	0	0	0	0	2	7

Table 1. Cohort overview. PMD = post-mortem delay (hours)

Lipid Shifts

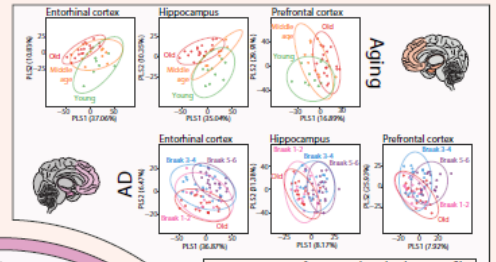


Figure 1. PLS-DA of aging and AD lipidomic profiles across brain regions.

Data analysis was further expanded to include Pearson correlations between lipid class abundance and age (Aging group) or Braak stage (AD group: Old = 0; Braak 1–2 = 2; 3–4 = 4; 5–6 = 6), as shown in Figures 2–4, followed by cross-regional correlation analysis (Figure 5).

BMPs in Aging

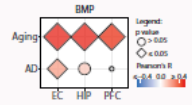


Figure 2. BMP changes across brain regions in aging and AD. Shape size indicates significance level ($-\log_{10}$ p value).

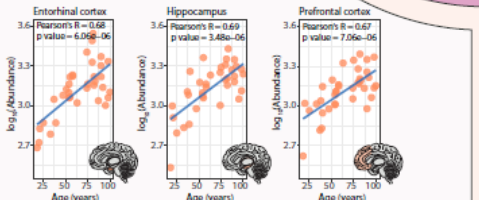


Figure 3. Age-dependent BMP accumulation in the human brain.

Regional Signatures

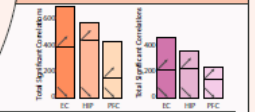


Figure 4. Significant lipid correlations in aging (right) and AD (left); positively correlated (top), negatively correlated (bottom) per column.

Cross-correlation (Figure 5): The entorhinal cortex exhibits a distinct disease-specific pattern, whereas age-related changes in the hippocampus and prefrontal cortex align with AD progression.

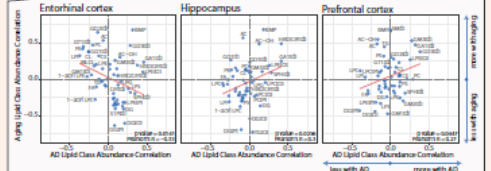


Figure 5. Distinct aging-AD relationships across brain regions.

Conclusions

- Samples displayed stratified clustering, reflecting progressive lipidomic shifts aligned with age and disease trajectories.
- Aging was consistently marked by accumulation of BMPs, lipids closely associated with lysosomal function.
- The entorhinal cortex exhibited the highest number of age-related lipid correlations, followed by the hippocampus and prefrontal cortex; AD-related associations were fewer but built upon aging-linked changes.
- Region-specific regression patterns revealed divergent trajectories: in the entorhinal cortex, AD-related lipid alterations diverged from normal aging, possibly due to impaired autophagic processes, whereas in the hippocampus and prefrontal cortex, AD-related changes positively correlated with aging-related lipid shifts, suggesting an accelerated aging-like progression.

Acknowledgments

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Maria Tretowicz

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Amsterdam Public Health

Causal associations between tobacco smoking and mental health: pathways of genetic risk through addiction and socioeconomics

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Background

- Mendelian Randomization (MR) studies using genome-wide association study (GWAS) data have provided evidence that smoking increases the risk of depression and schizophrenia [1].
- Genetic signals underlying smoking behaviors include confounders (SES and addiction vulnerability among others) [2].
- We want a refined genetic instrument for smoking.

- Using this refined instrument, we re-examine the causal effects of smoking on eight common psychiatric disorders.

Methods

1. Genomic structural equation modelling (GSEM) allows us to find a genetic architectural model that separates 'unique' smoking from confounders and correlates. We include 7 smoking, 8 substance use, and 4 SES traits.
2. We then evaluate the Unique Smoking Factor.
3. The causal association between Unique Smoking and 8 common psychiatric traits is studied after accounting for confounders.

