"Το Stress και σαρκοπενία:
Ιατρική ακριβείας στην καρδιομεταβολική νόσο - Επιλογή Θεραπείας"

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Παθολόγος-Κλινικός Διαιτολόγος

Definitions

- ***Precision*** (or stratified) medicine refers to processes that combine available data concerning human biology, behaviors and contexts to optimize the medical approach, usually by tailoring prevention strategies, diagnostics and therapeutics to subgroups of populations sharing similar characteristics; the objective is to minimize error and risk and maximize efficacy

- ***Personalized*** (or individualized) medicine refers to final step in the process of translating evidence into practice, taking into account individual's references, capabilities and circumstances

Ιατρική της ακρίβειας

- Παρόλο που πολλά είναι γνωστά για τους παράγοντες κινδύνου που οδηγούν στο καρδιομεταβολικό σύνδρομο (πχ. τρόπος ζωής, επίπεδο εκπαίδευσης και πρόσβαση στη θεραπεία) σε **επίπεδο πληθυσμού**, οι συγκεκριμένοι παράγοντες που οδηγούν το **κάθε ξεχωριστό άτομο** σε νόσο είναι λιγότερο προσδιορίσιμοι
- Τα διαγνωστικά κριτήρια κοινών νοσημάτων είναι **βασισμένα στα συμπτώματα**, όπως και η επιλογή και η αξιολόγηση της θεραπείας καθώς και τα συμπεράσματα για την πρόγνωση της νόσου
- Αυτό δεν αφήνει περιθώρια για αναγνώριση με ακρίβεια των χαρακτηριστικών της νόσου και συχνά προδιαθέτει σε ιατρικά σφάλματα
- Αυτές οι προκλήσεις έχουν ωθήσει την ανάπτυξη μεθόδων που αποσκοπούν στη βελτίωση της ακρίβειας και της ορθότητας στην ιατρική και τη δημόσια υγεία, μια έννοια που αναφέρεται συχνά ως **ιατρική της ακρίβειας**

Lancet Diabetes Endocrinol. 2023 Nov;11(11):822-835

In medical parlance precision means a

“relative lack of random error”

Τεκμηριωμένη ιατρική

- ✓ Η βέλτιστη πρακτική πρόληψης και θεραπείας σύνθετων νοσημάτων μέχρι σήμερα βασίζεται στην τεκμηριωμένη ιατρική, που τυπικά είναι αποτέλεσμα τυχαιοποιημένων κλινικών μελετών και μελετών παρατήρησης
- ✓ Άλλοι τύποι πειραματικών δεδομένων αλλά και μελετών πραγματικού κόσμου συμπληρώνουν την ιατρική λήψη αποφάσεων.
- ✓ Η ιατρική βασισμένη στην τεκμηρίωση εστιάζει περισσότερο στις εκτιμήσεις της μέσης έκθεσης του πληθυσμού σε κίνδυνο και στην αποτελεσματικότητα ή την ασφάλεια της θεραπείας, ή και τα δύο, υπό την προϋπόθεση ότι αυτοί οι μέσοι όροι έχουν νόημα για προβλέψεις σε ατομικό επίπεδο

Lancet Diabetes Endocrinol. 2023 Nov;11(11):822-835

Καρδιομεταβολικό σύνδρομο

- Το καρδιομεταβολικό σύνδρομο που περιλαμβάνει την **παχυσαρκία**, τον **σακχαρώδη διαβήτη**, την **καρδιαγγειακή νόσο** και τη **λιπώδη νόσο του ήπατος** καθώς και τις **επιπλοκές** τους, αποτελεί μεγίστη απειλή για την παγκόσμια υγεία
- Παρά την πρόοδο στην κατανόηση και τη διαχείριση του που οδηγούν σε καλύτερες εκβάσεις, παρουσιάζει ακόμη αυξημένη **νοσηρότητα** και **θνητότητα**, με την αυξανόμενη παγκόσμια επιβάρυνση αυτών των ασθενειών να αποδίδεται σε μεγάλο βαθμό σε **τροποποιήσιμους παράγοντες κινδύνου**
- Το 2022 περισσότεροι από το 10% του παγκόσμιου πληθυσμού (>500 εκατομμύρια άνθρωποι) ζουν με σακχαρώδη διαβήτη, με μεγαλύτερη αύξηση στον επιπολασμού της νόσου να αναμένεται στην Υποσαχάρια Αφρική, την Μέση Ανατολή και την Νότια Ασία έως το 2045

Lancet Diabetes Endocrinol. 2023 Nov;11(11):822-835

Καρδιομεταβολικό σύνδρομο

Το 2022

- **1 στα 8 άτομα ζουν με παχυσαρκία**
- 2,5 δισεκατομμύρια ενήλικες ζουν με υπερβάλλον βάρος, 890 εκατομμύρια εξ αυτών ζουν με παχυσαρκία
- 37 εκατομμύρια παιδιά, κάτω των 5 ετών ζουν με παχυσαρκία

- Ο επιπολασμός της MAFLD ανέρχεται στο 32% του πληθυσμού παγκοσμίως
- 10% του παγκόσμιου πληθυσμού έχει διαγνωστεί με καρδιαγγειακή νόσο (Στεφανιαία Νόσος,Καρδιακή Ανεπάρκεια, Αγγειακό Εγκεφαλικό Επεισόδιο)

World Health Organization 2024
Clin Mol Hepatol. 2023 Feb;29(Suppl):S32-S42
MMWR Morb Mortal Wkly Rep. 2024 Jan 25;73(3):51-56

Καρδιομεταβολικό σύνδρομο-Επιπολασμός

Region	Prevalence
Europe	29%
Asia	22%
Africa	18%
South America	31%
North America	34%

TABLE 1: Prevalence of cardiometabolic syndrome by region.

Cureus. 2023 Sep 19;15(9):e45542

Καρδιομεταβολικό σύνδρομο και σαρκοπενία

Research paper

Sarcopenia and the cardiometabolic syndrome: A narrative review

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ARTICLE INFO

Article history:
Received 14 September 2015
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Available online 21 January 2016

Keywords:
Sarcopenia
Metabolic syndrome
Cardiovascular disease
Sarcopenic obesity

ABSTRACT

Sarcopenia is a prevalent problem in the older population that is commonly considered for its well-known adverse functional associations. Cardiovascular diseases and metabolic syndrome are also significant problems whose prevalence dramatically increase with age and remain the main cause of mortality in older adults. These two entities have recently been suggested to be inter-related and significant evidence has accumulated. In this article, we review the current evidence on this proposed association and the possible related pathophysiologic mechanisms. In summary, it seems that lower muscle mass is associated with higher cardiometabolic diseases (CMD) when adjusted for weight, but lower CMD when adjusted for height squared. Sarcopenic obesity – obesity and sarcopenia combined – might be associated with a greater risk of CMD than sarcopenia and obesity alone. Sarcopenia and CMD seem to share a common pathway and interact with each other to facilitate mutual abnormalities.

European Geriatric Medicine. 7. 10.1016/j.eurger.2015.12.012

Sarcopenic Obesity and Cardiometabolic Health and Mortality in Older Adults: a Growing Health Concern in an Ageing Population

Sasiwarang Goya Wannamethee[1] · Janice L. Atkins[2]

Accepted: 31 July 2023 / Published online: 11 August 2023

Abstract

Purpose of Review Sarcopenic obesity (SO) is a growing public health problem in older adults. Whether SO confers higher risk of cardiometabolic disease and mortality than obesity or sarcopenia alone is still a matter of debate. We focus on recent findings on SO and cardiometabolic health and mortality in older adults.

Recent Findings SO is associated with increased mortality compared to non-sarcopenic obesity, but similar mortality risk compared to sarcopenia without obesity. SO is associated with a higher risk of cardiovascular disease (CVD), diabetes, and physical disability than obesity or sarcopenia alone. SO, in the presence of diabetes, is associated with the highest risk of CVD and chronic kidney disease. A definition and diagnostic criteria for SO has recently been proposed (ESPEN and EASO).

Summary SO is associated with more adverse outcomes overall than sarcopenia or obesity alone. Future research is required to assess the impact of the new SO definition on health outcomes.

Curr Diab Rep. 2023 Nov;23(11):307-314

Osteosarcopenic adiposity (OSA) phenotype and its connection with cardiometabolic disorders: Is there a cause-and-effect?

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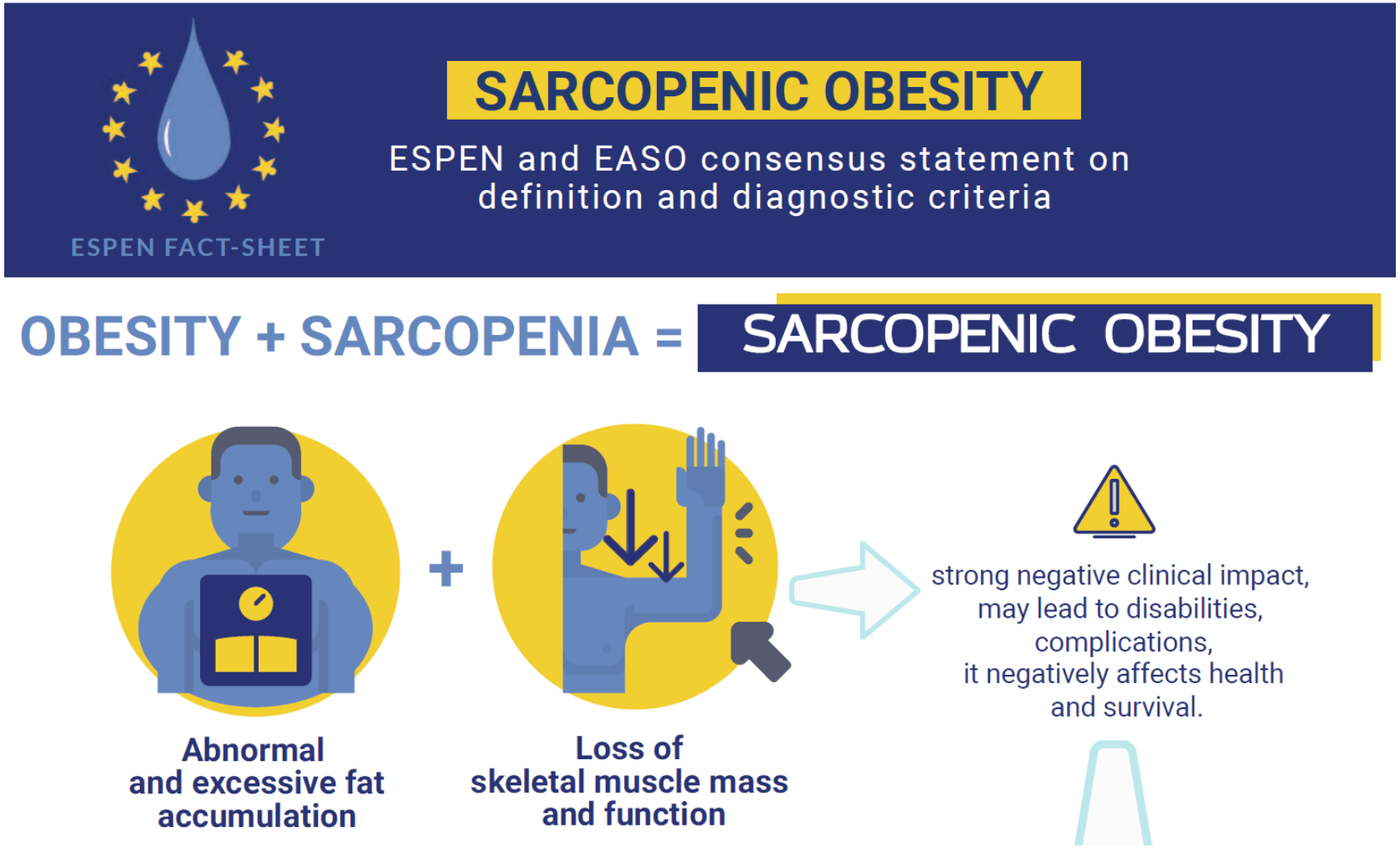
ARTICLE INFO

Keywords:
Osteosarcopenic adiposity/obesity
Cardiometabolic disorders
Cardiovascular disease
Cardiovascular risk factors
Metabolic abnormalities

ABSTRACT

The objectives were to examine if there is a causal relationship between osteosarcopenic adiposity (OSA) syndrome (coexistence of osteopenia/osteoporosis, sarcopenia, and excess adiposity) and cardiometabolic disorders or if these disorders initiate the development of OSA and its worsening. The search was conducted in PubMed, Scopus, and Web of Science to include articles up to the end of 2023. Of n=539 articles retrieved, n=15 met the eligibility criteria. Only studies conducted in adults and with all three body composition compartments (bone, muscle/lean, adipose) measured were considered. The results revealed that several cardiometabolic disorders, namely, hypertension, dyslipidemia (elevated total and LDL-cholesterol, lower HDL-cholesterol), insulin resistance, hyperglycemia, lower serum vitamin D, and some inflammatory markers were accompanied by OSA. In most cases, the OSA phenotype was associated with worse outcomes than cases with healthy or less impaired body composition. Our initial questions about the reciprocal cause-and-effect relationships could be surmised with more certainty for the OSA and some cardiovascular risks (hypertension, dyslipidemia) and some metabolic abnormalities (several inflammatory markers). The results of this review underscore the importance of body composition in health and from a clinical perspective, all three body composition compartments should be measured by standardized technologies using regulated diagnostic criteria to identify OSA. Randomized trials and prospective studies in diverse groups of older and younger individuals are necessary to determine if the relationships between OSA and clinical endpoints are causal and reversible through intervention and to uncover the mechanisms.

