The contribution of genetics and enviroment to obesity

Berne, Nov 14th 2024

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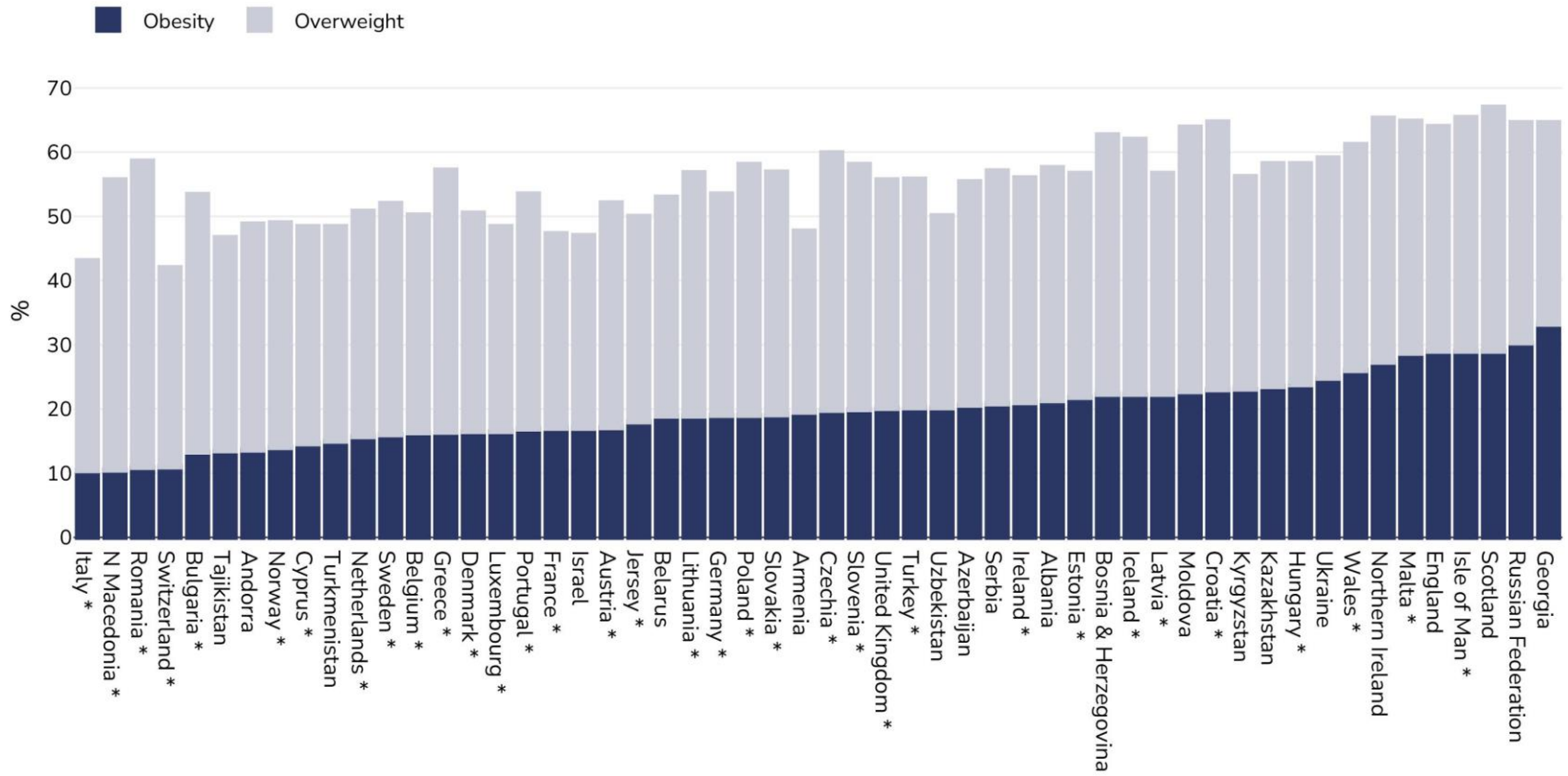
Conflicts of interest

- Novo Nordisk travel support

Biggest conflict: neither pediatrician seeing patients with monogenic/syndromic obesity nor specific knowledge in genetics, which I have declared to the organising comittee