Conclusions

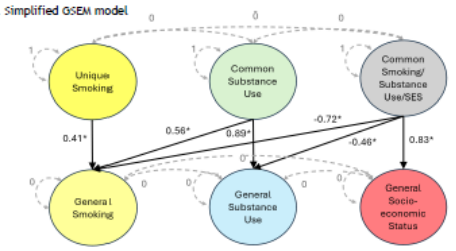
- We find a specific genetic component that is unique to tobacco smoking.
- This Unique Smoking Factor reflects mostly heaviness of smoking, with hits in the *CHRNA3* and *CHRNA5* nicotine receptor genes.
- Even after subtraction of overlapping confounders, smoking remains causally associated with several mental health disorders, most of which share many causal SNPs.
- This finding supports the existence of causal pathways by which smoking increases the risk of psychiatric disorders.

Take home message

Tobacco smoking increases the risk of suffering mental health disorders. Even after correcting for SES and other substance use.

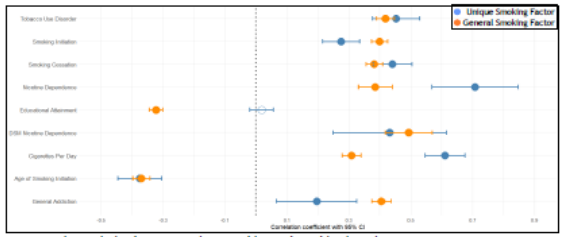
Results

1. Simplified GSEM model

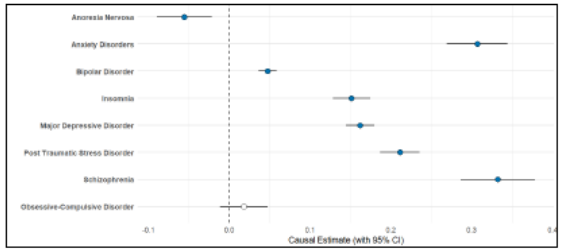


* Significant at p<0.005

2. Trait correlations with Unique and General Smoking Factors



3. Causal association between Unique Smoking and psychiatric traits



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Adrià Túnez

Bone Phenotype in a Novel Mouse Model of Mild Haploinsufficient Osteogenesis Imperfecta

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Category: Animal Models

A novel mouse model of **haploinsufficient Osteogenesis Imperfecta type 1 (hiOI)** was developed using CRISPR/Cas9 technology. The model harbors a heterozygous deletion of the entire *Col1a1* gene.

The hiOI mice exhibit collagen deficiency, as reflected by a lower *Col1a1/Col1a2* mRNA ratio, reduced P1NP collagen biosynthesis marker levels in the serum, and decreases in total collagen type I protein in bone tissue compared to WT animals. These mice also show impaired bone structure and altered biomechanical properties.

BACKGROUND

Osteogenesis Imperfecta (OI) is a genetic disorder causing bone fragility, with **OI type 1** being the mildest form. It is caused by a deficiency of collagen type I due to ***COL1A1* gene variants**, leading to fractures. Despite representing **>30% of OI patients**, research has been limited by **the lack of effective mouse models.**

Figure 1. Clinical Sillence classification of OI. Adapted from Zhytnik *et al.*, Orphanet Journal of Rare Diseases (2020).