Σαρκοπενική παχυσαρκία



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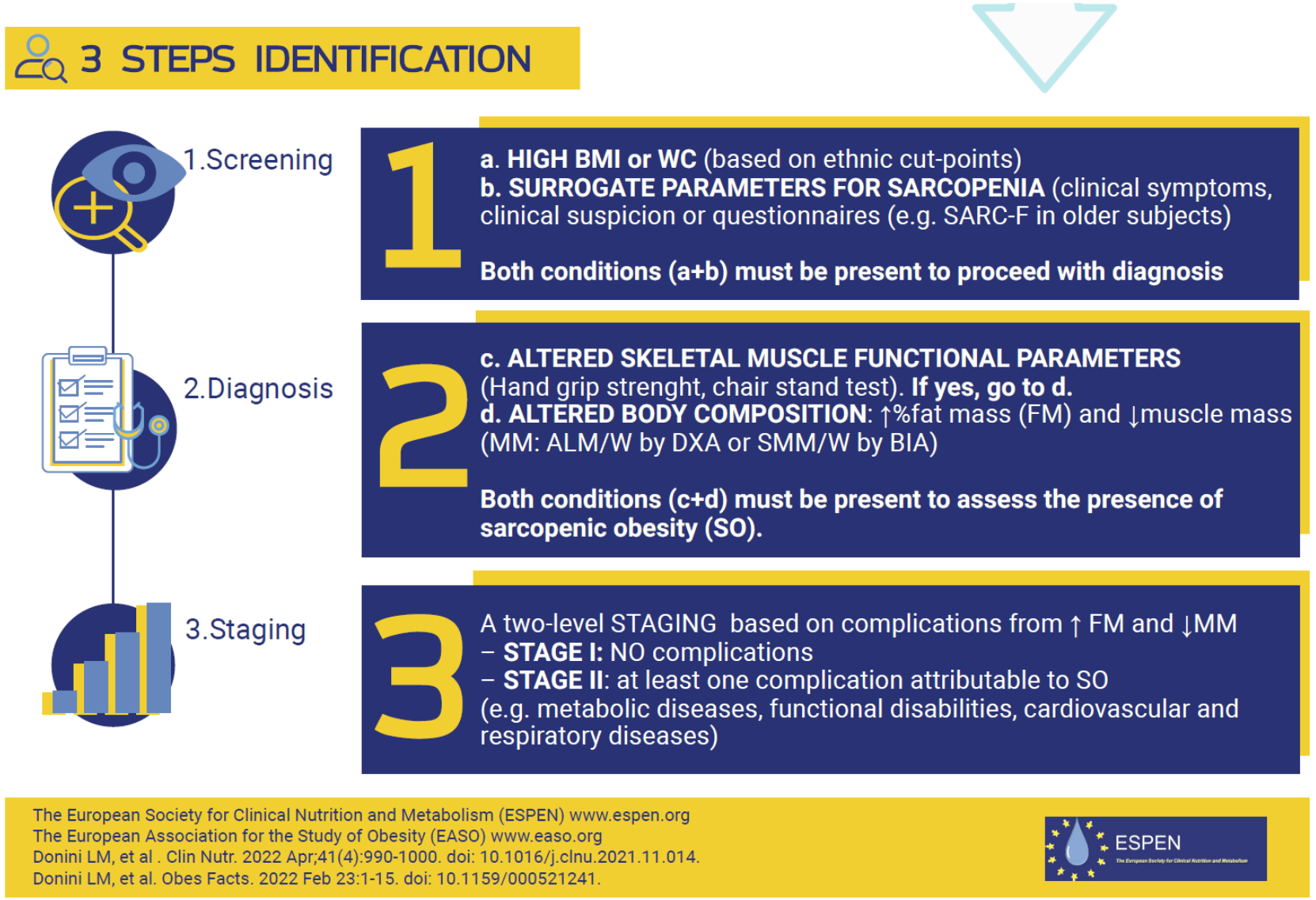
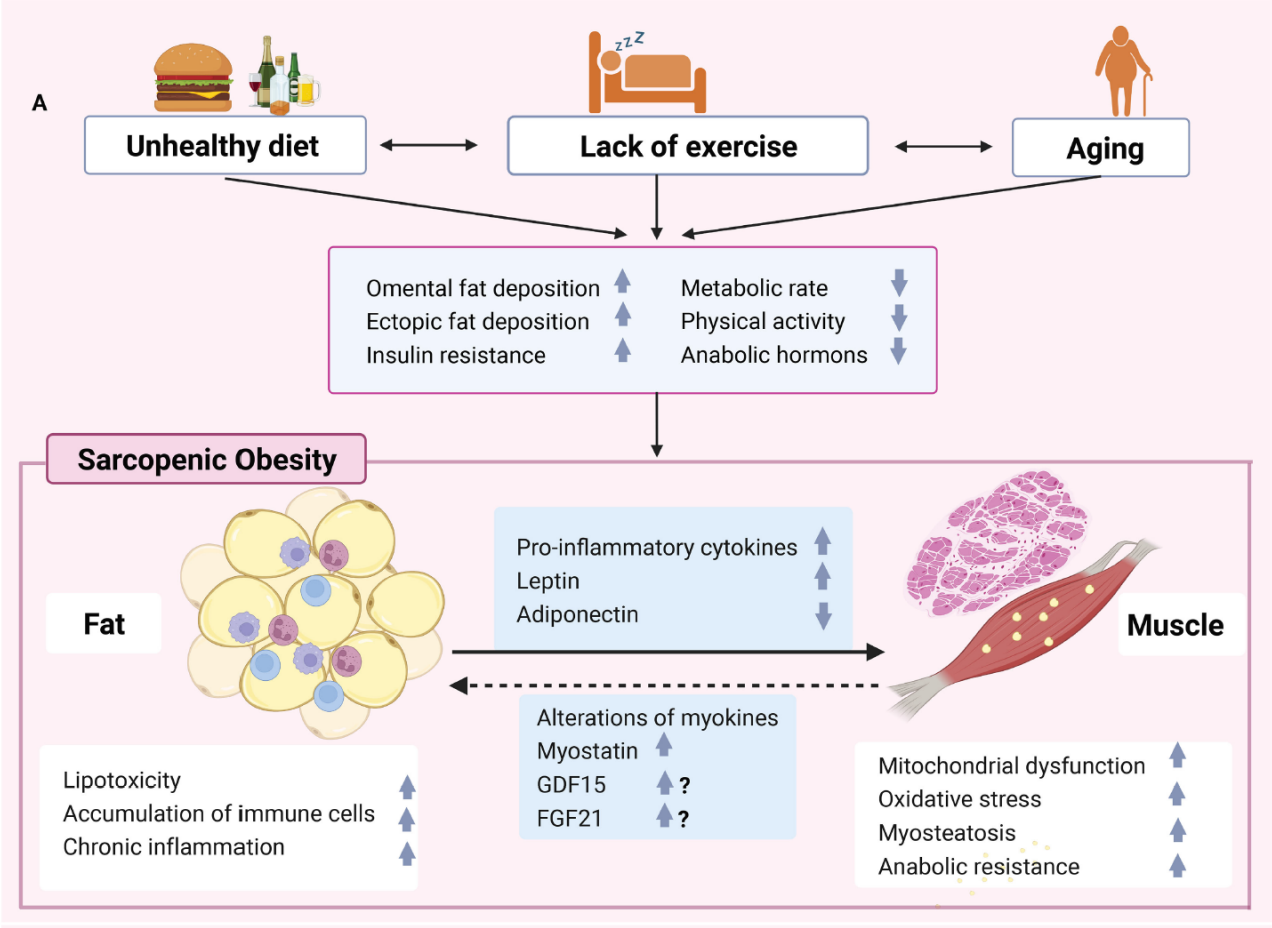
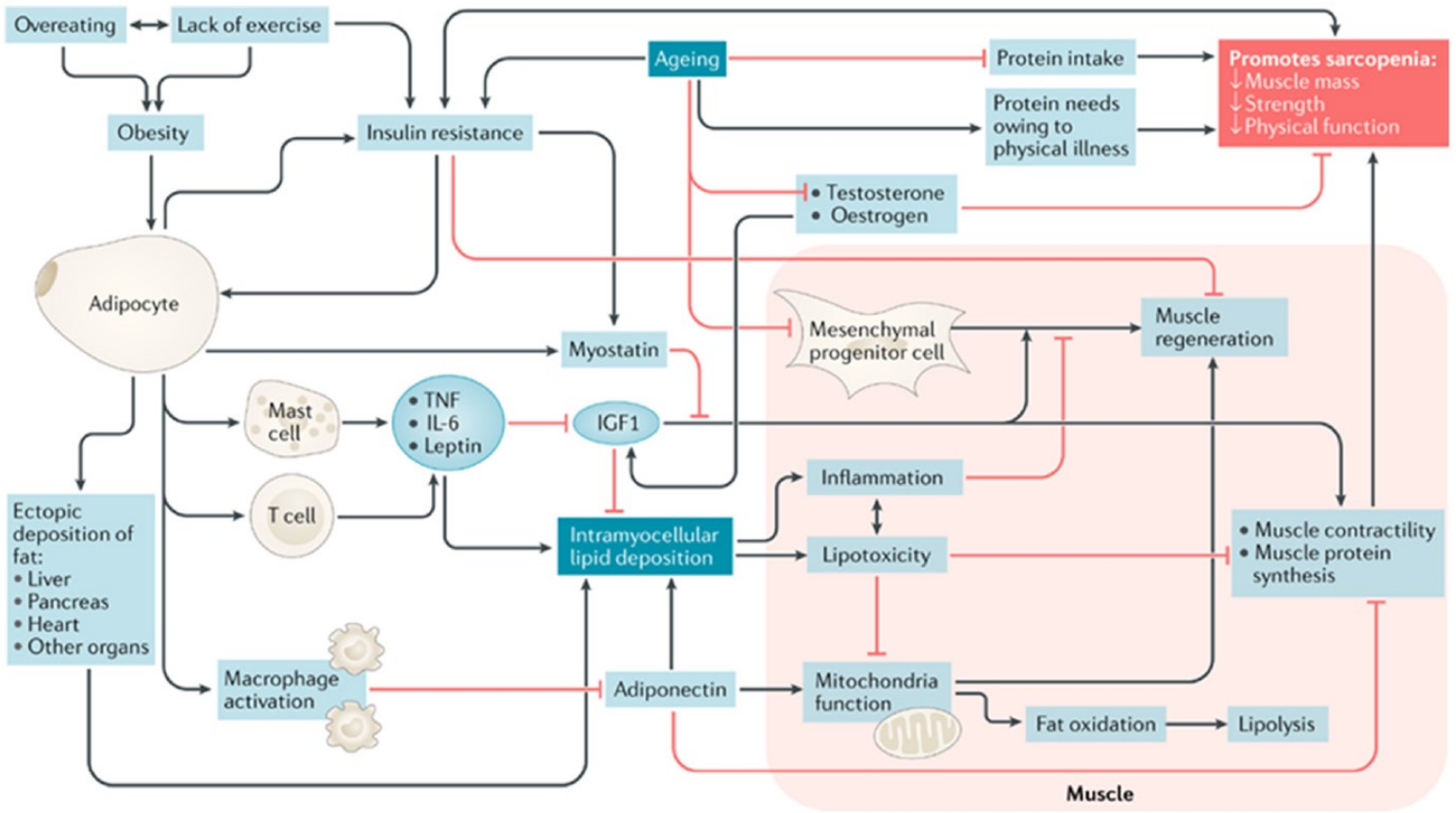


Παθοφυσιολογία



Front Endocrinol (Lausanne). 2023 Jun 30;14:1185221

Παθοφυσιολογία



Nutrients. 2022 Mar 26;14(7):1384

Obesity Facts

Consensus Statement

Obes Facts 2022;15:321–335
DOI: 10.1159/000521241

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Published online: February 23, 2022

Definition and Diagnostic Criteria for Sarcopenic Obesity: ESPEN and EASO Consensus Statement

Lorenzo M. Donini[a] Luca Busetto[b] Stephan C. Bischoff[c] Tommy Cederholm[d]
Maria D. Ballesteros-Pomar[e] John A. Batsis[f] Juergen M. Bauer[g] Yves Boirie[h]
Alfonso J. Cruz-Jentoft[i] Dror Dicker[j] Stefano Frara[k] Gema Frühbeck[l] Laurence Genton[m]
Yftach Gepner[n] Andrea Giustina[k] Maria Cristina Gonzalez[o] Ho-Seong Han[p]
Steven B. Heymsfield[q] Takashi Higashiguchi[r] Alessandro Laviano[a] Andrea Lenzi[a]
Ibolya Nyulasi[s] Edda Parrinello[a] Eleonora Poggiogalle[a] Carla M. Prado[t] Javier Salvador[u]
Yves Rolland[v] Ferruccio Santini[w] Mireille J. Serlie[x] Hanping Shi[y] Cornel C. Sieber[z]
Mario Siervo[A] Roberto Vettor[b] Dennis T. Villareal[B] Dorothee Volkert[z] Jianchun Yu[C]
Mauro Zamboni[D] Rocco Barazzoni[E]

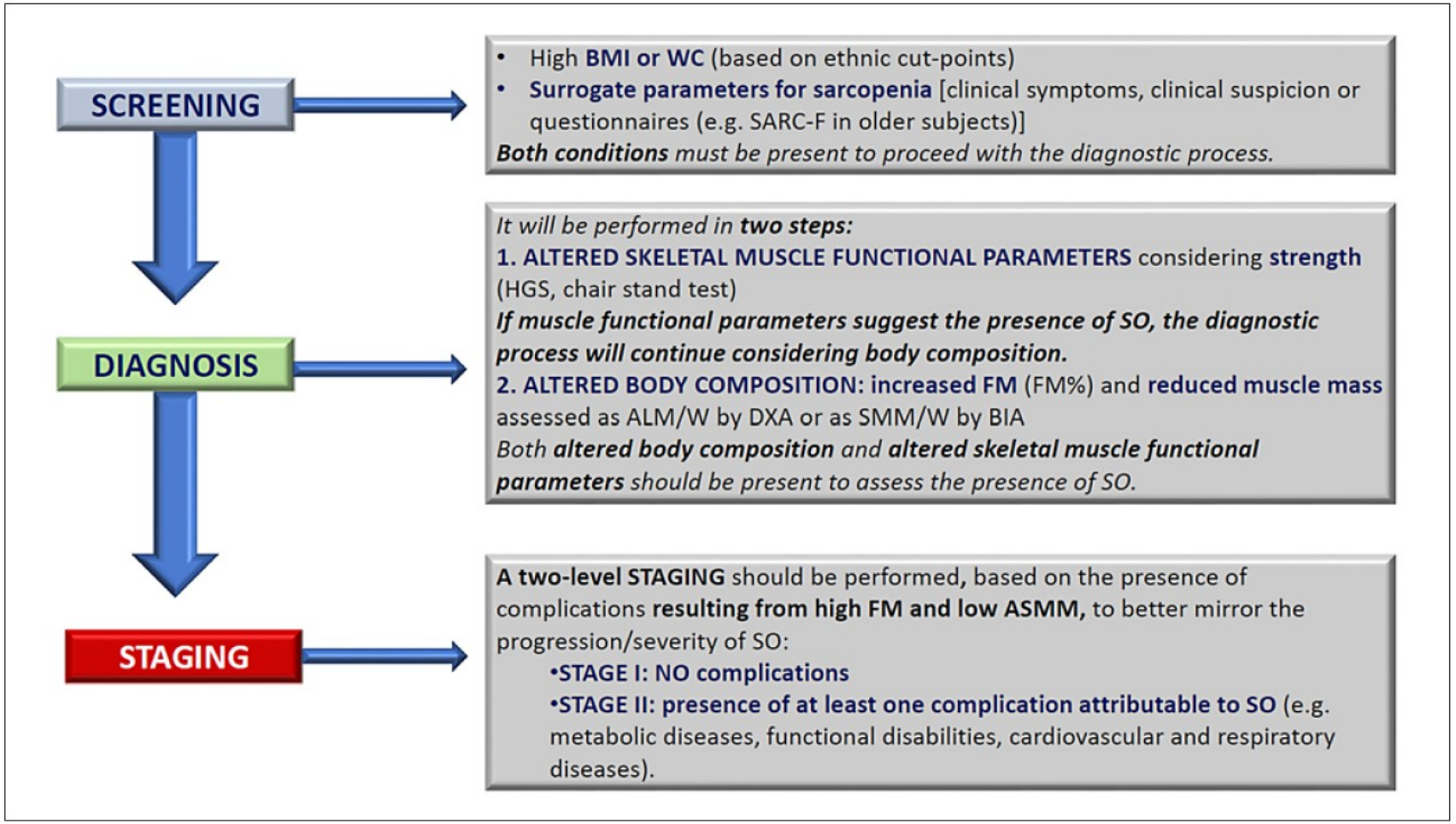
Υποψία Σαρκοπενικής Παχυσαρκίας

Table 1. Clinical symptoms or suspicion factors for the screening of sarcopenic obesity

Age >70 years
Chronic disease diagnosis (e.g., inflammatory diseases and organ failure or chronic disease) including but not limited to:
Chronic heart failure
Chronic kidney disease (particularly renal replacement therapy)
Chronic bowel failure or dysfunction
Chronic liver disease (particularly NASH and liver cirrhosis)
Chronic respiratory disease
Chronic neurologic and neurodegenerative diseases
Chronic cognitive impairment
Depression
Organ transplantation
Endocrine diseases (e.g., metabolic syndrome, diabetes mellitus, hypercortisolism, hypogonadism and corticoid treatment)
Osteoarthritis
Cancer (especially but not limited to chemotherapy of breast or prostate cancer)
Recent acute disease/nutritional events:
Recent hospitalization (particularly but not limited to COVID-19, ICU stay, surgery)
Recent major surgery or trauma with/without complications
Recent sustained immobilization or reduced mobility (e.g., trauma, fracture, orthopaedic disease)
Recent history of reduced food intake (e.g., <50% for >2 weeks)
Recent weight loss (including diet-induced voluntary weight loss and weight cycling syndrome)
Recent rapid increase in weight
Long-standing restrictive diets and bariatric surgery
History – complaint of:
Repeated falls
Weakness, exhaustion
Fatigability
Perceived progressive movement limitations

Obes Facts. 2022;15(3):321-335

Διάγνωση Σαρκοπενικής Παχυσαρκίας



Obes Facts. 2022;15(3):321-335

Ιατρική της ακρίβειας

Λαμβάνει υπόψη την ατομική μεταβλητότητα
- ✓ Γενετικό υπόβαθρο
- ✓ Επιγενετικές αλλαγές
- ✓ Εντερικό μικροβίωμα
- ✓ Περιβάλλον
- ✓ Τρόπο ζωής
- ✓ Απάντηση στην φαρμακευτική αγωγή

Στοχεύει στην καλύτερη στρατηγική
- Πρόγνωσης
- Διάγνωσης
- Πρόληψης και θεραπείας

Για κάθε ασθενή ξεχωριστά

From Obesity to Diabetes. Cham: Springer, 2022

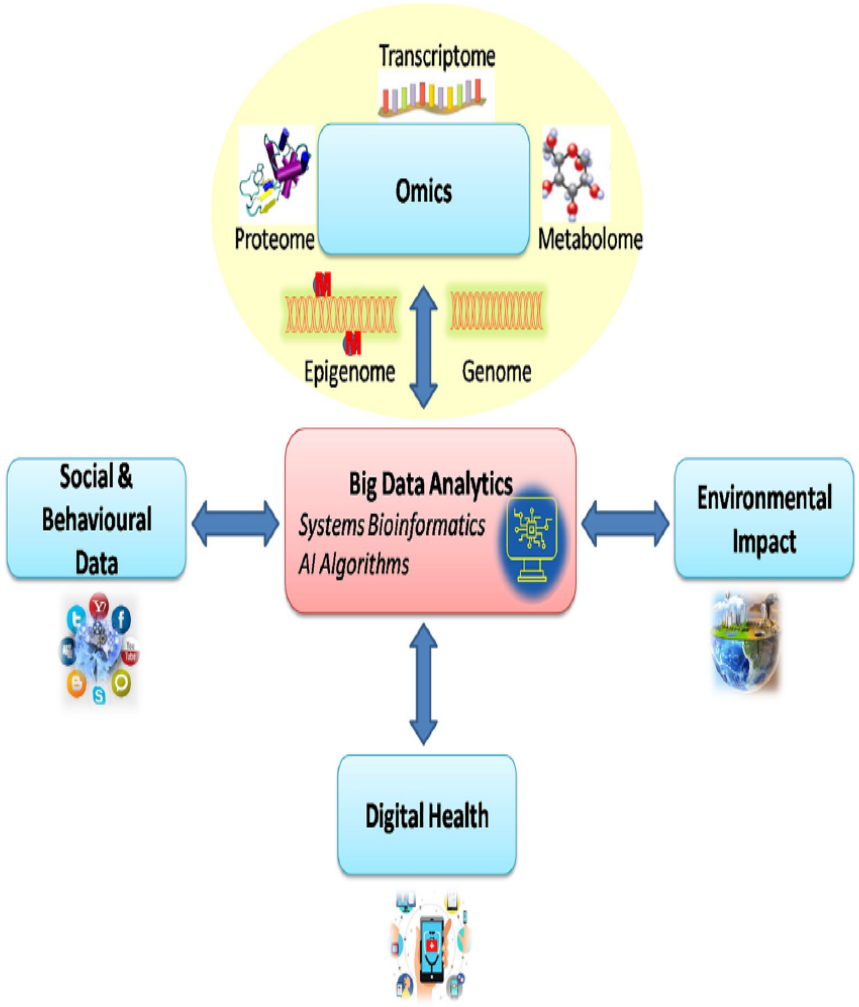
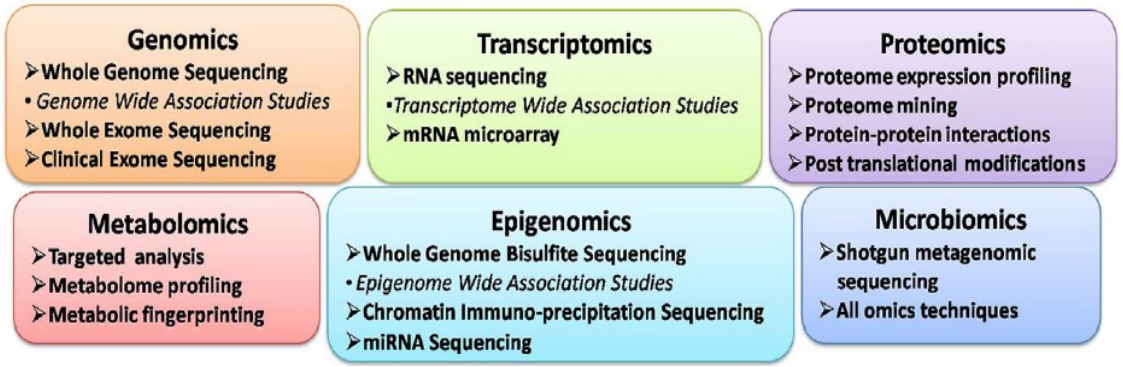


Fig. 1 – Tools of precision medicine.