WHO European region: Obesity prevalence

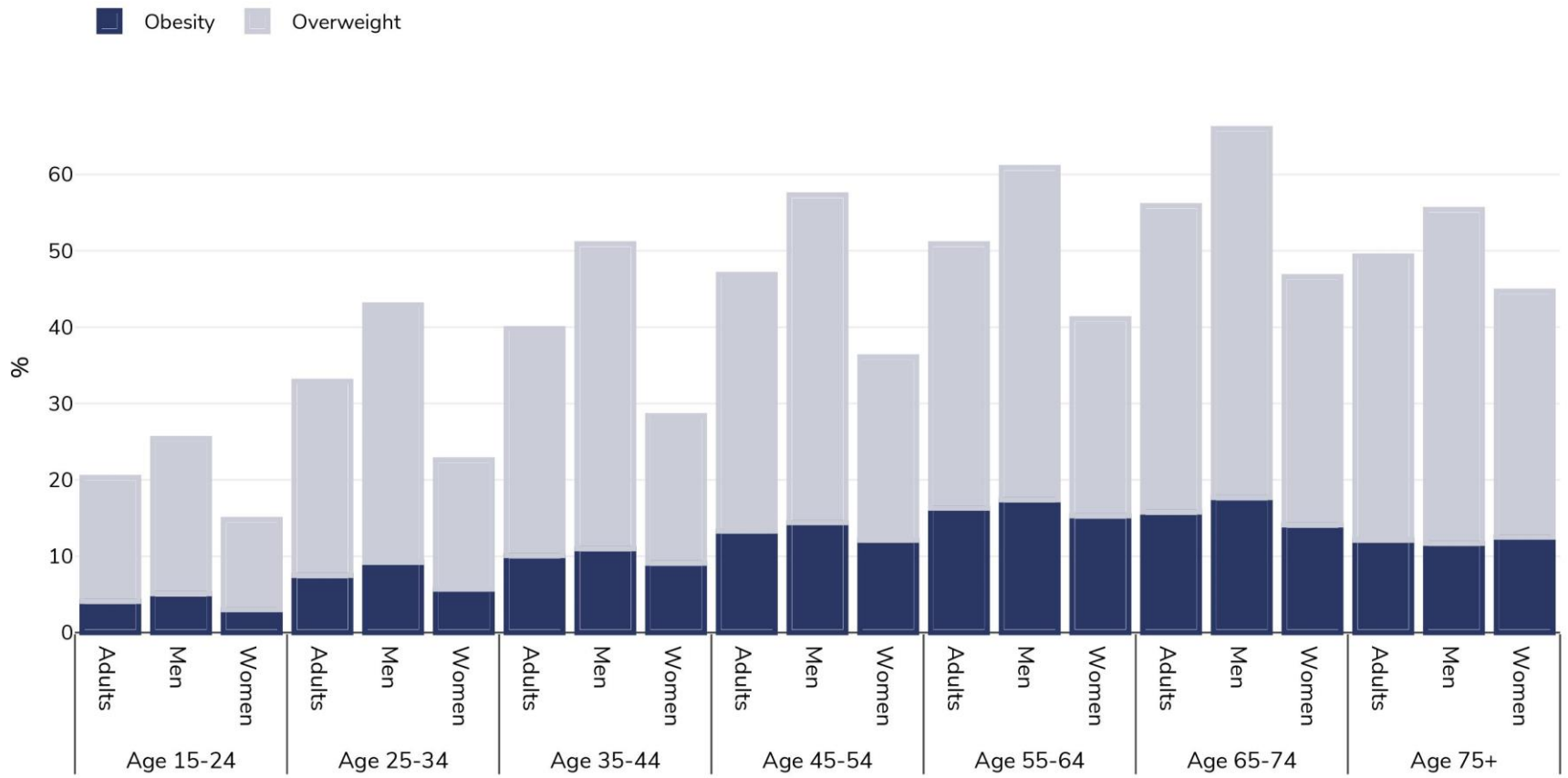
Adults



Survey type:	Countries marked with a * are using self-reported data.
Notes:	Different methodologies have been used to collect this data and so it is not strictly comparable.
	Unless otherwise noted, overweight refers to a BMI between 25kg and 29.9kg/m², obesity refers to a BMI greater than 30kg/m².

Switzerland: Overweight/obesity by age

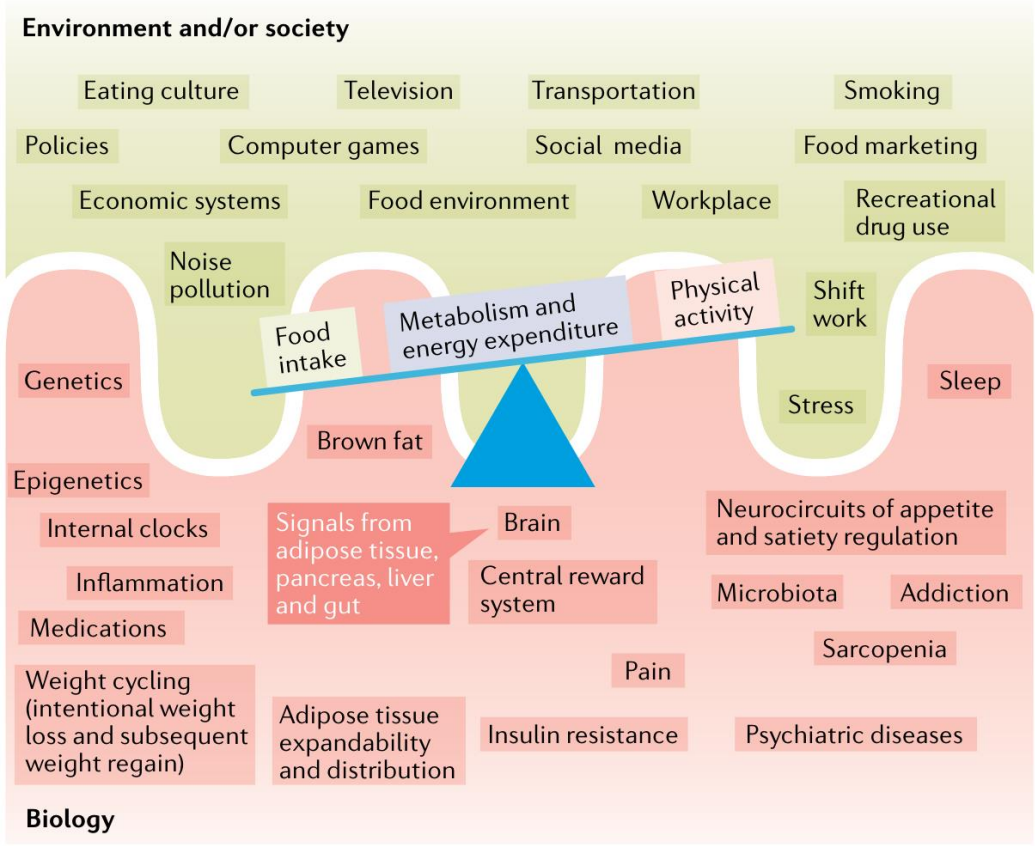
Adults, 2017



Survey type:	Self-reported
Sample size:	22000
Area covered:	National
References:	Swizz National Health Survey https://www.portal-stat.admin.ch/sgb2017/files/de/02b.xml (last accessed 09.08.23)

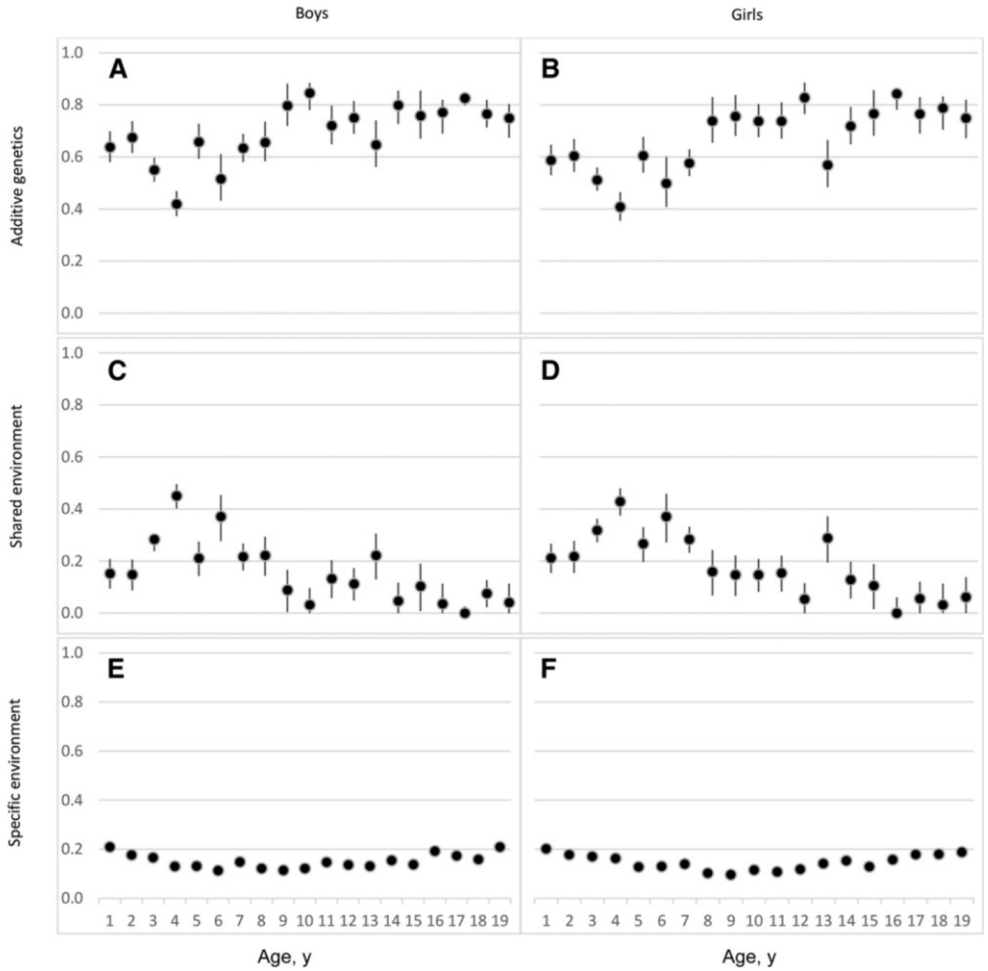
Unless otherwise noted, overweight refers to a BMI between 25kg and 29.9kg/m², obesity refers to a BMI greater than 30kg/m².