AIM

This study aimed to develop and characterize a new mouse model for mild haploinsufficient (HI) OI type 1 **(hiOI).**

METHODS

- **CRISPR/Cas9** was used to generate a heterozygous deletion of the *Col1a1* allele in C57BL/6N mice.
- 20 **hiOI** and 20 **wild-type (WT)** mice (50% males) at 8 weeks of age.
- **mRNA expression of collagen type I chains** in bone measured by **RT-qPCR** (LightCycler), using ***Tbp*** as the reference gene and **2-ΔΔCT** method.
- **Bone RNA sequencing** (n_{WT}=5, n_{hOI}=5; all males).
- **Collagen extraction & Western blotting** for **α1(I), α2(I)** and total **collagen type I** in ulnae (n_{WT}=3, n_{hOI}=3).
- **Bone formation and resorption markers** (P1NP, TRAcP5b) measured in blood serum by **ELISA.**
- **Bone analysis** included **micro-computed tomography, histology** (Masson Goldner's trichrome; n_{WT}=9, n_{hOI}=9, males), **three-point bending test** (n_{WT}=18, 50% males; n_{hOI}=13; 69% males).
- **Data analysis** was performed with **GraphPad Prism 9.** Normally distributed data (Kolmogorov-Smirnov test) analyzed with **unpaired t-test. Gender subgroup analysis** used **two-way ANOVA** with multiple comparisons. **$P \leq 0.05$** considered statistically significant.
- All animal experiments were **approved by the Central Committee for Animal Experiments (CCD)** of the Netherlands.

RESULTS

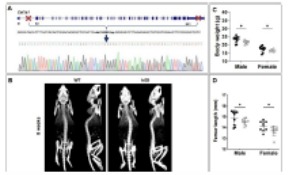

Fig. 2. Generation of a novel Col1a1 knockout mouse model for haploinsufficient OI (hiOI). (A) Knockout strategy with a 16350 bp deletion in the *Col1a1* gene for the hiOI mouse and Sanger sequencing of the mutated allele. **(B)** Computed tomography images showing absence of skeletal dysplasia or spontaneous fractures in the hiOI mice. **(C)** Reduced body weight and **(D)** femur length in male and female hiOI mice as compared to their WT littermates ($^*p \leq 0.05$; data shown as mean ± SD).

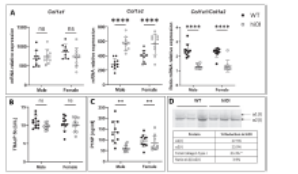

Fig. 3. Reduced bone collagen expression and serum biomarkers in the hiOI mice. (A) Real-time quantitative analysis of *Col1a1* and *Col1a2* gene expression and their mRNA ratio. **(B-C)** Serum TRAcP 5b levels **(B)** remained normal in hiOI mice, while serum P1NP levels **(C)** were significantly reduced. **(D)** Western blot analysis of α1(I) and α2(I) collagen protein bands extracted from ulnae bones of WT and hiOI mice and quantification showed as percentage reduction relative to WT.

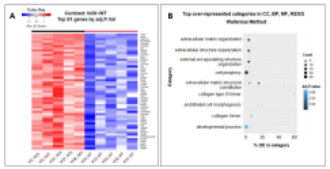

Fig. 4. RNA sequencing analysis reveals the upregulation of 51 genes in hiOI mice compared to WT mice. (A) Heatmap showing differentially expressed genes. **(B)** Top over represented Gene Ontology (GO) categories.

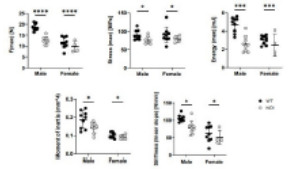

Fig. 5. Three-point bending test with femora. Maximum force, maximum stress, maximum energy, moment of inertia and stiffness were significantly reduced in hiOI mice. Data shown as mean ± SD. $^*p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$, $^{****}p \leq 0.0001$.

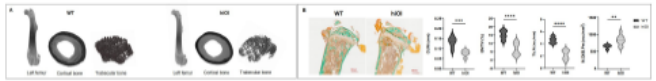

Fig. 6. Bone phenotype of the hiOI mice. (A) Representative micro-CT images from the left femur of 8-week old WT and hiOI males. **(B)** Representative images of Masson Goldner trichrome staining. Histomorphometry analysis confirmed reduction in cortical width (Ct.Wi), bone to tissue ratio (BV/TV), trabecular number (Tb.N) and increase in osteocyte number (Oc.N).