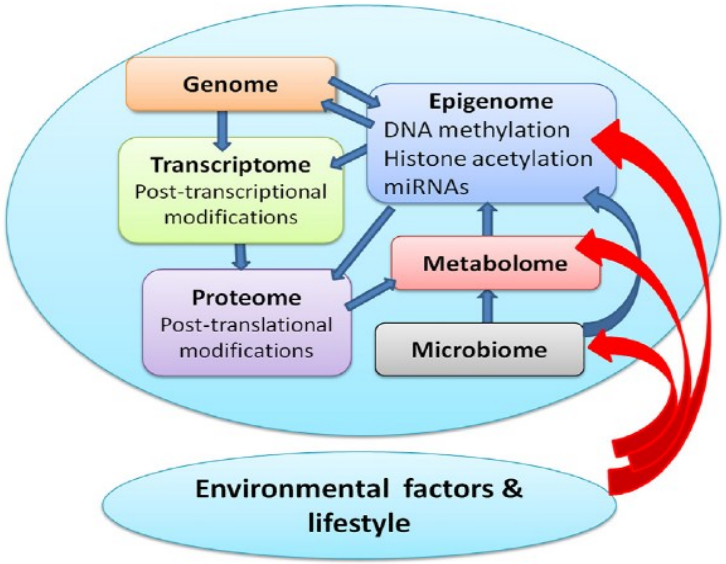


Fig. 3 – Factors affecting omics signature.

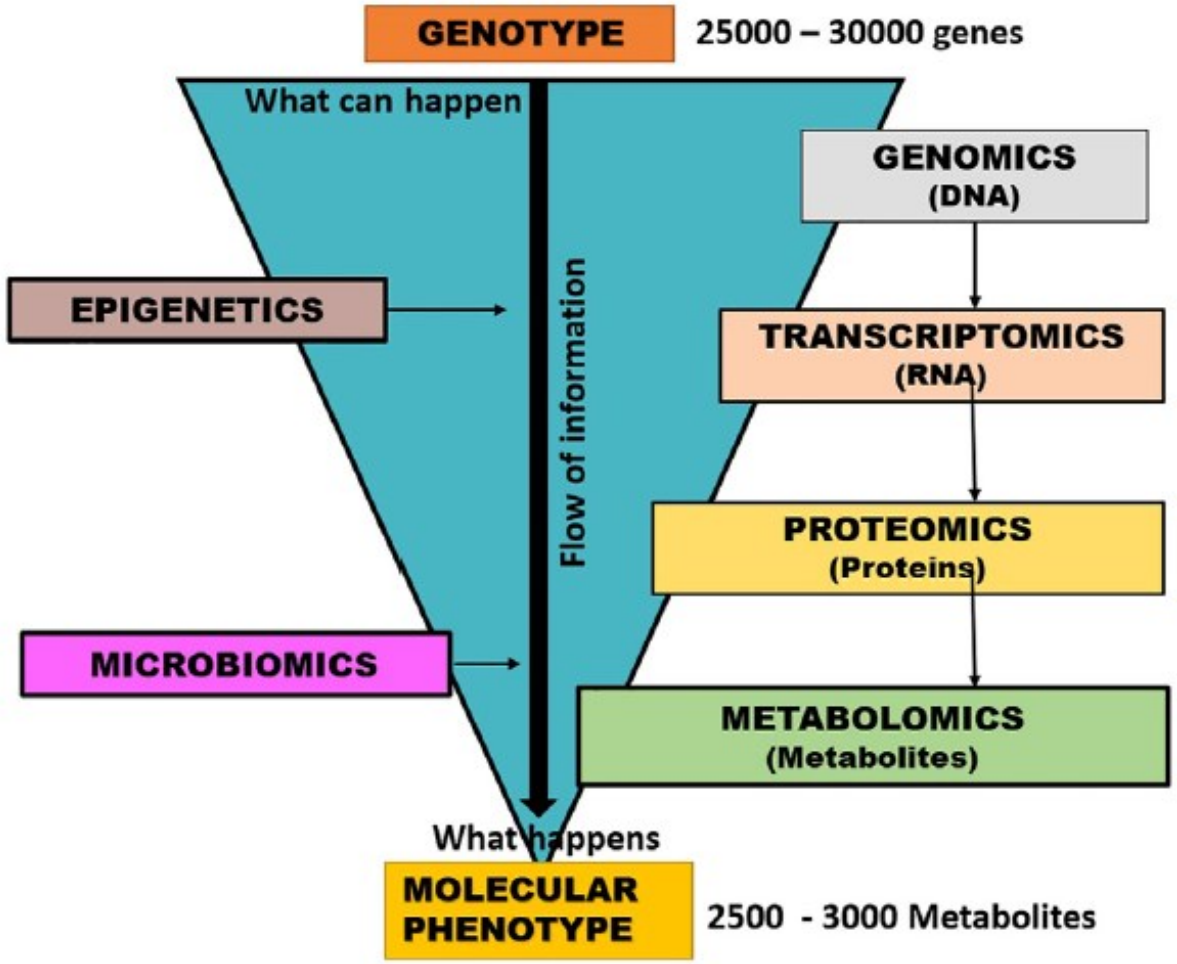
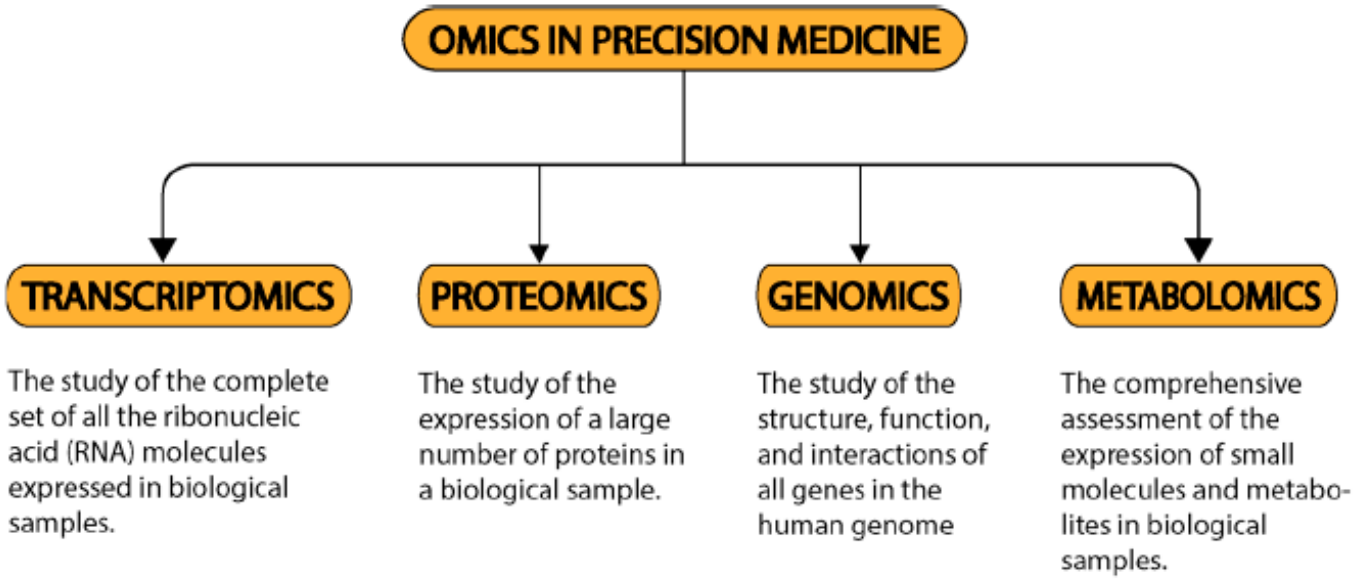
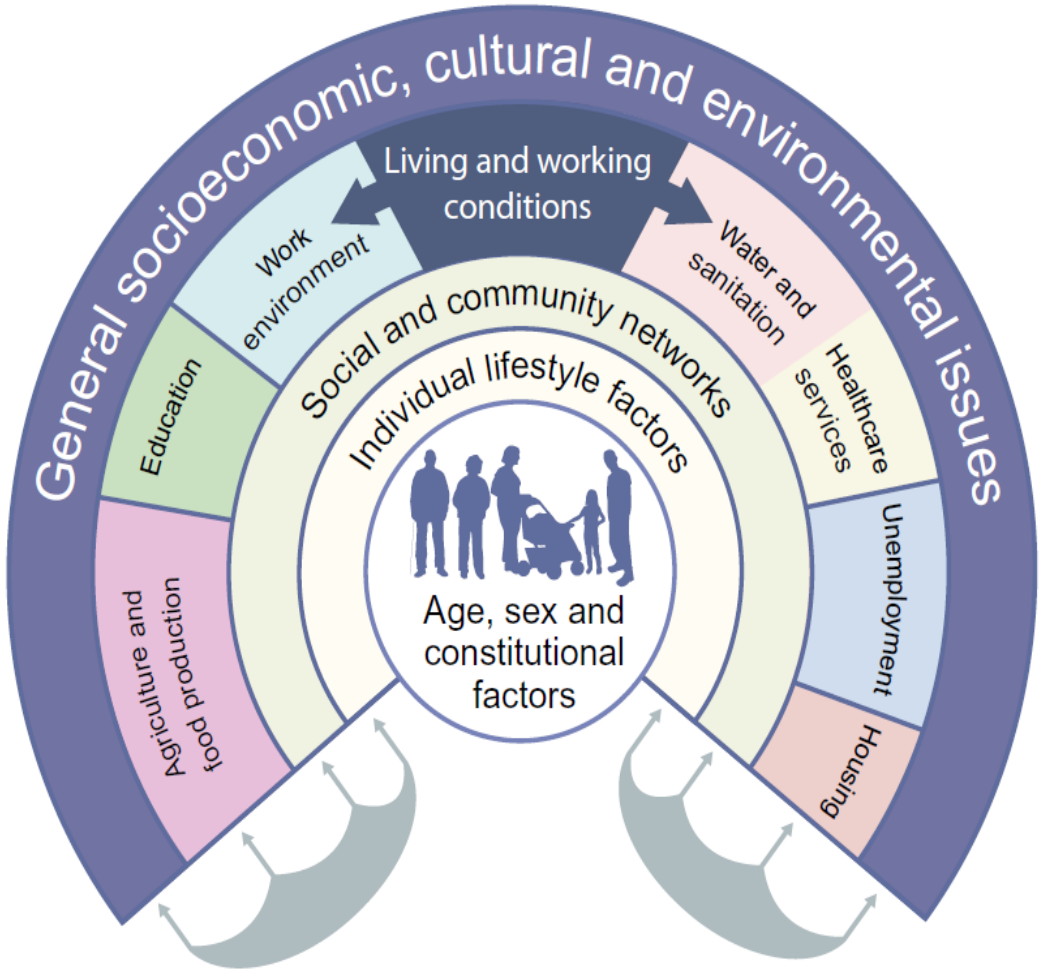


Fig. 4 – Translation of genetic polymorphisms to observable phenotypes.

Med J Armed Forces India. 2021 Jul;77(3):249-257



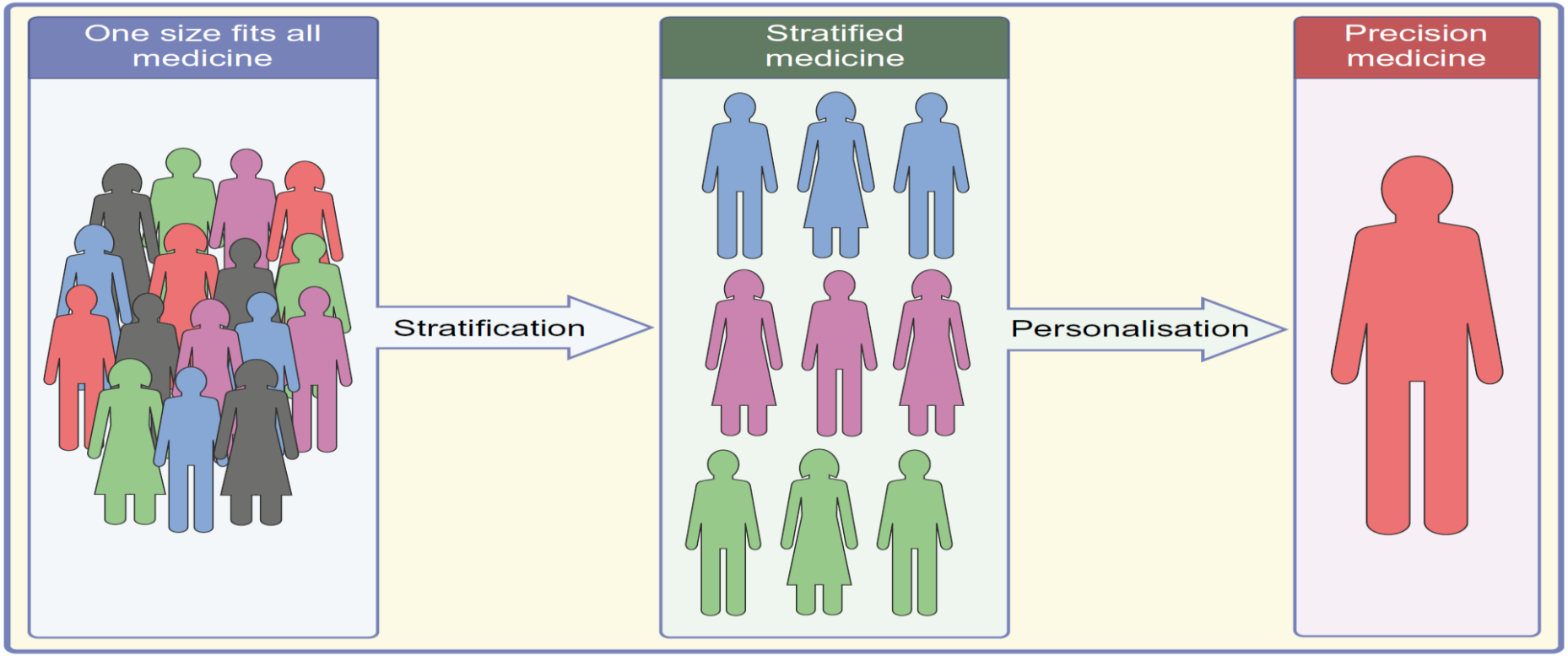
J Clin Med. 2023 Feb 23;12(5):1799



From Obesity to Diabetes. Cham: Springer, 2022

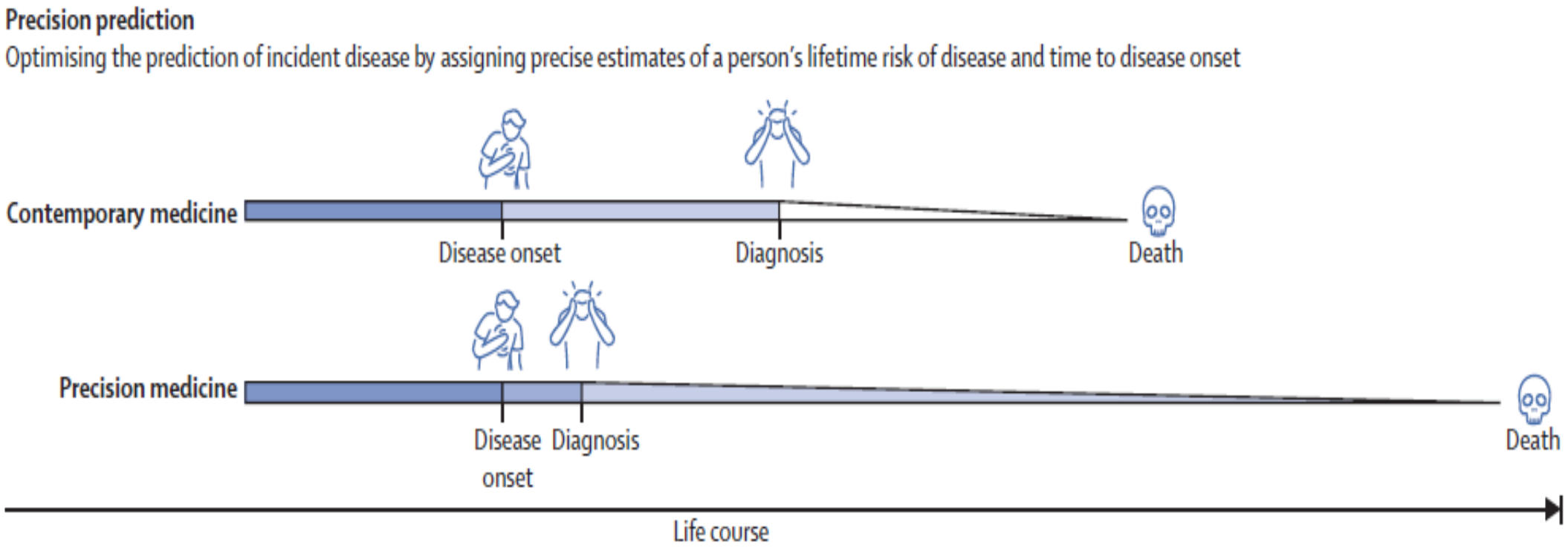
Ιατρική της ακρίβειας

Στόχος της ιατρικής της ακρίβειας είναι η εξατομίκευση των θεραπειών και η βελτίωση της αποτελεσματικότητας της θεραπείας, μειώνοντας τις παρενέργειες και παρέχοντας πιο στοχευμένη φροντίδα