Complex biological, environmental and societal factors contributing to obesity



Blüher M, Nature Rev Endo 15: 288, 2019

Genetic and environmental effects on body mass index from infancy to the onset of adulthood: an individual-based pooled analysis of 45 twin cohorts



Silventoinen et al., Am J Clin Nutr 2016;104:371

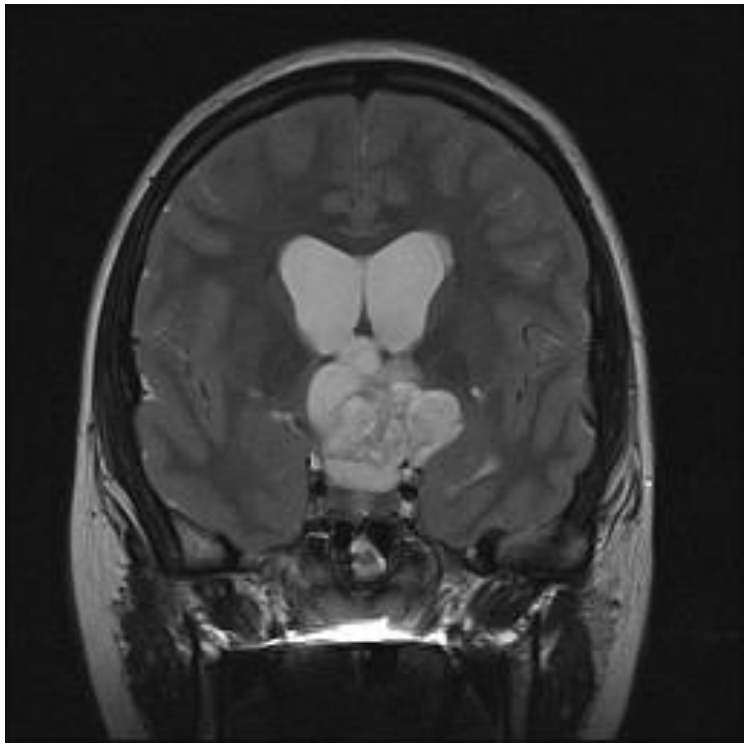
Summary of current evidence

… Crucially, there is a strong genetic component underlying the large interindividual variation in body weight that determines people's response to this 'obesogenic' environment. Twin, family and adoption studies have estimated the heritability of obesity to be between 40% and 70% …

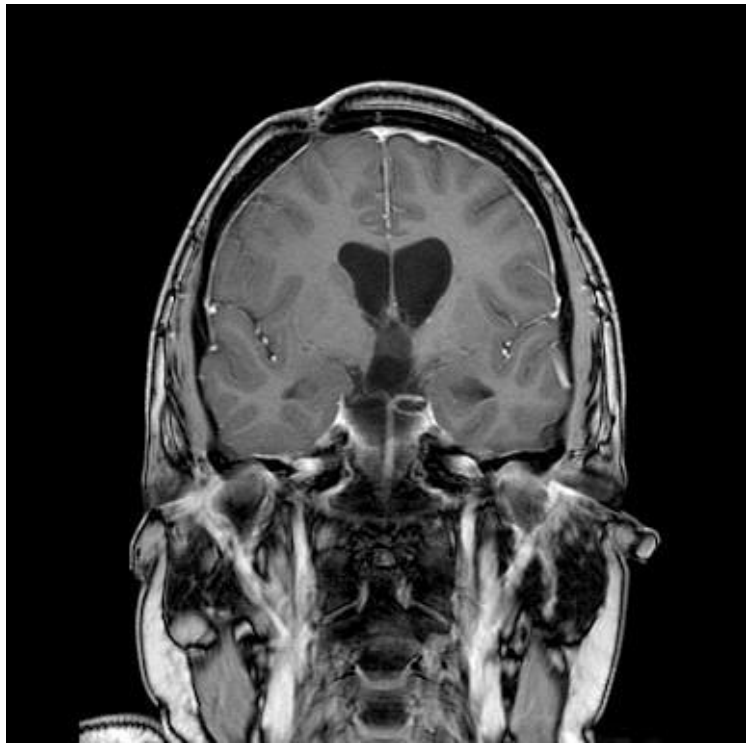
Loos et al., Nature Rev Genetics 23:120, 2022