CONCLUSION

The hiOI mice exhibit key features of HI OI type 1, making it a valuable tool for advancing research and therapies in this large group of OI patients.

ACKNOWLEDGEMENTS

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I thank the Amsterdam Reproduction & Development (AR&D) and Amsterdam Movement Sciences (AMS) research institutes of Amsterdam UMC for their support.
Special thanks to Wendy Noort, Behrouz Zandieh Doulabi and Wendy Runderkamp for their contributions.
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horstingstuit

Surgical Care for Rheumatic Heart Disease Patients: Insights from the Netherlands Heart Registration

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Amsterdam UMC

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Introduction

40 million patients;
300.000 deaths annualy

Surgical mitral valve replacement

Rising prevalence of RHD in High Income Countries

Addressing the need for evaluation of the overall surgical care for RHD patients in the Netherlands

Methods

NHR data: quality registration for cardiothoracic surgery
MVR patients screened: 2488 → RHD MVR patients included: 435
Period: 2017-2023

All cardiothoracic centers in the Netherlands (n=16)

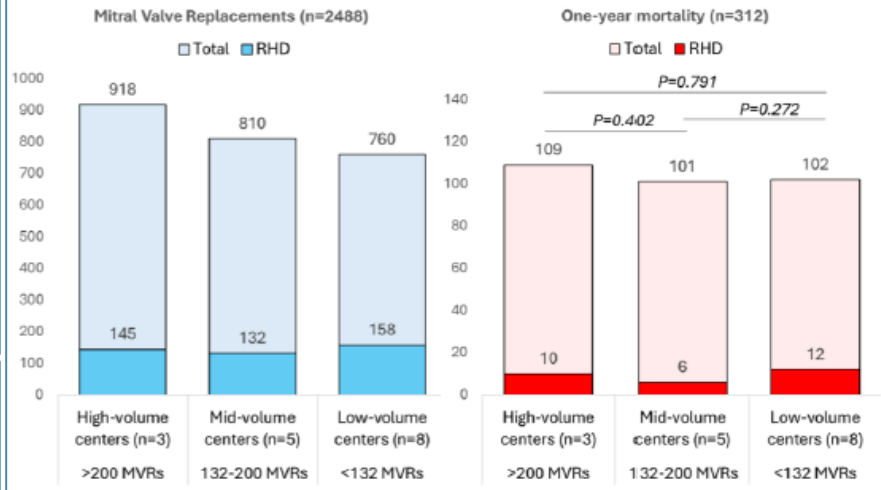
Inclusion: RHD-related MVR patients aged ≤ 75 years
Exclusion: endocarditis

Follow-up data available up to 5 years after surgery

Baseline characteristics, admission data, procedural details & outcome data (including mortality)

Subanalysis:
i) High- vs. low-volume centers
ii) RHD MVR vs. non-RHD MVR

Mitral Valve Replacements and Mortality by Center Volume 2017-2023



Conclusion

Surgical care for patients with RHD-related MVR in the Netherlands:

- Of all MVRs performed between 2017 and 2023, 17.5% involved RHD patients aged 18 to 75 years
- Acceptable mortality rate, at the lower bounds of international reported data
- No difference in mortality between high- and low-volume centers
- No difference in mortality between RHD and non-RHD MVR patients

This suggests that RHD MVR patients can be managed similarly as non-RHD MVR patients.