Diabetologia. 2022 Nov;65(11):1913-1921

Πρόληψη

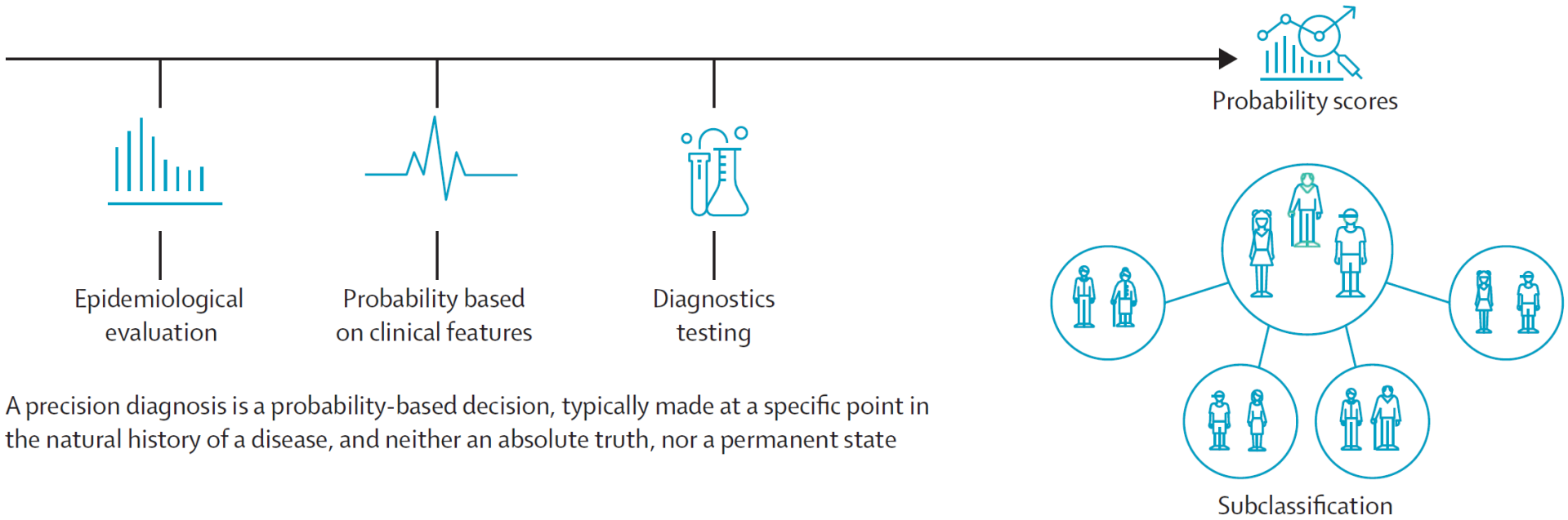


Diabetologia. 2020 Sep;63(9):1671-1693

Διάγνωση

Precision diagnostics

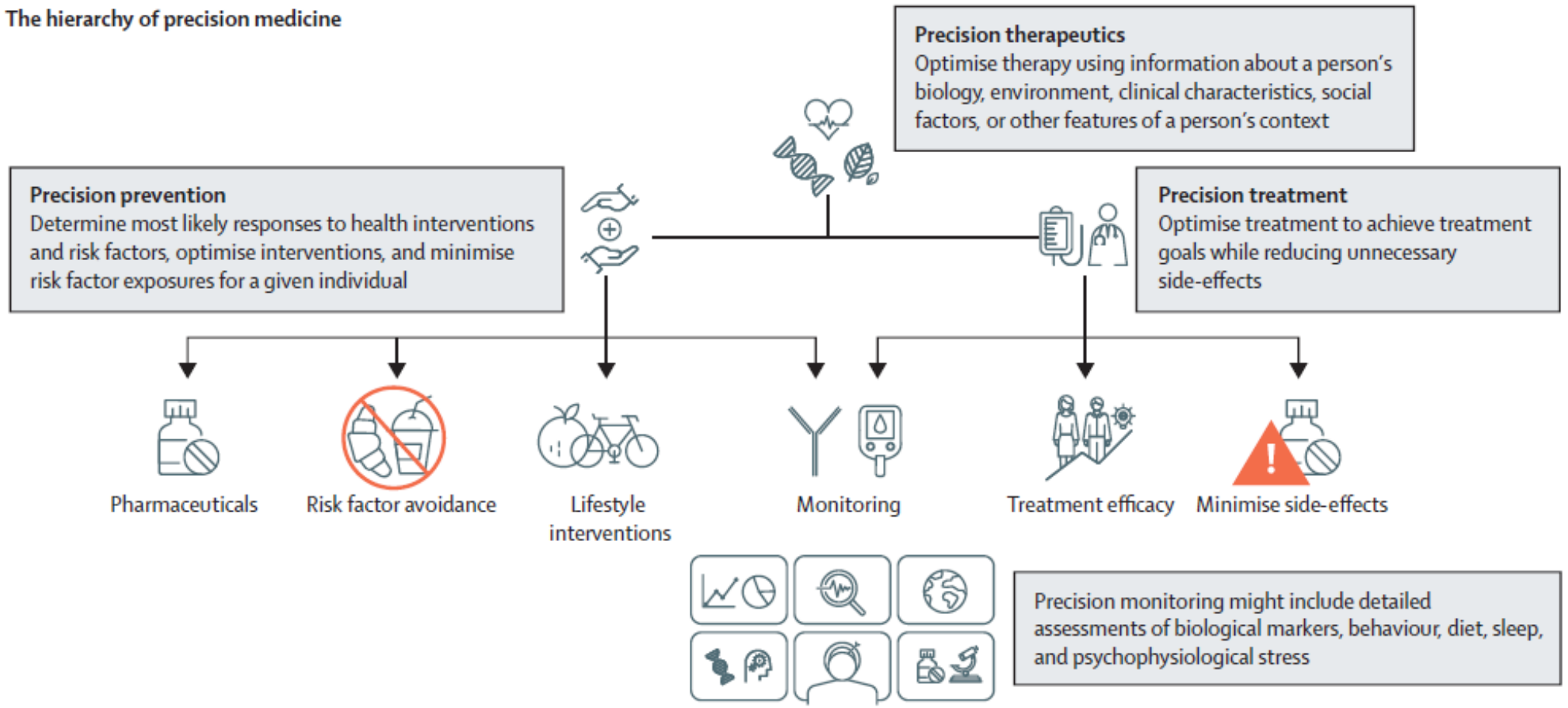
Refining the characterisation of cardiometabolic disease to optimise therapies or prognostication using information about a person's biology, environment, clinical characteristics, social factors, or other features of their context



A precision diagnosis is a probability-based decision, typically made at a specific point in the natural history of a disease, and neither an absolute truth, nor a permanent state

Diabetologia. 2020 Sep;63(9):1671-1693

Πρόληψη και θεραπεία

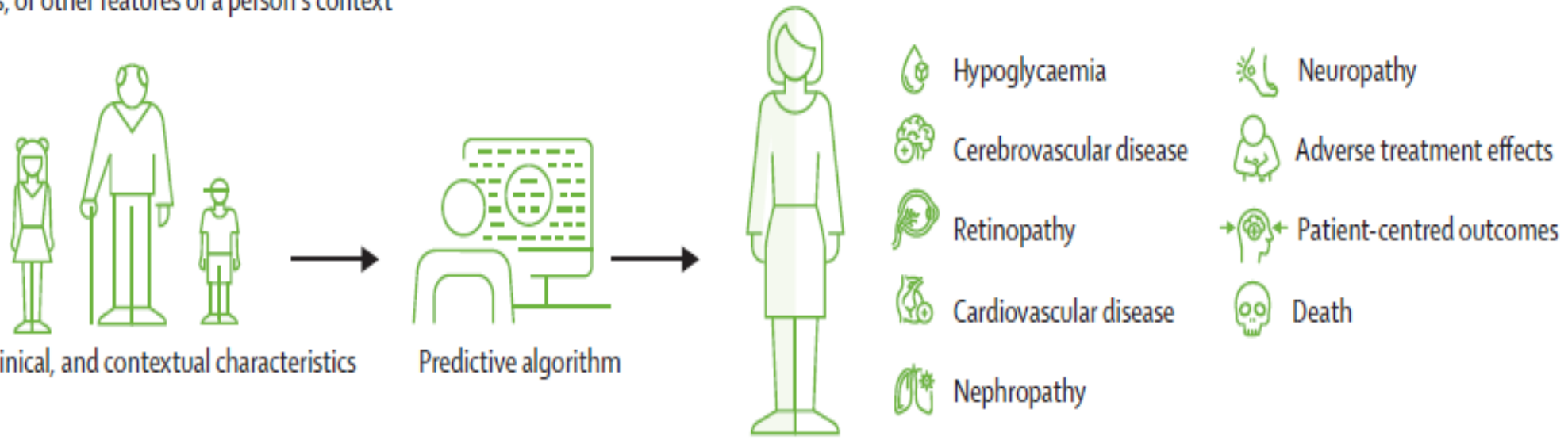


Diabetologia. 2020 Sep;63(9):1671-1693

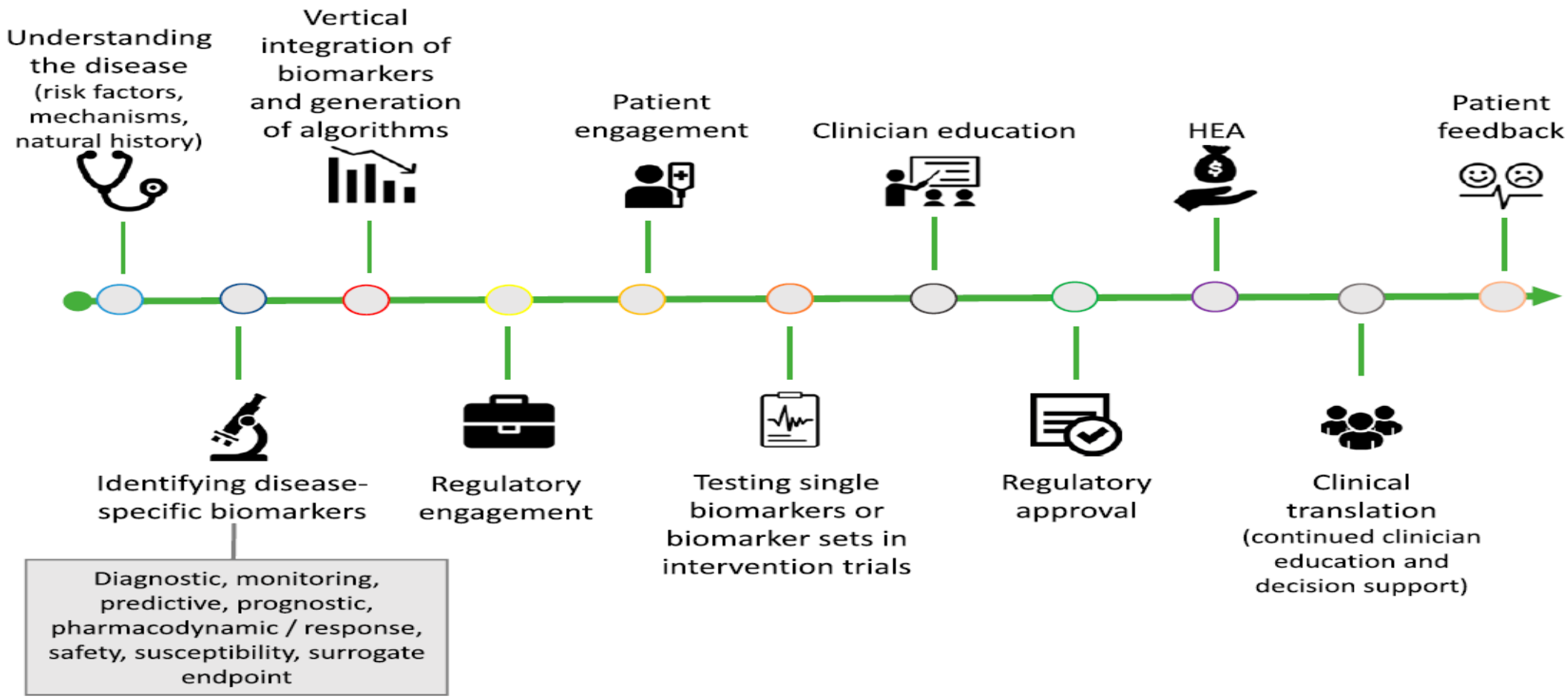
Πρόγνωση της νόσου

Precision prognostics

Improve the precision and accuracy with which a person's disease-related outcomes are predicted using information about their biology, environment, clinical characteristics, social factors, or other features of a person's context



Diabetologia. 2020 Sep;63(9):1671-1693



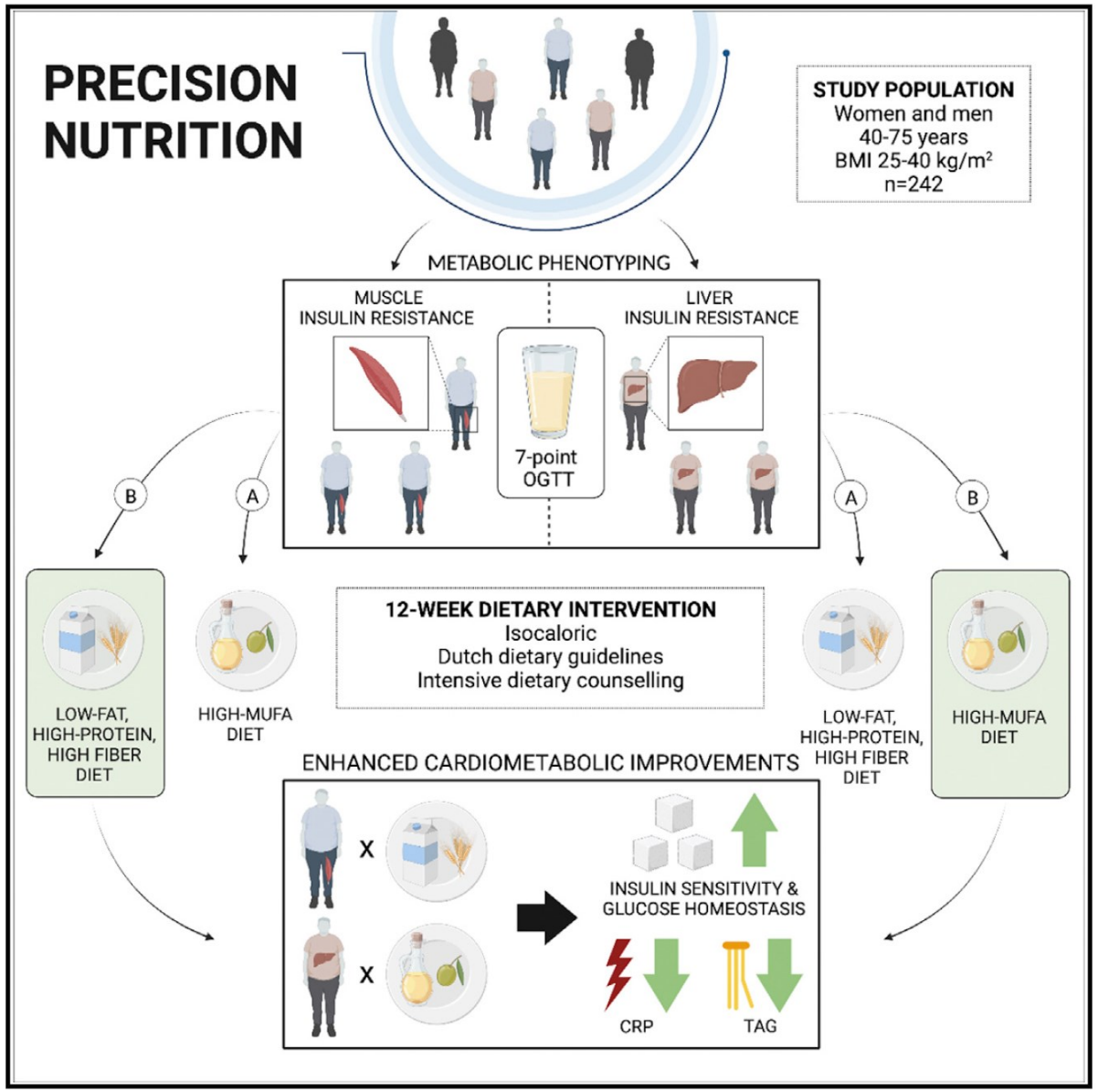
Diabetologia. 2020 Sep;63(9):1671-1693

Cell Metabolism Clinical and Translational Report

Cardiometabolic health improvements upon dietary intervention are driven by tissue-specific insulin resistance phenotype: A precision nutrition trial