Hypothalamic obesity in a 22y old woman

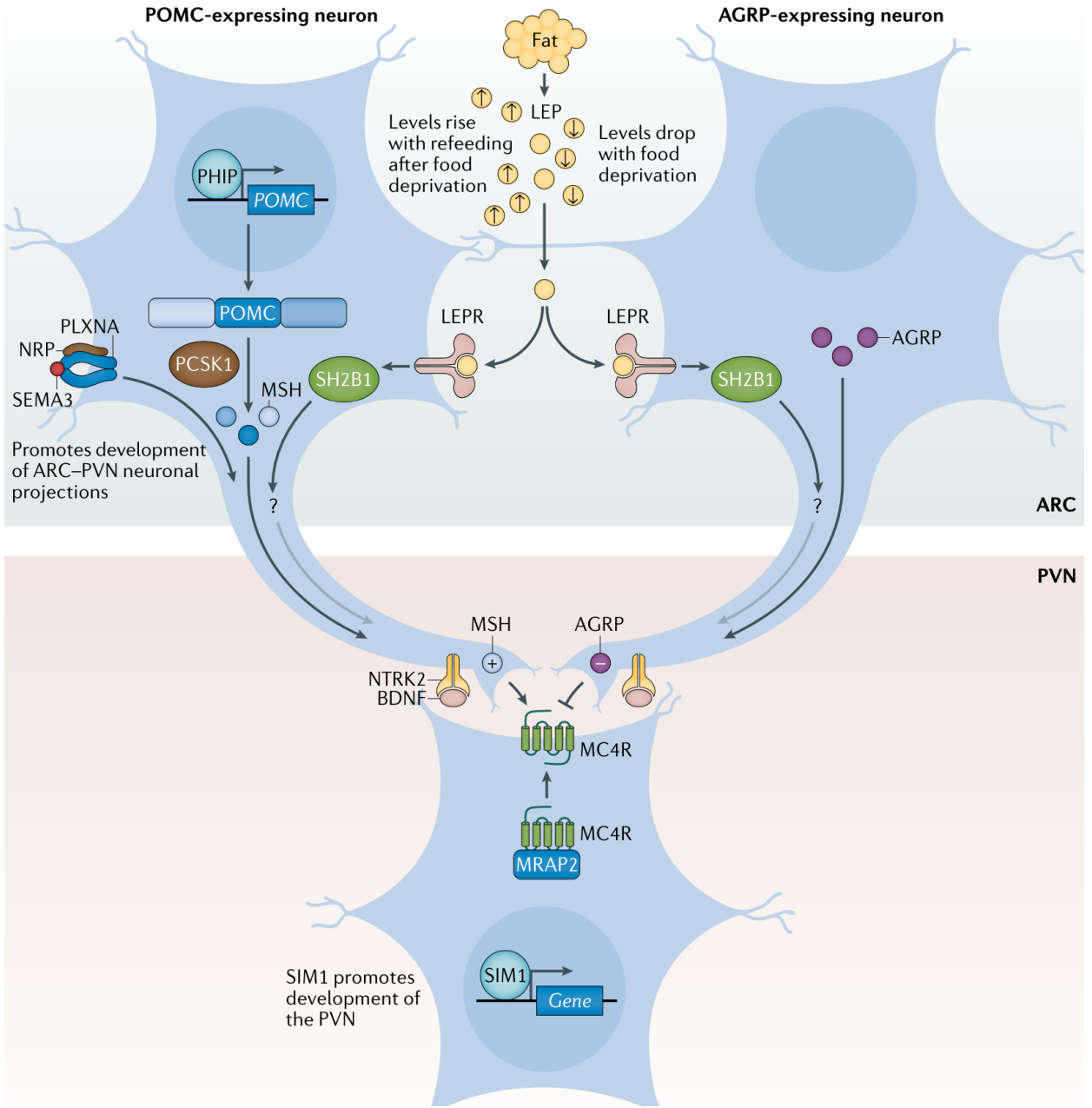
2008: 56 kg, BMI 20.8 kg/m^2



2010: 109 kg, 40.5 kg/m^2



Neurons of the leptin-melanocortin pathway are located in the hypothalamus



Loos et al., Nature Rev Genetics 23:120, 2022

Monogenic obesity involving the leptin pathway

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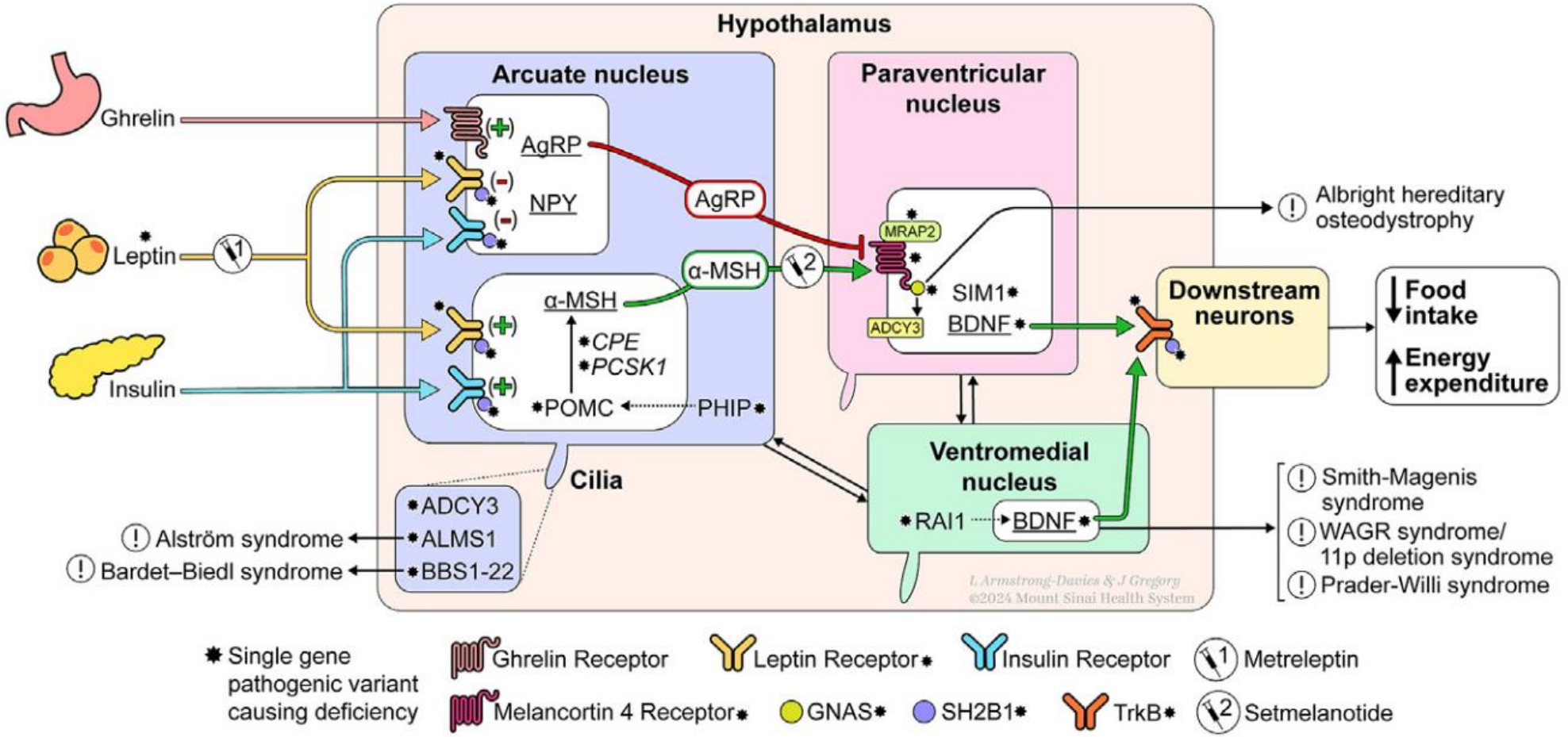
Gene	Prevalence	Inheritence	Clinical features	Treatment
LEP	1 : 4.4-17.8 *10^6	aut.- recessive	hyperphagia, central hypogonadism & hypothyroidism, infections	Metreleptin
LEPR	1 : 8-75*10^4	aut.- recessive	hyperphagia, central hypogonadism & hypothyroidism, infections	Setmelanotide
POMC	1 : 5*10^5	aut.- recessive	hyperphagia, fair skin, red hair, cortisol deficiency	Setmelanotide HC
PCSK1	1 : 3.6*10^4	aut.- recessive	hyperphagia, pp hyper, hypoglycemia, diarrhea, central hypogonadism & hypothyroidism, diabetes insipidus	Setmelanotide
CPE	Single cases	aut.- recessive	hyperphagia, central hypogonadism, intellectual disability	??
MC4R	2-5% children, 1% adults with G3 obesity	aut.-dominant	hyperphagia, tall stature, attention deficit disorder	
BDNF NTRK 2	??	aut.-dominant	hyperphagia, intellectual disability, impaired pain perception	??