Results

Baseline characteristics
Age: 58±12 years
Female: 73.3%

Admission data
LVEF ≥ 55.0%: 72.6%
Atrial fibrillation: 40.2%
NYHA II-IV: 88.7%

Procedural details
Isolated MVR: 51%
Double valve surgery: 42%
Triple valve surgery: 7%

Mortality (uncensored)
Operative: 4.1%
Overall: 12.2%
Follow-up: 2.9 (1.1, 4.6) years

RHD MVR vs. non-RHD MVR
Adjusted HR for one-year mortality:
1.23; 95% CI 0.82-1.85; p=0.312

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NHR

Amsterdam UMC

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Revealing the relevance of BRCA2 status for the efficacy of cisplatin-based hyperthermia intraperitoneal chemotherapy (HIPEC) in ovarian cancer: evidence from *in vitro* models

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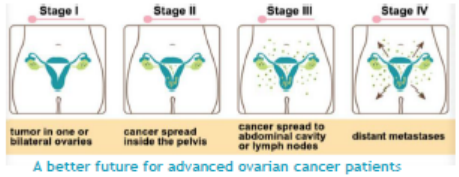

A better future for advanced ovarian cancer patients

Introduction

The addition of HIPEC to cytoreductive surgery for peritoneal metastases has shown promising survival outcomes. Hyperthermia is a treatment that inhibits the DNA damage repair (DDR) homologous recombination (HR) pathway by inducing degradation of BRCA2. However, the impact of BRCA2 status for cisplatin-based HIPEC's efficacy remains unclear, also when combining HIPEC with systemic chemotherapy. This study aims to evaluate the efficacy of cisplatin-based HIPEC and assess the impact of BRCA2 status on HIPEC sensitivity, for both high grade serous and non-high grade serous ovarian tumor profiles.

Results

All cell lines exhibited sensitivity to hyperthermia alone, with a more pronounced sensitivity of high grade serous ovarian cancer cell lines. Cisplatin demonstrated a temperature-dependent synergy with heat, resulting in increased DNA damage, apoptosis and G2-arrest. Both BRCA2 wild type and mutation show significant sensitivity to HIPEC. The benefit is even greater in BRCA mutated carriers, which increased 20% apoptosis level and reduced 30% survival rate.

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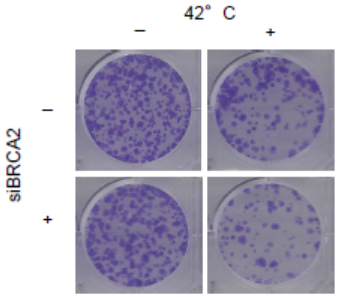
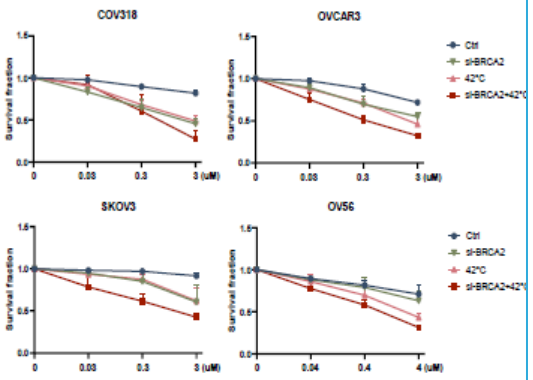
OvarianCancerUK



Conclusion/Discussion

Ninety minutes hyperthermic exposure to cisplatin effectively targets both high and non-high grade serous ovarian cancer cells, suggesting that cisplatin-based HIPEC could be clinically effective in both subtypes, also for BRCA2 mutated subtypes.



Universiteit van Amsterdam · LEXOR · Radiobiology

Fan Yang

DENTAL MINERALIZATION CHANGES IN OI TYPE 1 MICE

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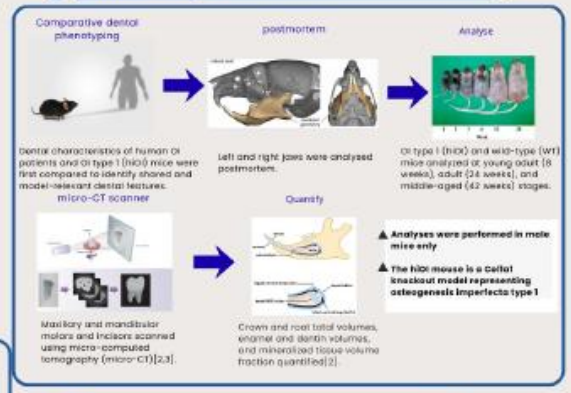
Research Background

- Osteogenesis Imperfecta (OI) type 1 is caused by defects in type I collagen, resulting in skeletal fragility and altered mineralization of hard tissues[1].
- In addition to bone, dental tissues such as enamel and dentin are affected in OI[2,3].
- Age-related changes in dental tissue volume and mineralization in OI remain poorly characterized.