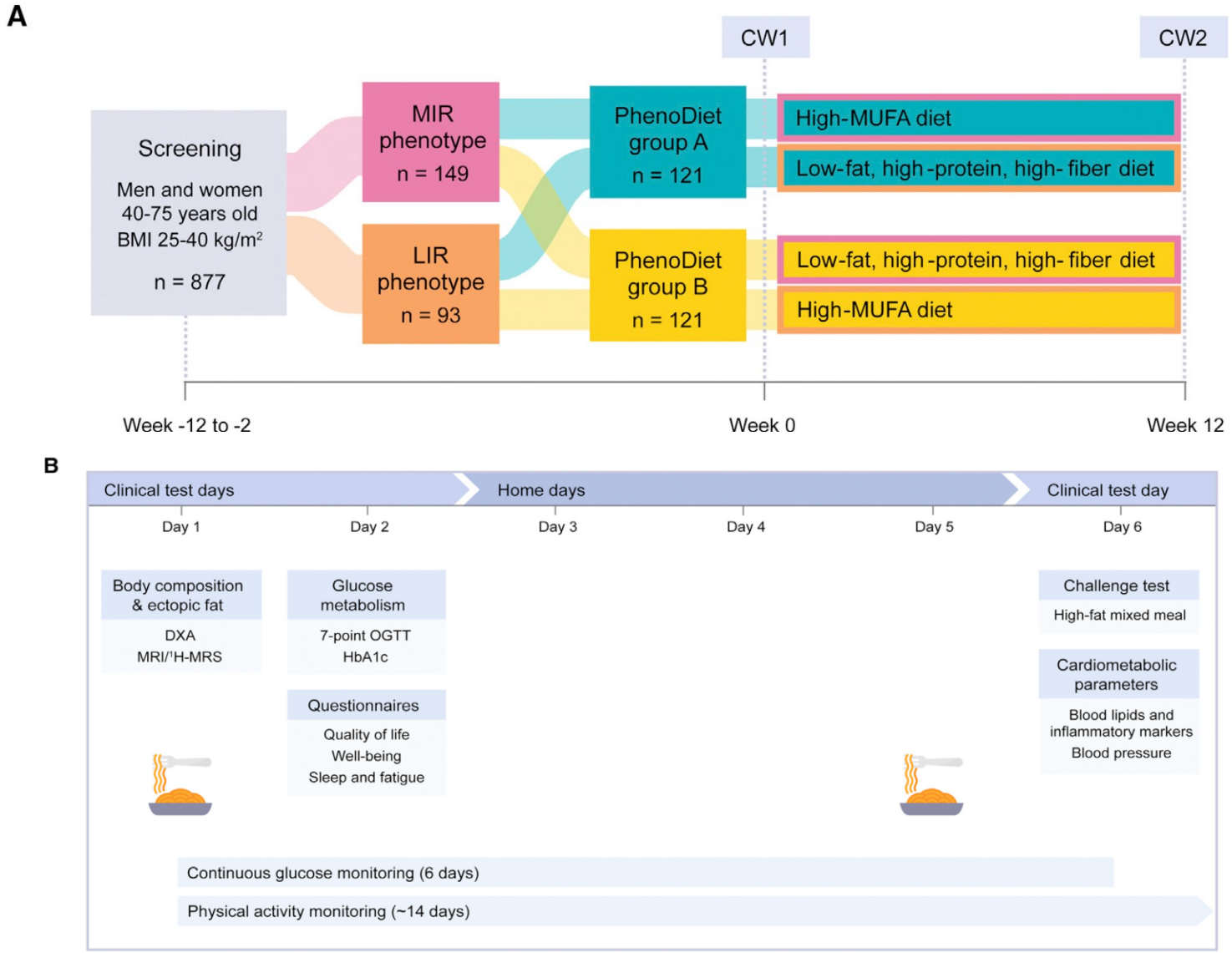
In brief

Trouwborst, Gijbels, and Jardon et al. included 242 adults with tissue-specific insulin resistance in a 12-week precision nutrition trial. Here, they demonstrate that modulation of macronutrient composition within the dietary guidelines based on tissue-specific insulin resistance phenotype enhances cardiometabolic health improvements.



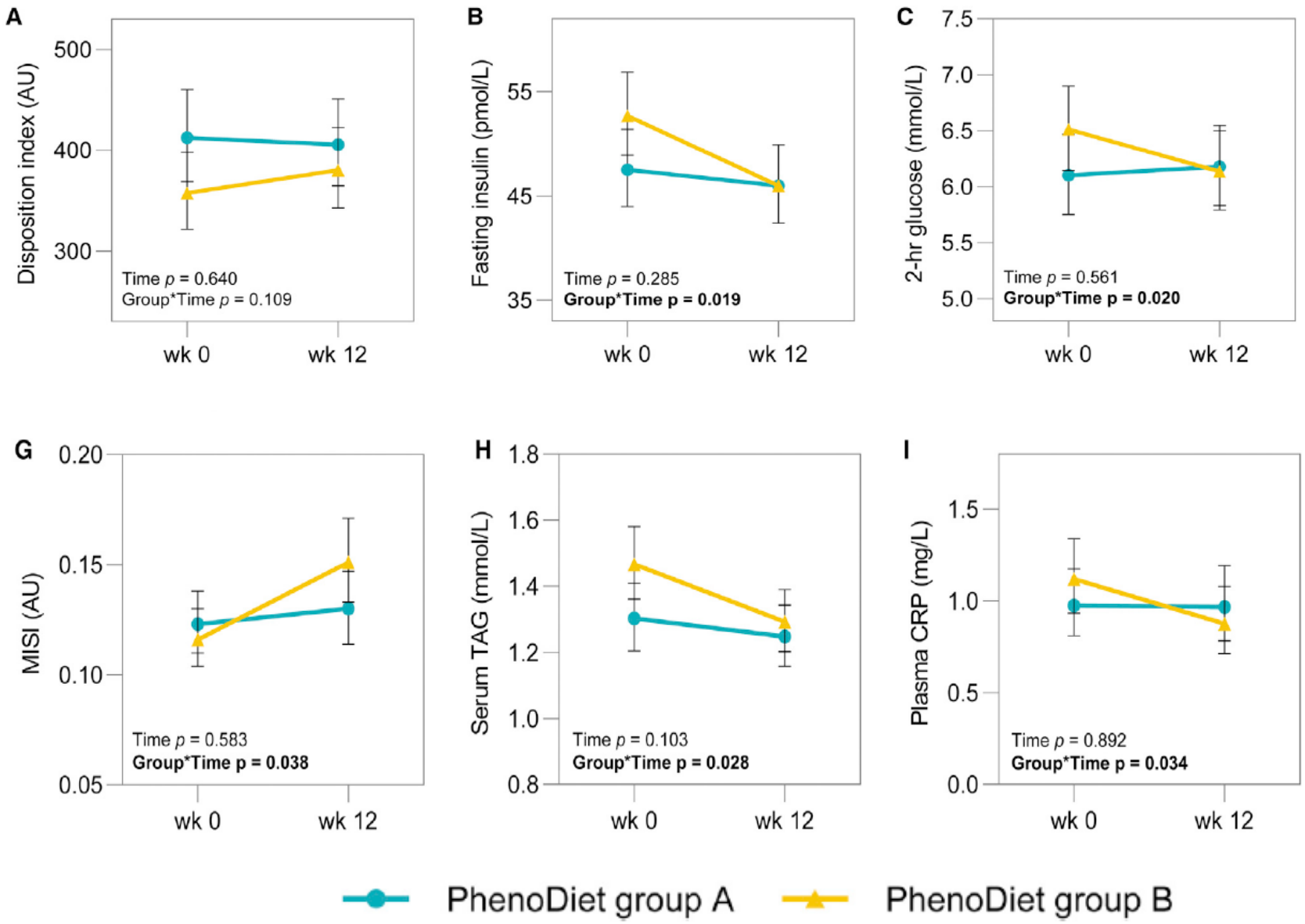
Cell Metab. 2023 Jan 3;35(1):71-83.e5

Study design of the PERSON study



Primary outcome: Disposition index - a composite measure of insulin sensitivity and insulin secretion

Cell Metab. 2023 Jan 3;35(1):71-83.e5



Μεγαλύτερη πρόοδος στην ινσουλινοευαισθησία, την ανοχή στην GLU, τα TAG νηστείας και τη CRP στην **PhenoDiet group B**

Genetic determinants of cardiometabolic risk: A proposed model for phenotype association and interaction

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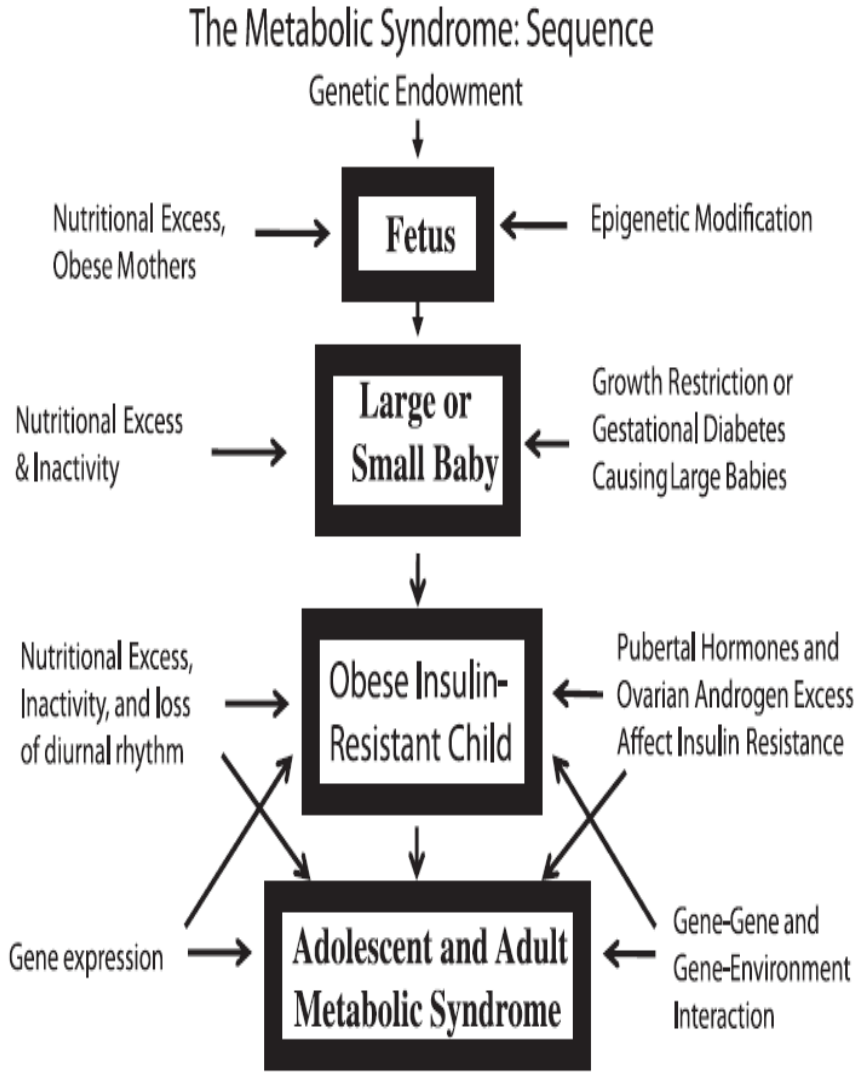
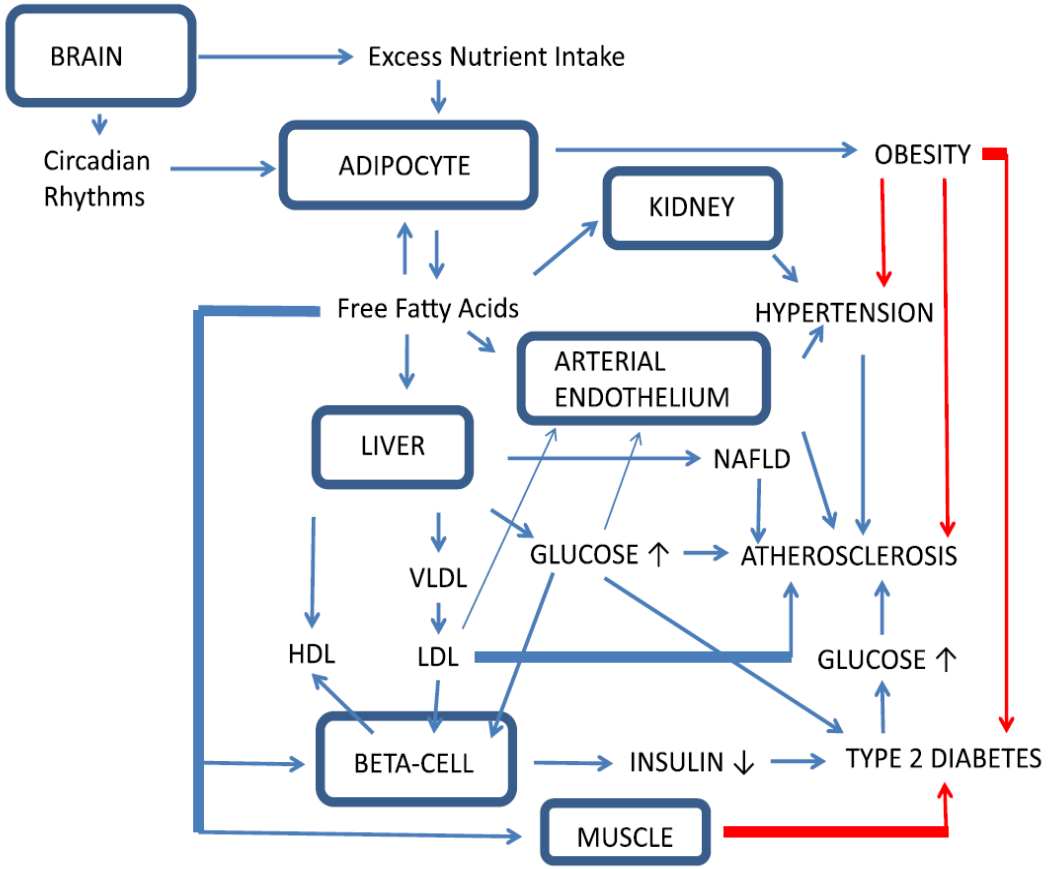
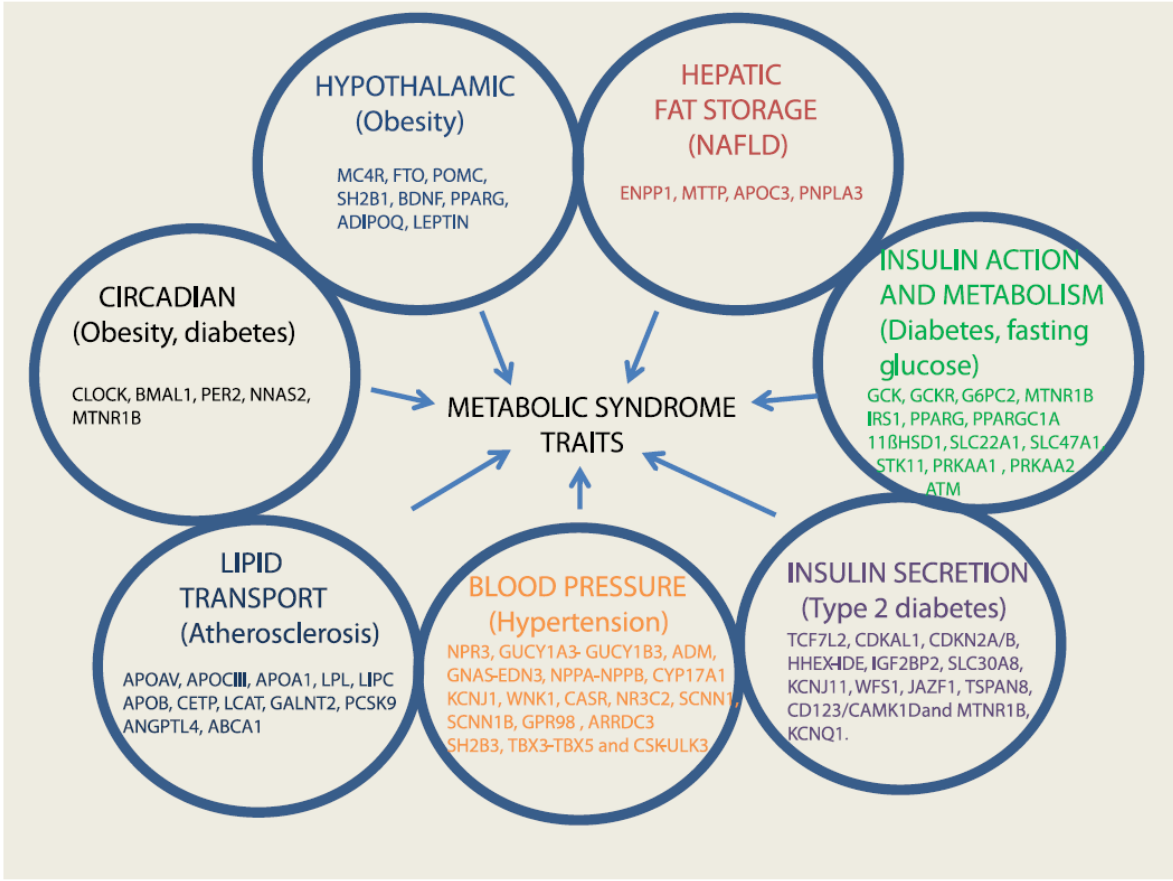
KEYWORDS:
Coronary artery disease;
Type 2 diabetes;
Metabolic syndrome;
Genes;
Environment

Abstract: This review provides a translational and unifying summary of metabolic syndrome genetics and highlights evidence that genetic studies are starting to unravel and untangle origins of the complex and challenging cluster of disease phenotypes. The associated genes effectively express in the brain, liver, kidney, arterial endothelium, adipocytes, myocytes, and β cells. Progression of syndrome traits has been associated with ectopic lipid accumulation in the arterial wall, visceral adipocytes, myocytes, and liver. Thus, it follows that the genetics of dyslipidemia, obesity, and nonalcoholic fatty liver disease are central in triggering progression of the syndrome to overt expression of disease traits and have become a key focus of interest for early detection and for designing prevention and treatments. To support the "birds' eye view" approach, we provide a road-map depicting commonality and interrelationships between the traits and their genetic and environmental determinants based on known risk factors, metabolic pathways, pharmacologic targets, treatment responses, gene networks, pleiotropy, and association with circadian rhythm. Although only a small portion of the known heritability is accounted for and there is insufficient support for clinical application of gene-based prediction models, there is direction and encouraging progress in a rapidly moving field that is beginning to show clinical relevance.