Loos et al., Nature Rev Genetics 23:120, 2022, Siddiqui et al., Pediatr Clin N Am 71 (2024) 897

Syndromic obesity involving the leptin pathway



Siddiqui et al., Pediatr Clin N Am 71 (2024) 897

Syndromic obesity involving the leptin pathway

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Syndrome	Leptin pathway disruption	
Prader Willi	Reduced expression of LEPR, POMC, PCSK1, BDNF	Weight gain and hyperphagia in early childhood
Bardet Biedl	Ciliopathy affecting LEPR trafficking and POMC neuronal function	Hyperphagia, and obesity begins in infancy
Alström	Ciliopathy affecting LEPR trafficking and POMC neuronal function	Obesity begin in infancy
AHO	MC4R	Obesity
Carpenter	For RAB23, ciliopathy affecting LEPR trafficking and POMC neuronal function; mechanism under investigation for MEGF8	High birth weight, subsequent obesity
MORM	Ciliopathy affecting LEPR trafficking and POMC neuronal function	Childhood-onset truncal obesity
SIM1, MRAP2, ADCY3	MC4R	Hyperphagia, severe obesity

Loos et al., Nature Rev Genetics 23:120, 2022, Siddiqui et al., Pediatr Clin N Am 71 (2024) 897

A Deletion in the Canine POMC Gene Is Associated with Weight and Appetite in Obesity-Prone Labrador Retriever Dogs

Sequencing of candidate genes for obesity in Labrador retriever dogs identified a **14 bp deletion in pro-opiomelanocortin (POMC)** with an **allele frequency of 12%**. The deletion disrupts the b-MSH and b-endorphin coding sequences and is associated with body weight (per allele effect of 0.33 SD), adiposity, and greater food motivation. The mutation is significantly more common in Labrador retrievers selected to become assistance dogs than pets. In conclusion, the deletion in POMC is a significant modifier of weight and appetite in Labrador retrievers and may influence other behavioral traits.

Raffan et al., 2016, Cell Metabolism 23, 893–900

Monogenic and syndromic forms of obesity

- Can be diagnosed in up to 13% of pediatric obesity cases with increading prevalence due to the identification of new genes
- Diagnosis of utmost importance for parents and their families who are who may be unfairly stigmatized as lacking self-discipline and control
- A definitive diagnosis can help family members manage the burden of uncertainty and address associated metabolic conditions at an early stage
- Novel, specific therapies available

Mainieri et al., European Journal of Pediatrics (2023) 182:4781

Genetic testing for monogenic/syndromic obesity

Endo Society Guidelines

- We suggest genetic testing in patients with extreme early onset obesity (before 5 years of age) and that have clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and/or a family history of extreme obesity.

Red flags supporting genetic testing in children

- „Early onset of severe obesity before the age of 5 years
- Rapid weight gain before the age of 2 years
- Normal weight of parents (usually seen in recessive forms)
- Consanguineous parents
- Additive clinical manifestations:
  - hyperphagia, developmental delay, pseudohypoparathyroidism, red hair and pale skin, hypogonadism and endocrine dysfunction, short stature, adrenal insufficiency, persistent diarrhea, immunodeficiency

Styne et al., J Clin Endocrinol Metab, 2017, 102: 709; Mainieri et al., European Journal of Pediatrics (2023) 182:4781
Siddiqui et al., Pediatr Clin N Am 71 (2024) 897

Do we need to consider monogenic or syndromic obesity in the adult clinic ?

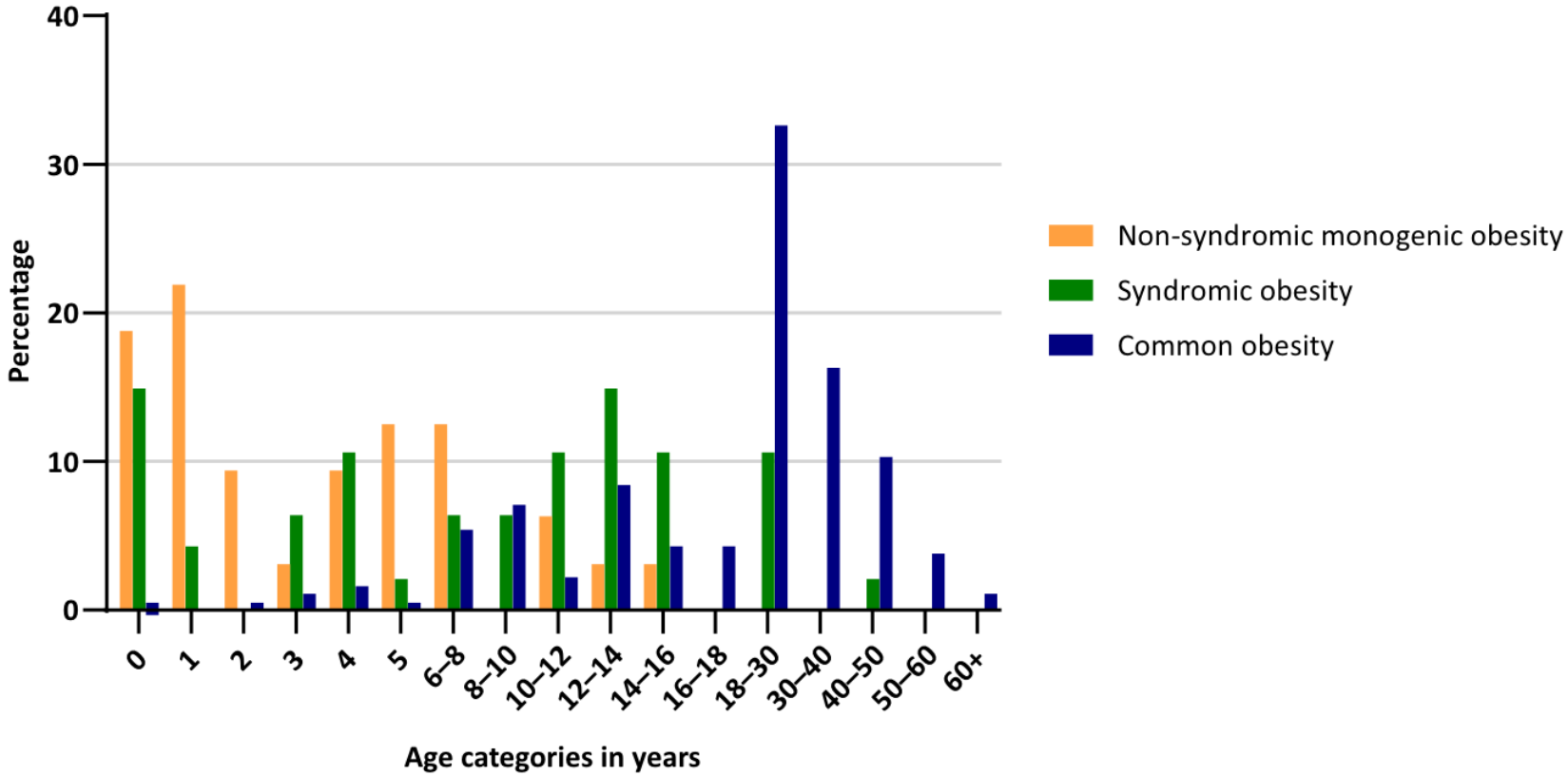

FIGURE 1 Age of onset of obesity (AoO), categorized per type of obesity.