Objective

To investigate age-dependent structural and compositional changes in dental tissues in an OI type I mouse model and assess their relevance to dental manifestations in OI patients.

Methodology



Dental characteristics of human OI patients and OI type 1 (Hir) mice were first compared to identify shared and model-relevant dental features.

Left and right jaws were analyzed postmortem.

OI type 1 (Hir) and wild-type (WT) mice analyzed at young adult (8 weeks), adult (24 weeks), and middle-aged (42 weeks) stages.

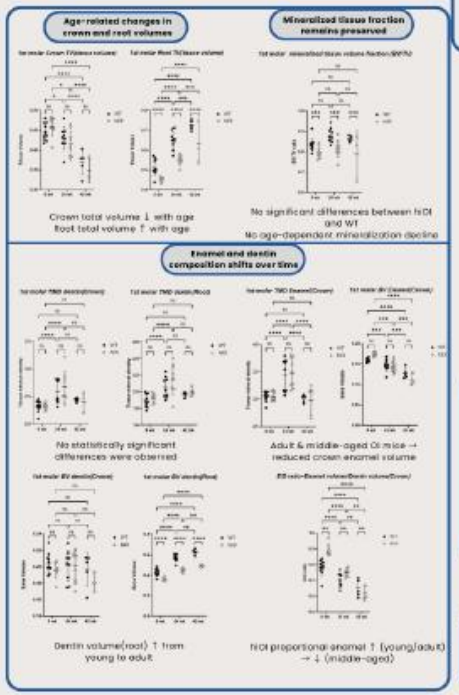
Maxillary and mandibular molars and incisors scanned using micro-computed tomography (micro-CT)[2,3].

Crown and root total volumes, enamel and dentin volumes, and mineralized tissue volume fraction quantified[2].

▲ Analyses were performed in male mice only

▲ The Hir mouse is a Col1a1 knockout model representing osteogenesis imperfecta type 1

Results



Discussion

- The age-related reduction in crown volume and enamel content indicates progressive enamel wear rather than impaired mineralization.
- The increase in root and dentin volumes likely reflects physiological post-developmental maturation and secondary dentin deposition in molars, which are finite-growth teeth.
- Importantly, overall mineralized tissue fraction remained preserved across genotypes, suggesting that OI type 1 affects tissue distribution and structural dynamics rather than total mineral content.
- These findings highlight altered dental tissue remodeling in OI and may help explain long-term enamel vulnerability observed in patients.

Conclusion

- Dental tissues in OI type 1 mice undergo pronounced age-dependent structural and compositional changes.
- Age-related enamel loss appears to be primarily driven by wear, while dentin and root growth continue with aging
- The use of E/D ratios provides a robust approach to assess relative dental tissue composition in rodent models.
- These structural changes may contribute to increased enamel wear and potential dental fragility in OI, highlighting the importance of long-term dental monitoring.

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Wenya Yang

Smoking and stress: triangulation of evidence from causally informative methods

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Introduction

Smoking and stress

- Smoking is associated with stress/anxiety, but the **causal nature** is unclear.

- RCTs are unfeasible or limited [1]
- All alternatives have shortcomings

Triangulation

- Strengthening causal inferences by integrating results from multiple methods, each with different **(uncorrelated) sources of bias** [2]
- **Prospectively** select methods
- Minimise the risk of incorrect conclusions
- Keep in mind:

RQ Sample Definition Timespan Bias

Research question

Does smoking causally increase stress and/or anxiety levels?