J Clin Lipidol. 2013 Jan-Feb;7(1):65-81





Αποτελέσματα ινσουλινοαντίστασης →

J Clin Lipidol. 2013 Jan-Feb;7(1):65-81

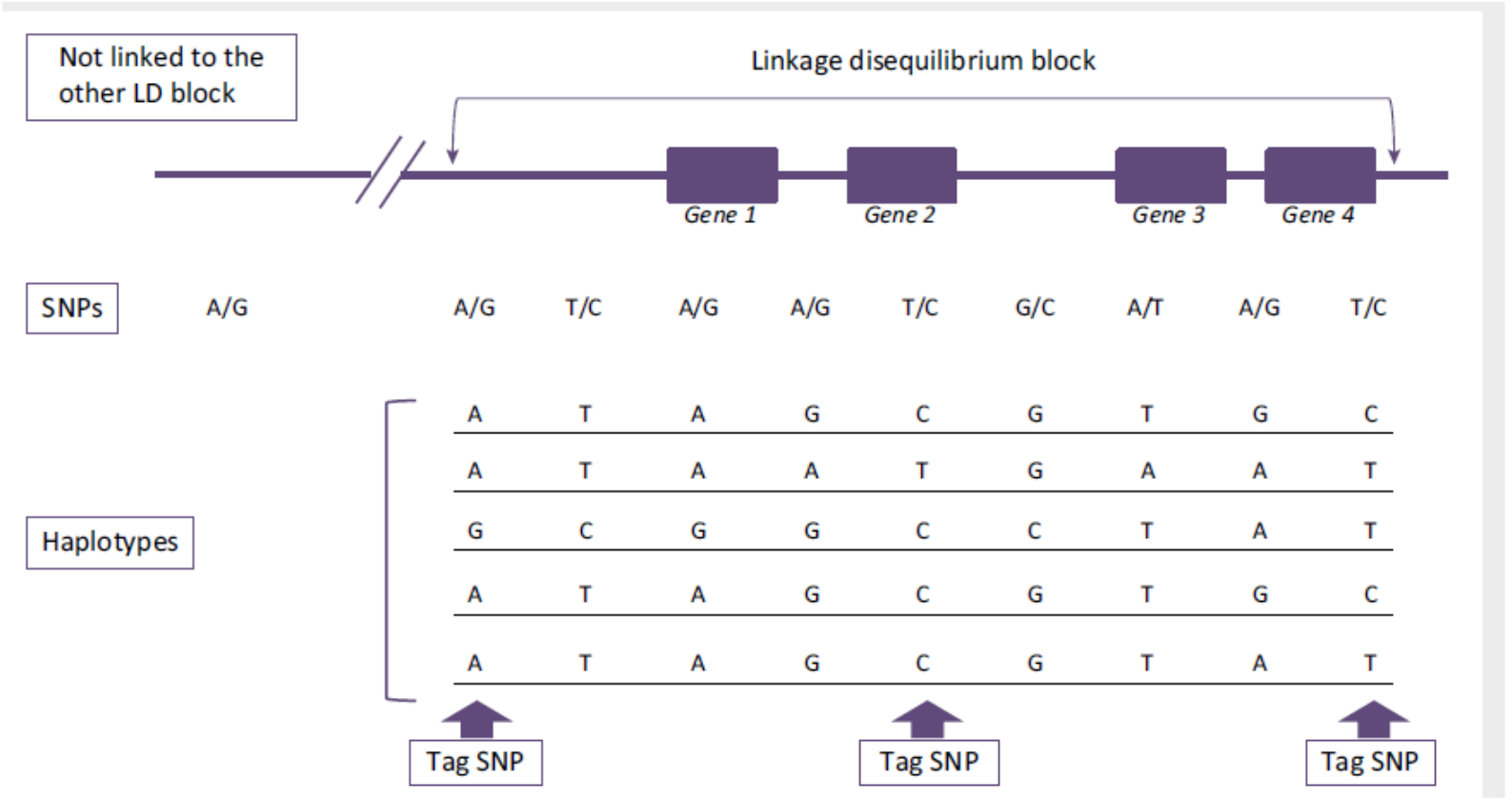
Special Issue: Systems Approach to Metabolic Disease

Review

GWAS as a Driver of Gene Discovery in Cardiometabolic Diseases

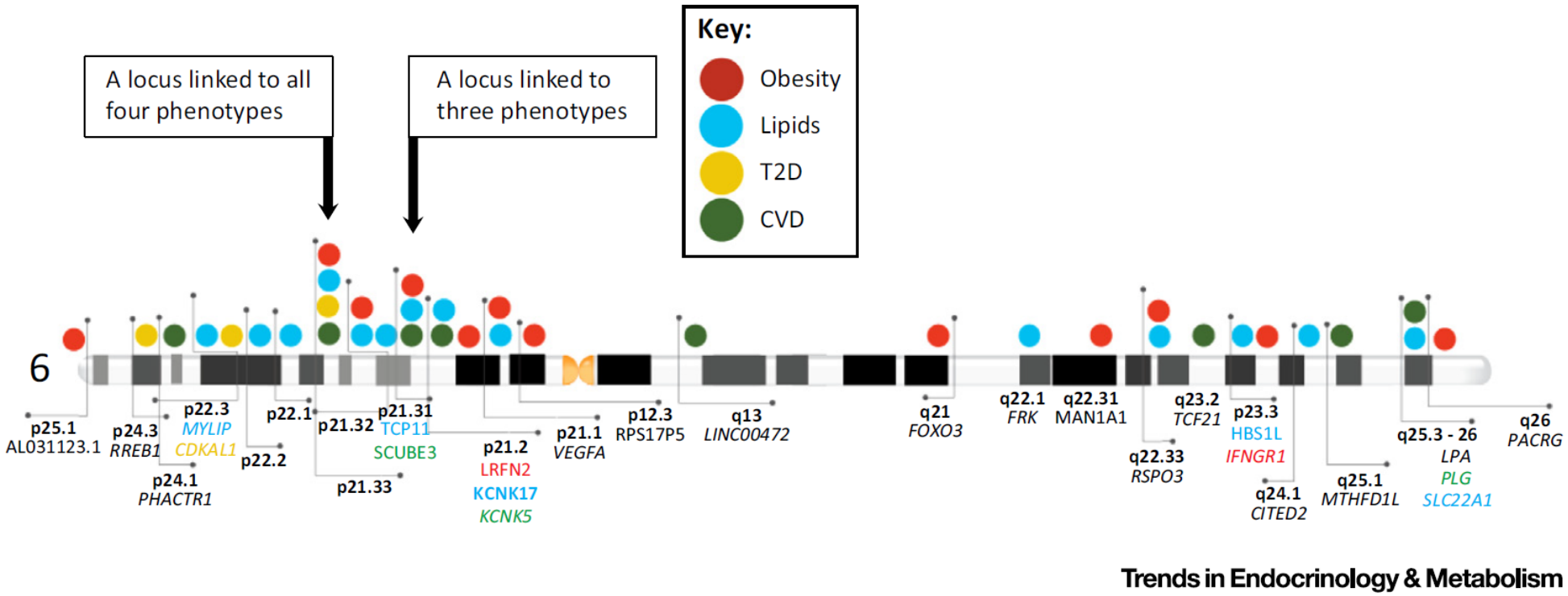
Cardiometabolic diseases represent a common complex disorder with a strong genetic component. Currently, genome-wide association studies (GWAS) have yielded some 755 single-nucleotide polymorphisms (SNPs) encompassing 366 independent loci that may help to decipher the molecular basis of cardiometabolic diseases. Going from a disease SNP to the underlying disease mechanisms is a huge challenge because the associated SNPs rarely disrupt protein function. Many disease SNPs are located in noncoding regions, and therefore attention is now focused on linking genetic SNP variation to effects on gene expression levels. By integrating genetic information with large-scale gene expression data, and with data from epigenetic roadmaps revealing gene regulatory regions, we expect to be able to identify candidate disease genes and the regulatory potential of disease SNPs.

Trends Endocrinol Metab. 2015 Dec;26(12):722-732



Linkage disequilibrium (**LD**) is a measure of non-random association between segments of DNA (alleles) at different positions on the chromosome (loci) in a given population based on a comparison between the frequency at which two alleles are detected together at the same loci versus the frequencies at which each allele is simply detected (alone or with the second allele) at that same loci. Loci are said to be in linkage disequilibrium when the frequency of being detected together (the frequency of association of their different alleles) is higher or lower than expected if the loci were independent and associated randomly

Trends Endocrinol Metab. 2015 Dec;26(12):722-732



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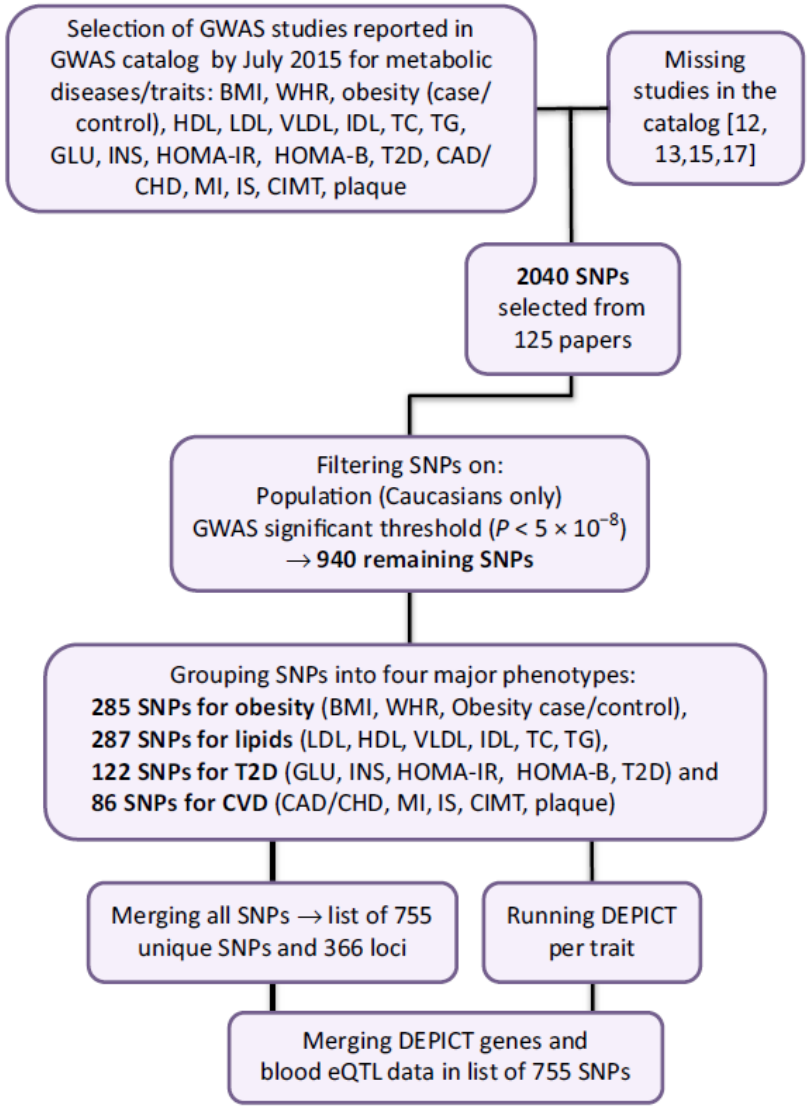

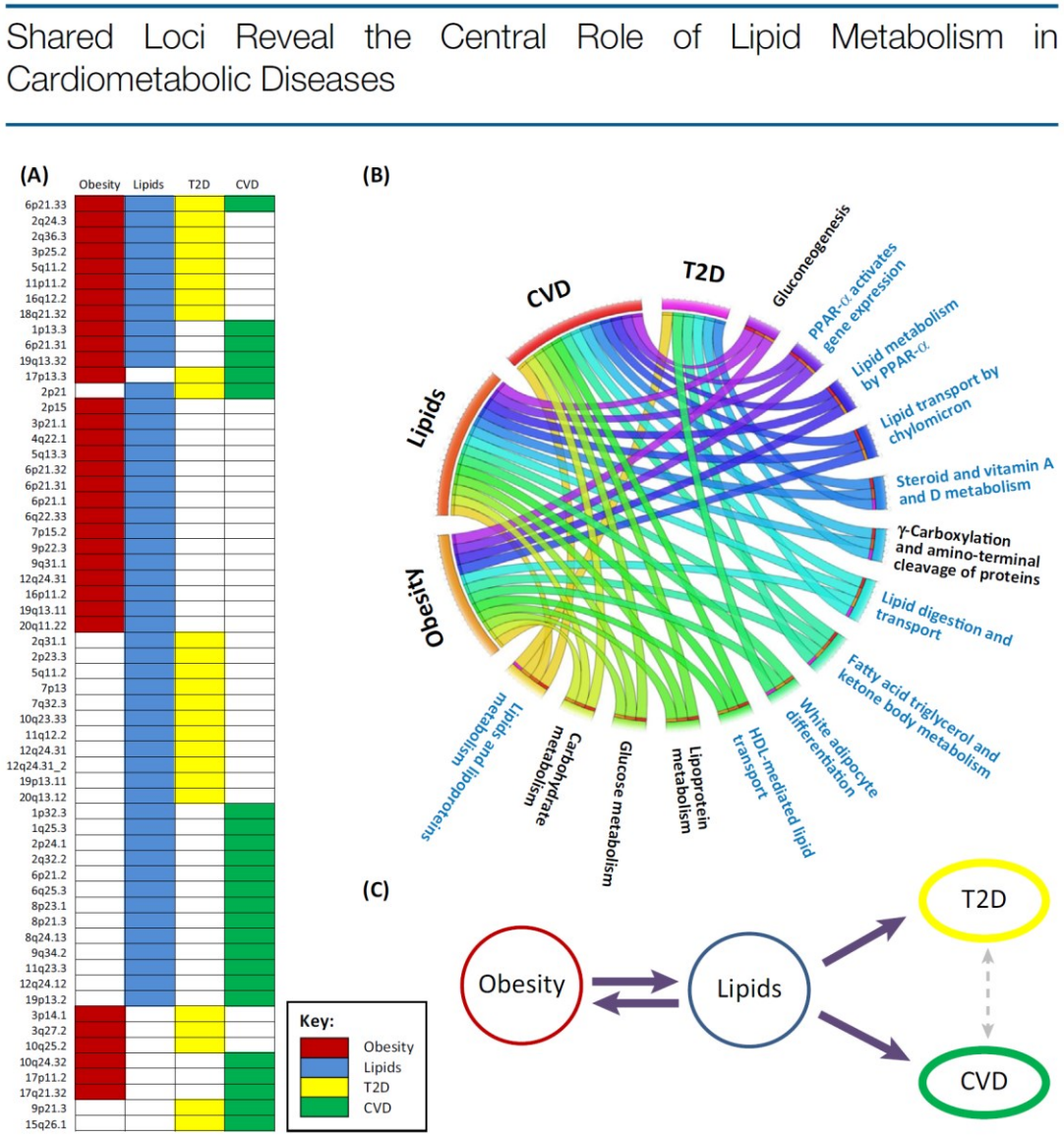

Trends Endocrinol Metab. 2015 Dec;26(12):722-732

ESC European Society of Cardiology

European Heart Journal (2023) **44**, 89–99
https://doi.org/10.1093/eurheartj/ehac648