Welling MS et al., Obesity (Silver Spring) 32:1257, 2024

TABLE 1 General characteristics in all groups.

	MO ($n = 32$)[a]	SO ($n = 47$)[b]	CO ($n = 186$)[c]	p value
Sex, female, *n* (%)	26 (81.3)	23 (48.9)	143 (76.9)	**<0.001**[d]
Age at intake (y)	25.8 (20.3–41.9)	25.5 (21.5–36.4)	45.2 (33.5–55.7)	**<0.001**[e]
Ethnicity, *n* (%)				**0.043**[f]
Dutch	24 (75.0)	43 (91.5)	131 (71.6)	
Western	2 (6.3)	0 (0.0)	20 (10.9)	
Non-Western	6 (18.8)	4 (8.5)	32 (17.5)	
Education level, *n* (%)				**<0.001**[g]
Low	9 (28.1)	30 (63.8)	12 (7.7)	
Middle	14 (43.8)	15 (31.9)	46 (29.7)	
High	9 (28.1)	2 (4.3)	97 (62.6)	
Weight (kg)	119.7 (98.4–150.1)	124.4 (96.0–141.0)	113.7 (101.5–125.7)	0.314
Height (cm)	170.3 ± 10.0	174.3 ± 11.4	171.2 ± 9.0	0.136
BMI (kg/m$^{2)}$	41.2 (36.8–48.3)	39.5 (34.5–45.7)	38.7 (36.0–42.6)	0.248
Obesity class, *n* (%)				**<0.001**[e]
Overweight	3 (9.4)	3 (6.4)	0 (0.0)	
I	3 (9.4)	9 (19.1)	39 (21.0)	
II	7 (21.9)	13 (27.7)	71 (38.4)	
III	19 (59.4)	22 (46.8)	76 (40.9)	
Waist circumference (cm)	113 (90–129)	120 (102–130)	113.0 (103.3–123.3)	0.402
SBP (mm Hg)	143 ± 23	140 ± 15	137 ± 15	0.195
DBP (mm Hg)	86 ± 16	80 ± 11	81 ± 12	0.093
HR	82 ± 23	83 ± 16	79 ± 16	0.179

TABLE 3 AoO, appetite characteristics, and other genetic characteristics in all groups.

	MO ($n = 32$)[b]	SO ($n = 47$)[c]	CO ($n = 186$)[d]	*p* value
AoO				
AoO (y)	3 (1–6)	9 (4–13)	21 (13–33)	**<0.001**[e]
AoO ≤ 5 y, *n* (%)	24 (75.0)	18 (38.3)	8 (4.3)	**<0.001**[f]
Appetite characteristics				
Appetite, *n* (%)				**<0.001**[e]
Increased	21 (65.6)	32 (68.1)	62 (33.9)	
Normal	9 (28.1)	12 (25.5)	117 (63.9)	
Decreased	2 (6.3)	3 (6.4)	4 (2.2)	
Satiation, *n* (%)	19 (61.3)	22 (48.9)	NA	0.286
Duration satiety, *n* (%)			NA	0.699
<1 h	10 (32.3)	10 (22.7)		
1–2 h	10 (32.3)	17 (38.6)		
2–4 h	8 (25.8)	10 (22.7)		
>4 h	3 (9.7)	7 (15.9)		
Change of appetite over time, *n* (%)			NA	0.855
Unchanged	16 (50.0)	23 (51.1)		
Increased	2 (6.3)	5 (11.1)		
Decreased	14 (43.7)	17 (35.4)		
Spontaneously	5 (35.7)	6 (35.3)		
Bariatric surgery	2 (14.3)	1 (5.8)		
Antiobesity agents	7 (50.0)	10 (58.8)		
Nocturnal eating, *n* (%)	5 (15.6)	7 (15.9)	NA	0.438
Binge eating, *n* (%)	17 (53.1)	30 (63.8)	95 (54.9)	0.509
Other specific traits				
Only person with obesity within family household, *n* (%)[a]	6 (20.0)	16 (36.4)	57 (33.7)	0.279
Parental obesity, *n* (%)[a]				**0.003**[g]
None	6 (25.0)	20 (52.6)	77 (46.4)	
Only 1 parent	7 (29.2)	8 (21.1)	64 (38.6)	
Both parents	11 (45.8)	10 (26.3)	25 (15.1)	
Age of menarche (y)	13 (12–14)	12 (11–13)	12 (12–13)	0.173
High birth weight, *n* (%)	4 (14.3)	11 (24.4)	25 (18.8)	0.540
Intellectual deficit, *n* (%)	1 (3.1)	25 (53.2)	0 (0)	**<0.001**[f]
ASD, *n* (%)	2 (6.3)	10 (21.3)	0 (0)	**<0.001**[e]
Retinal problems, *n* (%)	0 (0)	8 (17.0)	0 (0)	**<0.001**[h]
ES criteria				
Fulfilling ES criteria for genetic testing, *n* (%)	18 (56.3)	14 (29.8)	5 (2.7)	**<0.001**[e]

TABLE 2 Included genetic obesity disorders.

Affected gene	Name of disease	Number of patients (%)
Non-syndromic MO		
Heterozygous *MC4R*		26 (81.3)
Biallelic *MC4R*		3 (9.4)
Biallelic *LEPR*		2 (6.3)
Biallelic *POMC*		1 (3.1)
SO		
16p11.2 deletion	16p11.2 deletion syndrome	29 (61.7)
Distal (including *SH2B1*)		14 (48.3)
Proximal (excluding *SH2B1*)		15 (51.7)
Bardet-Biedl syndrome genes	Bardet-Biedl syndrome	7 (14.9)
GNB1		2 (4.3)
PHIP	Chung-Jansen syndrome	2 (4.3)
ALMS	Alström syndrome	1 (2.1)
MAGEL2	Schaaf-Yang syndrome	1 (2.1)
MYT1L		1 (2.1)
SIM1		1 (2.1)
DNMT3A	Tatton-Brown-Rahman syndrome	1 (2.1)
STX16	Pseudohypoparathyroidism type 1B	1 (2.1)
TRIP12	Clark-Baraitser syndrome	1 (2.1)

Proposal for tailored genetic testing in adult obesity

TABLE 6 Key considerations for developing recommendations regarding genetic testing in adults with obesity.