Methods

Datasets

- UK Biobank: 502,542 adult British participants [3]
- Lifelines: 141,200 adult Dutch participants [4]
- Summary-level data from genome-wide association studies (GWAS):
  - Smoking initiation + cigarettes per day [5]
  - Perceived stress; anxiety [6]
  - Educational attainment [7]

Statistical methods

- Confounder-adjusted **regression** (baseline)
- Sibling-control design [8]
  - Include **sibship average** and **sibling's deviation** from average in a regression model.
- Mendelian Randomization [9]
  - Use **genetic IVs** of smoking to predict stress and anxiety outcomes, reducing population-level and individual-level confounding.
- Random-intercept cross-lagged panel model [10]
  - Tests **within-person** versus between-person variation in a longitudinal setting.
- Positive and negative control outcomes
  - Positive: lung cancer
  - Negative: right-handedness [11]

Sources

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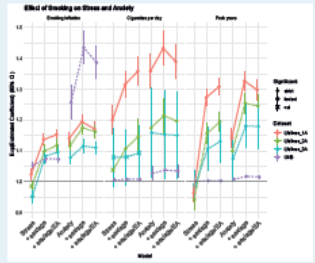
Results

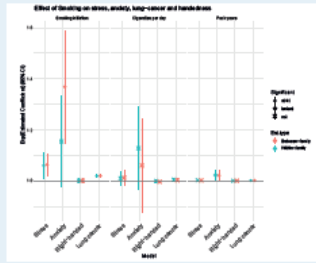
Confounder-adjusted regression

- Datasets: UKB and Lifelines



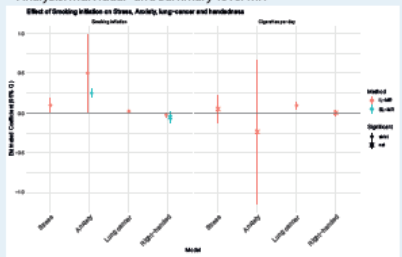
Sibling-control design

- Dataset: UKB

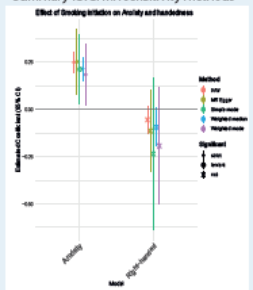


Mendelian Randomization

- Analysis: Individual- and summary-level MR



Summary-level MR sensitivity methods

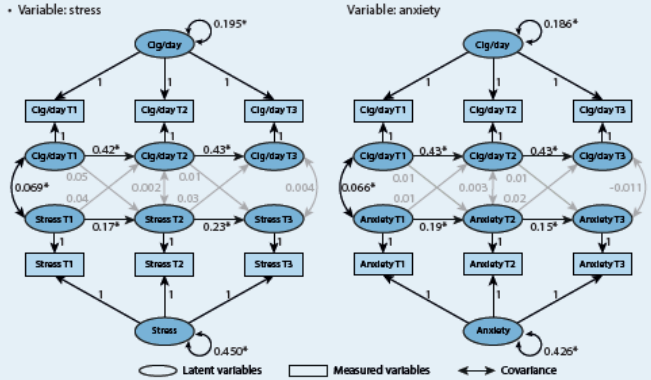


- Datasets: UKB (IL-MR) and GWAS summary statistics (SL-MR)
- Within-family MR has not yet been performed

Random-intercept cross-lagged panel model

- Dataset: Lifelines
- Variable: stress

Variable: anxiety



Discussion

- The importance of triangulation keeps increasing, but it is rarely applied systematically.
- Smoking seems to be associated with increased stress and anxiety values, more so for anxiety.
- Not each method found significant results:
  1) Cig/day has a small sample size; 2) Time between measurements in RI-CLPM might be too long.

* There are no potential conflicts of interest

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