STATE OF THE ART REVIEW

Genetics

Polygenic risk scores for the prediction of cardiometabolic disease

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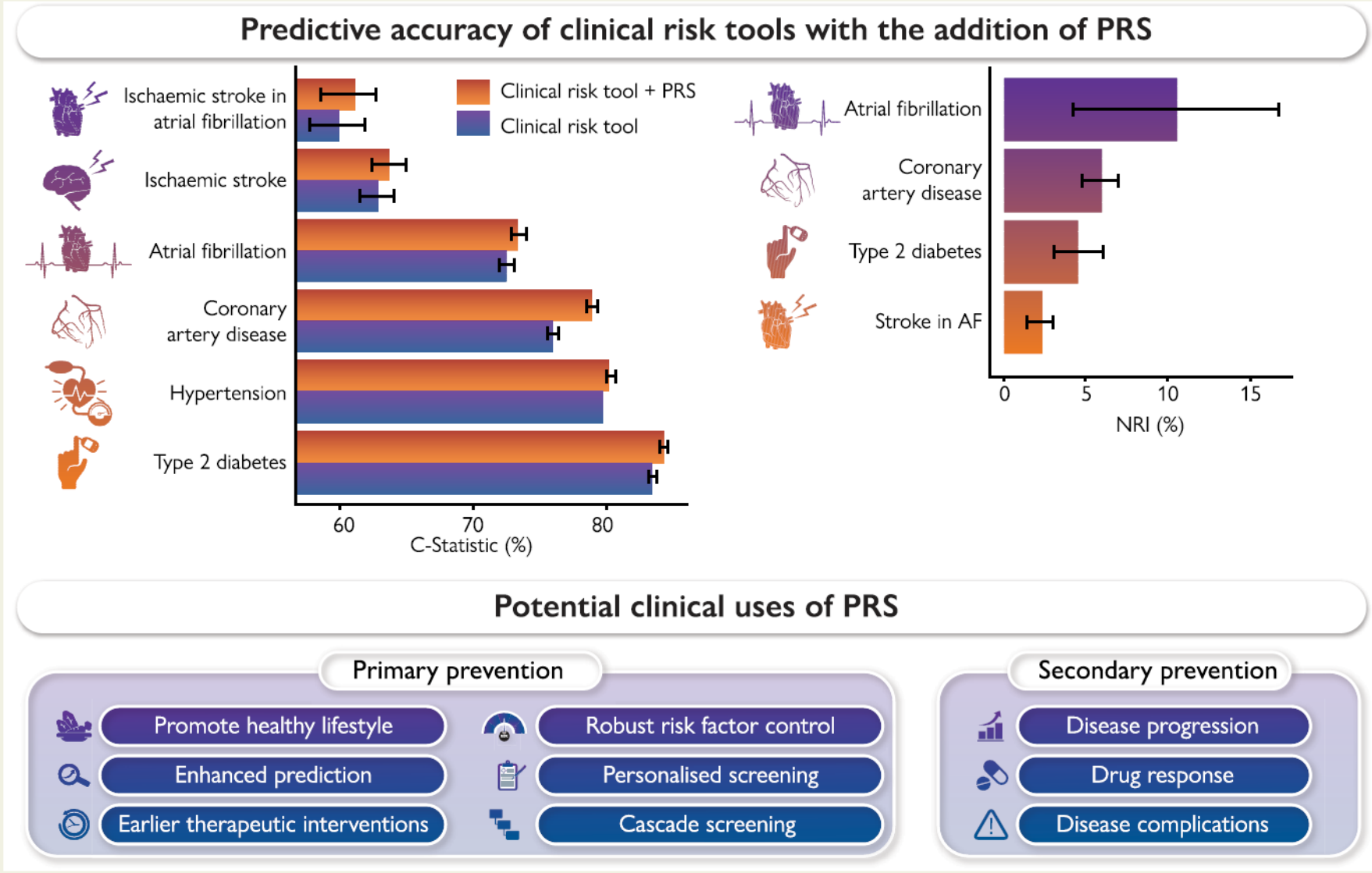
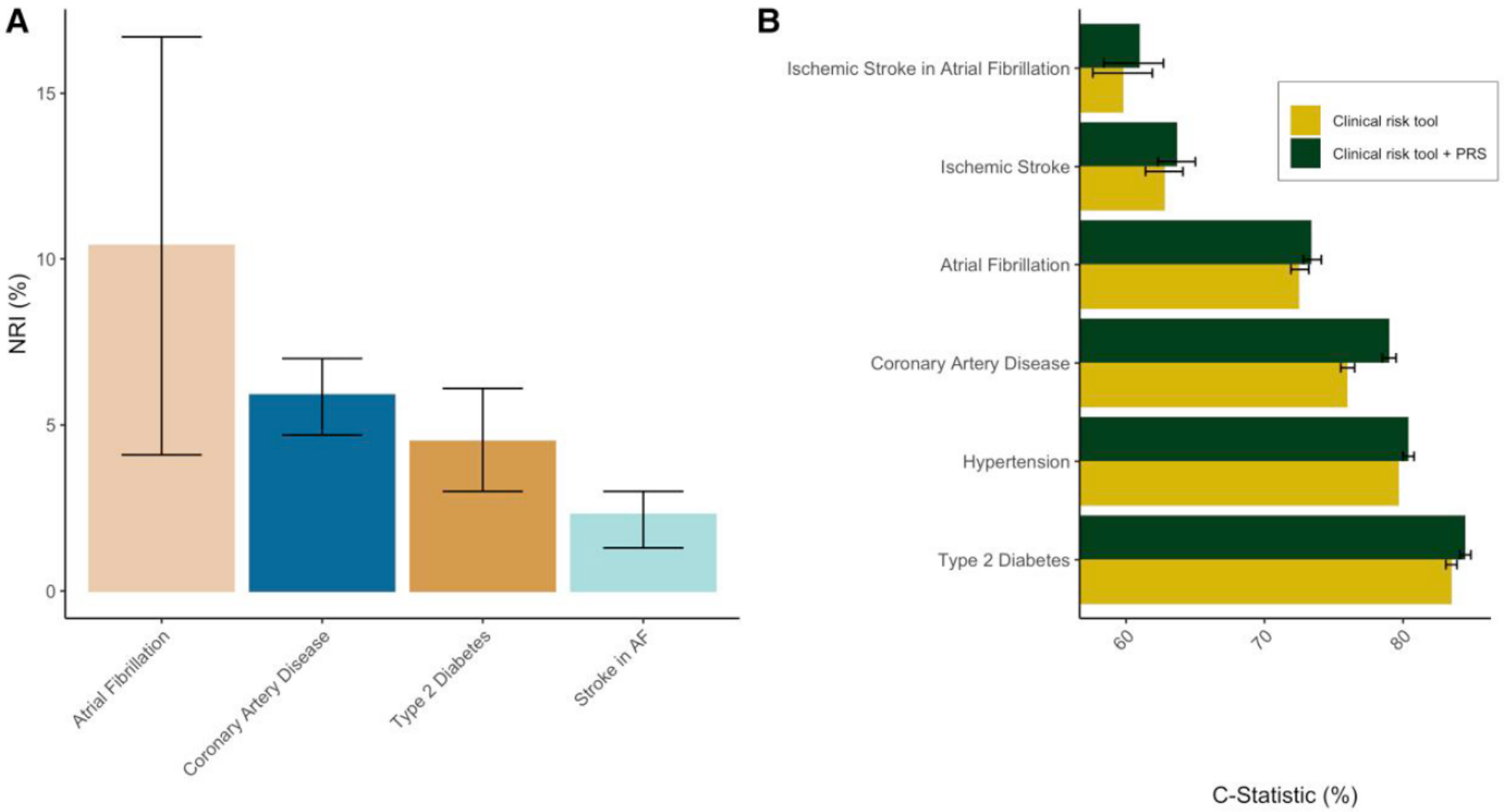
Received 8 December 2021; revised 28 August 2022; accepted 27 October 2022; online publish-ahead-of-print 7 December 2022

Graphical Abstract



Eur Heart J. 2023 Jan 7;44(2):89-99



Eur Heart J. 2023 Jan 7;44(2):89-99

Table 2 **Potential clinical utility of cardiometabolic PRS**

Primary prevention	Promote a healthy lifestyle	Communicating a patient's risk may promote a healthier diet and increased exercise, although data examining this are mixed.
	Enhanced prediction	For a number of cardiometabolic diseases, the addition of PRS enhances the prediction of classification.
	Earlier therapeutic interventions	Patients at high risk may benefit from early interventions, such as those at high risk of CAD.
	Robust risk factor control	Many cardiometabolic diseases are risk factors for other cardiometabolic diseases, such as hypertension for coronary artery disease. Identification of those at high risk could facilitate more robust risk factor control, e.g. lower blood pressure target for those at high risk of CAD.
	Personalized screening	Those at higher PRS may benefit from earlier routine screening to facilitate earlier intervention, such as regular HbA1c screening. Although long-term data is required.
	Cascade screening	For patients who have a PRS that is similar to that inferred by monogenic risk. This may mean families may benefit from screening, as is recommended for monogenic diseases
Secondary prevention	Drug response	For some cardiometabolic diseases, there is an array of medication options. PRS may indicate which medication or which combination of medicines is most beneficial.
	Disease progression	At diagnosis, the trajectory of disease is largely unknown, PRS could indicate which participants will develop mild or severe disease.
	Disease complications	Prediction of complications from cardiometabolic conditions, such as ischaemic stroke in patients with atrial fibrillation.

Eur Heart J. 2023 Jan 7;44(2):89-99

The relationship of genetic risk score with cardiometabolic risk factors: a cross-sectional study

Fatemeh Gholami[1], Niloufar Rasaei[1], Mahsa Samadi[1], Mir Saeid Yekaninejad[2], Seyed Ali Keshavarz[3], Gholamali Javdan[4], Zahra Karimi[2] and Khadijeh Mirzaei[1,5*]

Abstract

Background & aims For more than eight decades, cardiovascular disease (CVD) has remained the leading cause of death in the world. CVD risk factors are multifaceted, with genetics and lifestyle both playing a role. The aim of this study was to investigate the association between a genetic profile risk score for obesity GRS and cardio-metabolic risk factors in overweight and obese women.

Methods The current cross-sectional study was conducted on 391 overweight and obese women. The genetic risk score was created by combining three single nucleotide polymorphisms [MC4R (rs17782313), CAV-1 (rs3807992), and Cry-1 (rs2287161)]. Anthropometric measurements, blood pressure, and some blood parameters were measured by standard protocols.

Results A significant association between the GRS and some of cardiometabolic risk factors variables such as body mass index (β = 0. 49, 95%CI = 0.22 to 0.76, p < 0.001), waist circumference (β = 0. 86, 95%CI = 0.18 to 1.54, p = 0.01), body fat mass (β = 0. 82, 95%CI = 0.25 to 1.39, p = 0.005), %body fat (β = 0. 44, 95%CI = 0.06 to 0.82, p = 0.02), and hs-CRP (β = 0.46, 95% CI = 0.14 to 0.78, p = 0.005) was observed in crude model. After adjustment for confounding factors (age, BMI, and physical activity), a significant positive association was observed between BMI (p = 0.004), WC (p = 0.02), body fat mass (p = 0.01), %BF (p = 0.01), hs-CRP (p = 0.009), and GRS. In addition, we discovered a significant negative association between the GRS and BMC (= -0.02, 95%CI = -0.05 to -0.001, p = 0.04). But other variables did not show any significant association with GRS among obese and overweight women.

Conclusion We found a significant positive association between GRS, including MC4R (rs17782313), CAV-1 (rs3807992), and Cry-1 (rs2287161) and cardiometabolic risk factors among overweight and obese Iranian women.

Keywords Cardiometabolic risk factors, Genetic risk score, Obesity

Table 3 Association of GRS on cardiometabolic risk factors among obese and overweight female subjects

Variables	GRS						
	Crude			Model1			
	B	95 CI	P-value	B	95 CI	P-value	R2
BMI (Kg/m^2)	0.49	0.22 to 0.76	**<0.001**	0.42	0.13 to 0.71	**0.004**	
Body composition							
WC (cm)	0.86	0.18 to 1.54	**0.01**	0.81	0.08 to 1.53	**0.02**[a]	0.01
WHR (ratio)	0.12	-0.20 to 0.45	0.46	0.004	0.00 to 0.008	**0.07**[a]	0.01
BFM (kg)	0.82	0.25 to 1.39	**0.005**	0.79	0.19 to 1.39	**0.01**[a]	0.01
BF (%)	0.44	0.06 to 0.82	**0.02**	0.49	0.08 to 0.89	**0.01**[a]	0.01
BMR (kcal)	-1.49	-10.95 to 7.96	0.75	-4.66	-14.99 to 5.66	0.37 [a]	0.006
BMC (g)	-0.02	-0.44 to 0.005	0.12	-0.02	-0.05 to -0.001	**0.04**[a]	0.02
SMM (kg)	-0.01	-0.25 to 0.23	0.92	-0.09	-0.35 to 0.16	0.46 [a]	0.08
Blood pressure							
SBP (mmHg)	0.62	-1.20 to 2.44	0.50	-0.21	-2.10 to 1.67	0.82	0.081
DBP (mmHg)	0.20	-1.09 to 1.50	0.75	-0.47	-1.81 to 0.86	0.48	0.071
Blood parameters							
FBS (mg/Dl)	0.54	-0.85 to 1.95	0.44	0.26	-1.13 to 1.66	0.71	0.10
Total cholesterol (g/dl)	-3.63	-8.74 to 1.47	0.16	-3.78	-9.09 to 1.53	0.16	0.09
TG (mg/dl)	2.28	-7.68 to 12.25	0.65	1.12	-9.65 to 11.90	0.83	0.07
HDL (mg/dl)	-1.13	-2.66 to 0.40	0.14	-0.42	-2.05 to 1.21	0.61	0.008
LDL (mg/dl)	-2.5	-5.95 to 0.92	0.15	-2.24	-5.81 to 1.31	0.21	0.084
hs-CRP (mg/L)	0.46	0.14 to 0.78	**0.005**	0.44	0.11 to 0.78	**0.009**	0.15
HOMA index	0.04	-0.13 to 0.23	0.61	-0.03	-0.22 to 0.16	0.76	0.10
Insulin (mIU/ ml)	0.01	-0.01 to 0.05	0.33	0.01	-0.02 to 0.04	0.45	0.07
MCP-1 (ng/ml)	0.43	-8.21 to 9.07	0.92	0.91	-8.00 to 9.83	0.84	0.009
Galectin3 (ng/ml)	0.09	-0.93 to 1.12	0.85	0.04	-1.17 to 1.26	0.93	0.03
PAI-1 (ng/ml)	-0.68	-3.80 to 2.43	0.66	-2.13	-5.41 to 1.15	0.20	0.06

SD: Standard deviation; R2: R-squared; GRS: Genetic risk score; BMI: Body mass index; WC: waist circumference; WHR: waist height ratio; BFM: body fat mass; BF: body fat; BMR: Basal metabolic rate; BMC: bone mineral content; SMM: skeletal muscle mass; SBP: Systolic blood pressure; DBP: Diastolic Blood Pressure; FBS: fasting blood sugar; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; hs-CRP: High-sensitivity C-reactive protein; MCP-1: monocyte chemoattractant protein; PAI-1: Plasminogen Activator Inhibitor 1

† Calculated by linear regression

Model1: Adjusted for age, BMI, physical activity, and energy intake

a BMI considered as collinear and this variable adjusted for age, physical activity, and smoking

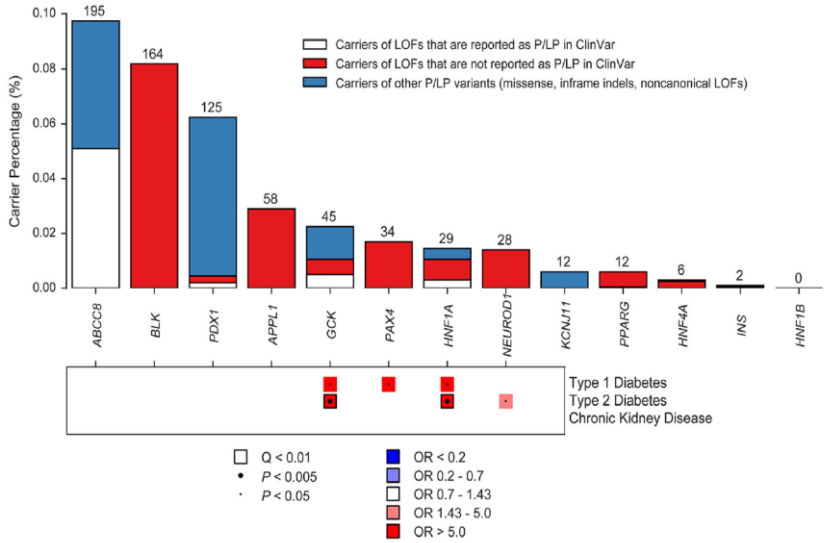
Θετική συσχέτιση με Περίμετρο μέσης, Αναλογία μέσης γοφών, Σωματικού λίπους (Απόλυτος αριθμός-Ποσοστιαία αναλογία) και Υψηλής ευαισθησίας CRP

Αρνητική συσχέτιση με Περιεκτικότητα του οστού σε άλατα

Published in final edited form as:

Nat Genet. 2022 March ; 54(3): 240–250. doi:10.1038/s41588-021-01011-w.

Analysis of rare genetic variation underlying cardiometabolic diseases and traits among 200,000 individuals in the UK Biobank



Showed that a PRS had greater predictive accuracy than any clinical risk factor: PRS C-statistic: 0.623 (95% CI 0.615–0.631), compared with a range of ~0.550 to 0.594 for clinical risk factors [smoking, T2DM, self-reported family history of heart disease, body mass index (BMI), hypertension, high cholesterol].