Considerations before performing genetic testing in an adult with obesity when a combination is present of the following signs and symptoms
1. Different aspects of hyperphagia should be assessed across different life stages, spanning from childhood to adulthood, including the following: • Increased appetite • Decreased satiation and/or satiety • Shortened duration of satiety • Presence of binge eating • Presence of nocturnal eating
2. The recommended age cutoff for early-onset obesity in children is ≤5 years of age. For adults who are suspected of having genetic obesity, our data suggest age cutoffs for early-onset obesity of the following: • ≤7 years of age for MO • ≤15 years of age for SO
3. In addition to hyperphagia and early-onset obesity, it is essential to also evaluate other specific genetic obesity features and/or striking weight differences with first-degree family members and family history of extreme and early-onset obesity[a].
4. In case of suspicion of SO, specific syndromic genetic obesity features such as intellectual deficit, ASD, organ-specific congenital malformations, and dysmorphic features should be considered.

Welling MS et al., Obesity (Silver Spring) 32:1257, 2024

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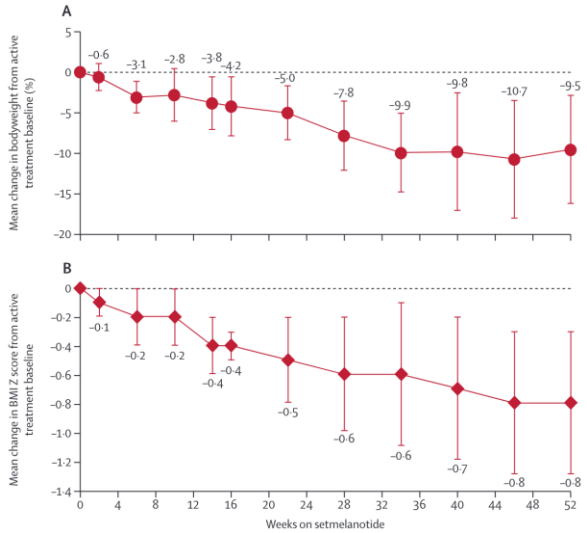
Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials

Karine Clément, Erica van den Akker*, Jesús Argente, Allison Bahm, Wendy K Chung, Hillori Connors, Kathleen De Waele, I Sadaf Farooqi, Julie Gonneau-Lejeune, Gregory Gordon, Katja Kohlsdorf, Christine Poitou, Lia Puder, James Swain, Murray Stewart, Guojun Yuan, Martin Wabitsch†, Peter Kühnen†, for the Setmelanotide POMC and LEPR Phase 3 Trial Investigators‡*

Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period

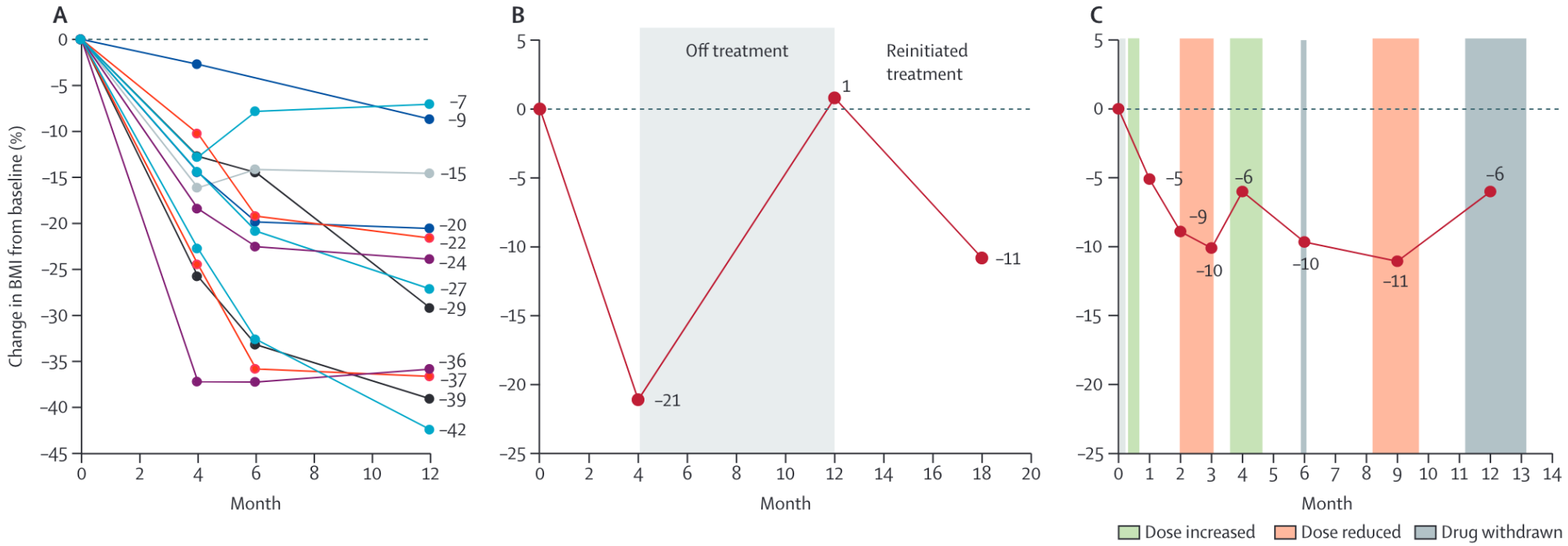
Andrea M Haqq, Wendy K Chung, Hélène Dollfus, Robert M Haws, Gabriel Á Martos-Moreno, Christine Poitou, Jack A Yanovski, Robert S Mittleman, Guojun Yuan, Elizabeth Forsythe, Karine Clément, Jesús Argente



Lancet Diab Endo 8: 960, 2020; Lancet Diab Endo 10: 859, 2022;

Setmelanotide for the treatment of acquired hypothalamic obesity: a phase 2, open-label, multicentre trial

Christian L Roth, Cecilia Scimia*, Ashley H Shoemaker, Michael Gottschalk, Jennifer Miller, Guojun Yuan, Sonali Malhotra, M Jennifer Abuzzahab*