Nat Genet. 2022 Mar;54(3):240-250

Metabolic health and cardiometabolic risk clusters: implications for prediction, prevention, and treatment

Norbert Stefan, Matthias B Schulze

Among 20 leading global risk factors for years of life lost in 2040, reference forecasts point to three metabolic risks—high blood pressure, high BMI, and high fasting plasma glucose—as being the top risk variables. Building upon these and other risk factors, the concept of metabolic health is attracting much attention in the scientific community. It focuses on the aggregation of important risk factors, which allows the identification of subphenotypes, such as people with metabolically unhealthy normal weight or metabolically healthy obesity, who strongly differ in their risk of cardiometabolic diseases. Since 2018, studies that used anthropometrics, metabolic characteristics, and genetics in the setting of cluster analyses proposed novel metabolic subphenotypes among patients at high risk (eg, those with diabetes). The crucial point now is whether these subphenotyping strategies are superior to established cardiometabolic risk stratification methods regarding the prediction, prevention, and treatment of cardiometabolic diseases. In this Review, we carefully address this point and conclude, firstly, regarding cardiometabolic risk stratification, in the general population both the concept of metabolic health and the cluster approaches are not superior to established risk prediction models. However, both subphenotyping approaches might be informative to improve the prediction of cardiometabolic risk in subgroups of individuals, such as those in different BMI categories or people with diabetes. Secondly, the applicability of the concepts by treating physicians and communication of the cardiometabolic risk with patients is easiest using the concept of metabolic health. Finally, the approaches to identify cardiometabolic risk clusters in particular have provided some evidence that they could be used to allocate individuals to specific pathophysiological risk groups, but whether this allocation is helpful for prevention and treatment still needs to be determined.

Lancet Diabetes Endocrinol. 2023 Jun;11(6):426-440

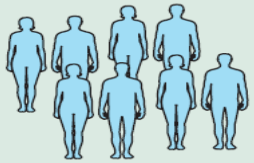
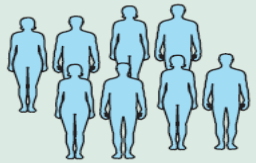
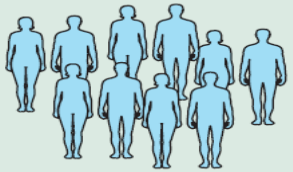
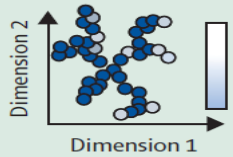
Risk stratification	Metabolic health	Diabetes clusters	Genetic-based clusters in type 2 diabetes	Clusters with elevated type 2 diabetes risk	Tree method in type 2 diabetes
Parameters	Blood pressure, triglycerides HDL-cholesterol, glycaemia insulin resistance, waist-to-hip ratio (fatty liver)	GAD autoantibodies, HbA_{1c}, BMI, age at diagnosis, HOMA2-B, HOMA2-IR	94 independent type 2 diabetes genetic variants and 47 diabetes-related traits	Insulin sensitivity, insulin-secretion index using insulin and glucose concentrations at fasting and at 120 min during OGTT, fasting insulin, fasting triglycerides, waist circumference, hip circumference, BMI and HDL-cholesterol	HbA_{1c}, BMI, total cholesterol, HDL-cholesterol, triglycerides, alanine aminotransferase, creatinine, and systolic and diastolic blood pressure
Phenotype	 Normal weight Overweight Obesity Either metabolically healthy or metabolically unhealthy	 SAID SIDD SIRD MOD MARD	 Impaired IS and high PI Impaired IS and low PI IR and obesity IR and lipodystrophy IR and impaired liver, or lipid metabolism	 Very low risk Low risk Impaired IS IR Fatty liver Visceral obesity	
Application	Risk prediction ++ Risk communication ++ Pathomechanisms - Treatment +	Risk prediction + Risk communication ++ Pathomechanisms + Treatment +	Risk prediction ? Risk communication - Pathomechanisms ++ Treatment ?	Risk prediction + Risk communication + Pathomechanisms + Treatment ?	Risk prediction + Risk communication - Pathomechanisms + Treatment +

Figure 4: **Metabolic health and selected data-driven cluster approaches for cardiometabolic risk stratification**
Depicted are the concept of metabolic health and four cluster approaches that were proposed for cardiometabolic risk stratification in patients at risk of diabetes or with diagnosed diabetes. Metabolic health is defined by the most widely used methods,[11,13,14] diabetes clusters have been proposed by Ahlqvist and colleagues,[60] genetic-based clusters in type 2 diabetes have been proposed by Udler and colleagues,[62] clusters with elevated type 2 diabetes risk have been proposed by Wagner and colleagues,[66] and the two dimensional tree in type 2 diabetes has been proposed by Nair and colleagues.[64] Displayed are the variables that were used for risk stratification, the phenotypes or clusters that resulted from the methodological approach, and a summary about the possible application of these risk stratification approaches. ++=well supported. +=supported. -=not supported. ?=unknown. HOMA2-B=homeostasis model assessment of β-cell function. HOMA2-IR=homeostasis model assessment of insulin resistance. IR=insulin resistance. IS=insulin sensitivity. MARD=mild age-related diabetes. MOD=mild obesity-related diabetes. OGTT=oral glucose tolerance test. PI=proinsulin. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes.

JIM Review

doi: 10.1111/joim.12859

Precision medicine in type 2 diabetes

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From the [1]Genomics, Diabetes and Endocrinology, Department of Clinical Sciences, Clinical Research Centre, Lund University, Malmö, Sweden; and [2]Finnish Institute of Molecular Medicine (FIMM), Helsinki University, Helsinki, Finland

Abstract. Prasad RB, Groop L (Lund University, Malmö, Sweden; Finnish Institute of Molecular Medicine (FIMM), Helsinki University, Helsinki, Finland). Precision medicine in type 2 diabetes (Review). *J Intern Med* 2019; **285**: 40–48.

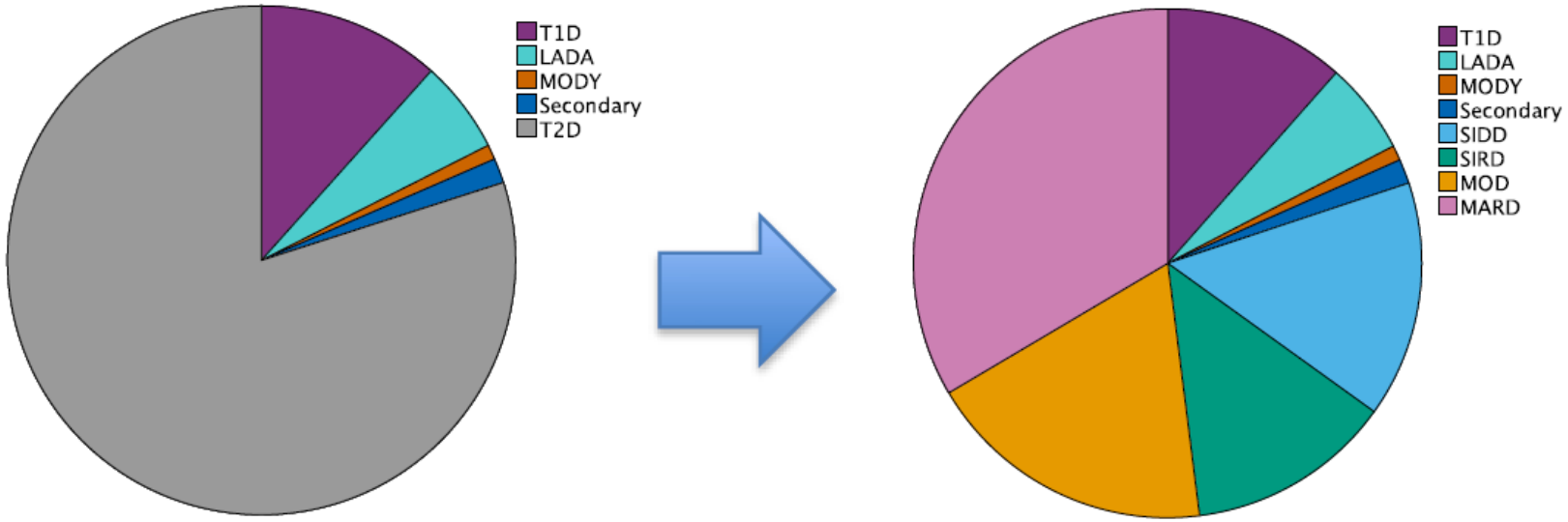
The Precision Medicine Initiative defines precision medicine as 'an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person'. This approach will facilitate more accurate treatment and prevention strategies in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for generalized usage. Diabetes is clearly more heterogeneous than the conventional subclassification into type 1 and type 2 diabetes. Monogenic forms of diabetes like MODY and neonatal diabetes have paved the way for precision medicine in diabetes, as carriers of unique mutations require unique treatment. Diagnosis of diabetes in the past has been dependent upon measuring one metabolite, glucose. By instead including six variables in a clustering analysis, we could break down diabetes into five distinct subgroups, with better prediction of disease progression and outcome. The severe insulin-resistant diabetes (SIRD) cluster showed the highest risk of kidney disease and highest prevalence of nonalcoholic fatty liver disease, whereas patients in the insulin-deficient cluster 2 (SIDD) had the highest risk of retinopathy. In the future, this will certainly be improved and expanded by including genetic, epigenetic and other biomarker to allow better prediction of outcome and choice of more precise treatment.

Keywords: diabetes.

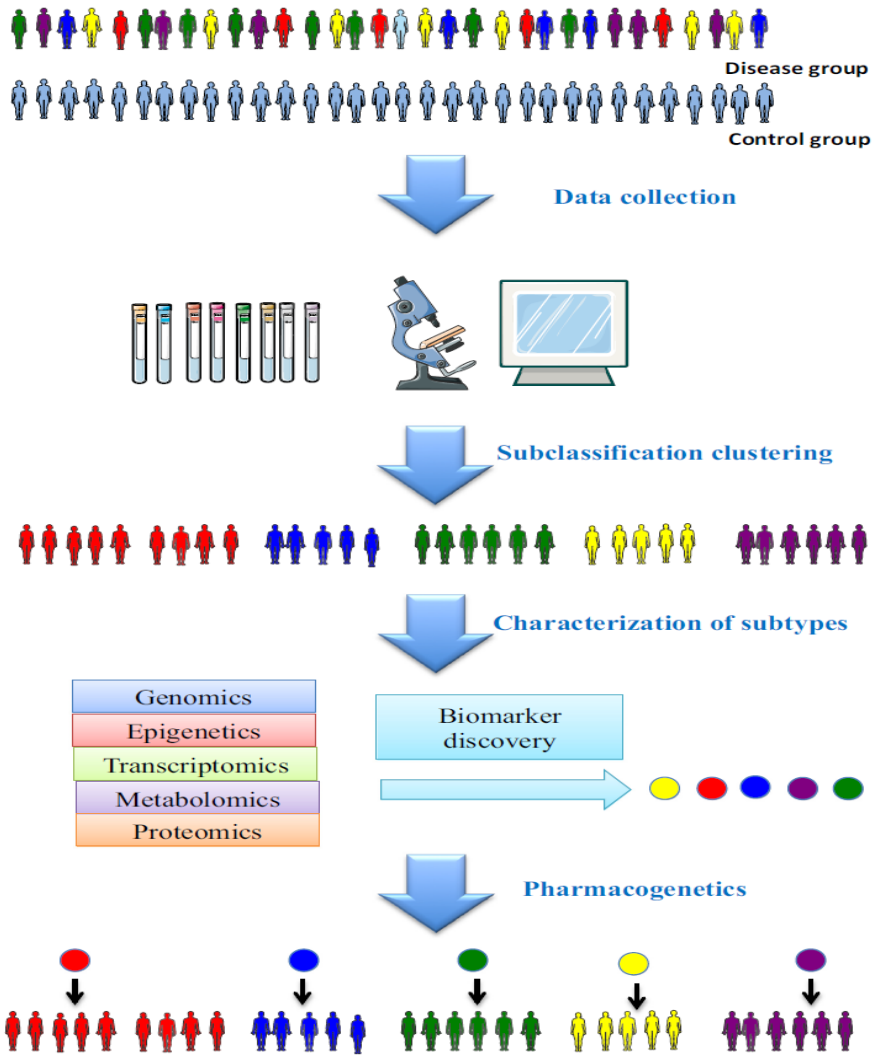
Table 1 *Diabetes clusters, characteristics and outcomes*

	Cluster/ characteristics	SAID	SIDD	SIRD	MOD	MARD
Phenotypic characteristics	HbA1c	High	High	Moderate	Moderate	Moderate
	Age at onset	Early	Early	Late	Late	Latest
	BMI	Low	Low	High	High (obese)	High
	GADA	+(by definition)	-	-	-	-
	ZnT8A autoantibodies	+(common)	-	-	-	-
	Insulin deficiency	++	++	+-	+ -	+ -
	Insulin resistance	+	+	+++	+	+
	Ketoacidosis at diagnosis	Frequent	Frequent			
Complications	Complications	Little risk of early development of complications	High risk of retinopathy	High risk of diabetic kidney disease Highest prevalence of nonalcoholic fatty liver disease	Little risk of complications	Little risk of complications
Treatment	Insulin	42% Need insulin	29% Mistreated by metformin, need often insulin	<4% Need treatment which enhances insulin sensitivity	<4% Lifestyle, metformin	<4% Lifestyle, metformin

GADA, glutamic acid decarboxylase autoantibodies; MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes; ZnT8A antibodies, zinc transporter 8 autoantibodies.



J Intern Med. 2019 Jan;285(1):40-48



Pharmacogenetics

There is still some light in the tunnel, mainly using genetic variants to predict treatment responses, that is, pharmacogenetics. Genetic variants regulating genes encoding for proteins involved in drug transport or metabolism are plausible candidates. Metformin is the most commonly used drug for treatment of T2D, and several studies have identified genetic variants which influence the glucose-lowering effect of metformin. A variant in the *SLC22A1* gene encoding for the organic cation transporter 1 (OCT1), which is involved in transport of metformin into the cell, was associated with response to metformin [49]. Similarly, a variant in another metformin transporter, *MATE1* (multidrug and toxin extrusion 1), influenced response to metformin in a small study.[50]. The large metformin consortium (MetGen) demonstrated that a variant in the *SLC2A2* gene encoding for glucose transporter 2 (GLUT2) also was associated with metformin response [51]. Finally, a GWAS exploring glycemic response to metformin identified variants near the ATM gene (Ataxia Teleangiectasia) [52].

J Intern Med. 2019 Jan;285(1):40-48

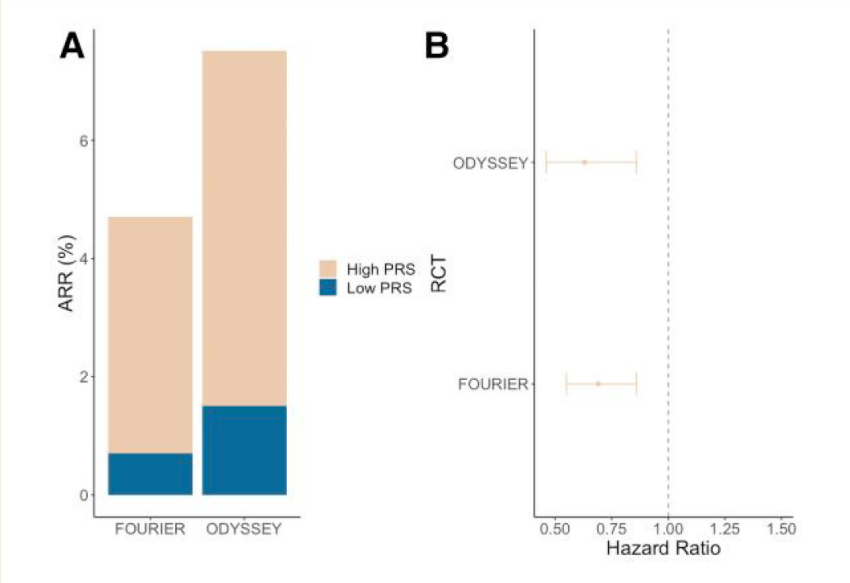


Figure 2 Derived from randomized clinical trials: the effect of PCSK9 inhibitors (*A* and *B*) on major vascular events (coronary heart death, myocardial infarction, coronary revascularization, stroke) stratified by polygenic risk scores. Panel *A* shows the absolute risk reduction by polygenic risk score group in the FOURIER trial [absolute risk reduction: 4% vs 0.7%, $P = 0.004$, hazard ratio: 0.69 (0.55–0.86) for high polygenic risk score][104] and ODYSSEY OUTCOMES trial (absolute risk reduction: 6% vs. 1.5%, interaction $P = 0.04$).[103] High polygenic risk score was defined as top 20% in FOURIER, and top 10% in ODYSSEY OUTCOMES. Panel *B* shows the hazard ratios for PCSK9 inhibitors in the high risk polygenic risk score groups in each trial: FOURIER: hazard ratio: 0.69 (0.55–0.86), and ODYSSEY OUTCOMES: 0.63 (0.46–0.86).

Η μείωση απόλυτου κινδύνου εμφάνισης καρδιαγγειακής νόσου με τη χρήση PCSK9 είναι μεγαλύτερη σε άτομα με υψηλό σκορ εκτίμησης γενετικού κινδύνου

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Challenges and Future Directions

- **Access and Equity**: Precision medicine requires advanced technologies, specialized expertise, and data access, which **may not be equally available** across populations or regions
- **Ethical and Privacy Concerns**: The use of genetic data and patient information for precision medicine raises **concerns about privacy and potential misuse of sensitive health data**
- **Integration into Clinical Practice**: Widespread adoption of precision medicine in routine care requires overcoming barriers in terms of **education, cost, infrastructure, and regulatory approval**

"Το Stress και σαρκοπενία:
Ιατρική ακριβείας στην καρδιομεταβολική νόσο - Επιλογή Θεραπείας"

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