Lancet Diab Endo 12: 380, 2024

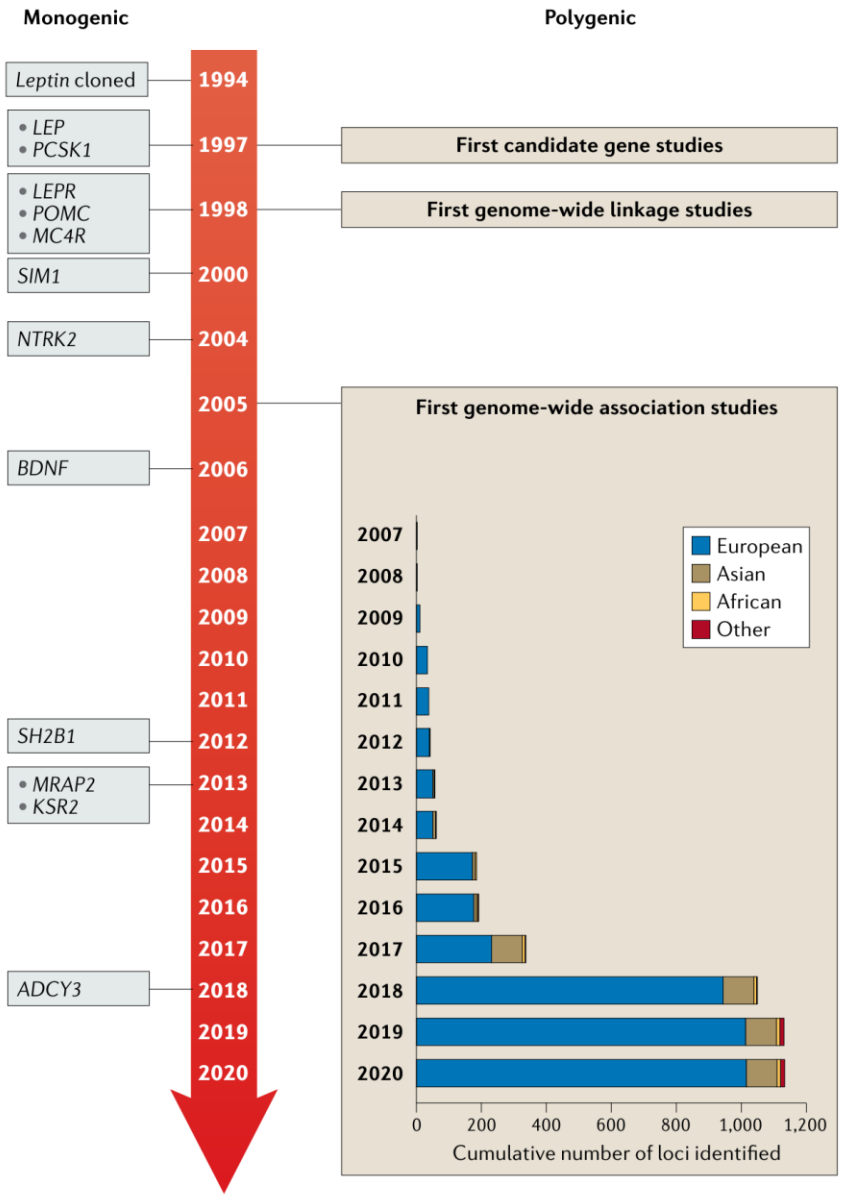


Fig. 3 | **Timeline of key discoveries in obesity genetics.** Genes identified for monogenic obesity in a given year are shown on the left. Discoveries made for polygenic obesity are shown on the right, including a cumulative count of newly discovered loci per year and by ancestry. Although candidate gene and genome-wide linkage studies became available in the late 1990s, findings were limited, and these study designs are not as frequently used as genome-wide association studies.

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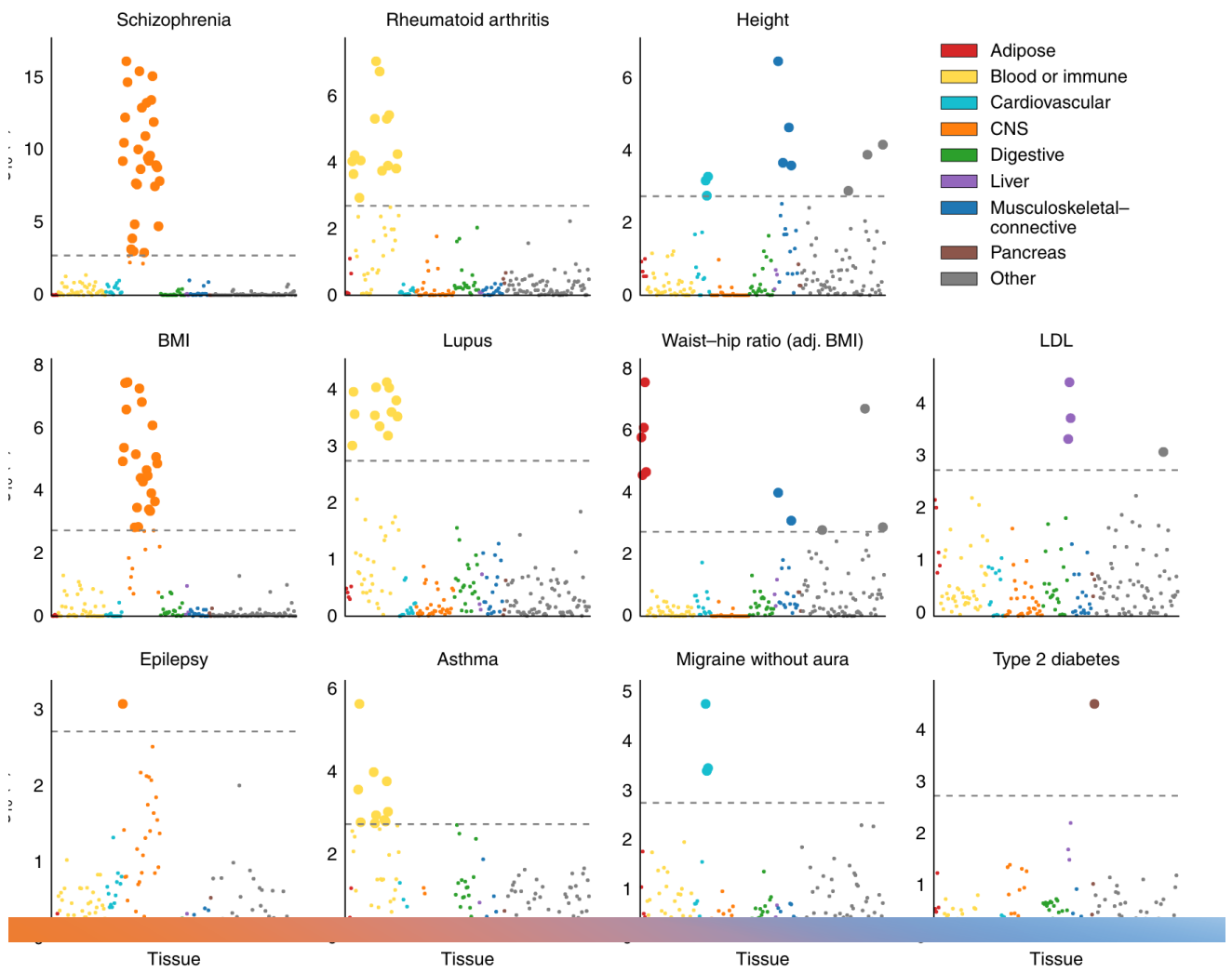
Common / polygenic obesity

- Genome wide association studies identified > 1‘100 loci associated with BMI
- FTO locus common in European ancestry
- Most recent results show that GWAS loci explain 6% of the variation in BMI

Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types

… to test whether disease heritability is enriched in regions surrounding genes with the highest specific expression in a given tissue …



Finucane et al. Nat Genetics 50: 621, 2018

Representation of monogenic vs. polygenic obesity genes in different brain regions

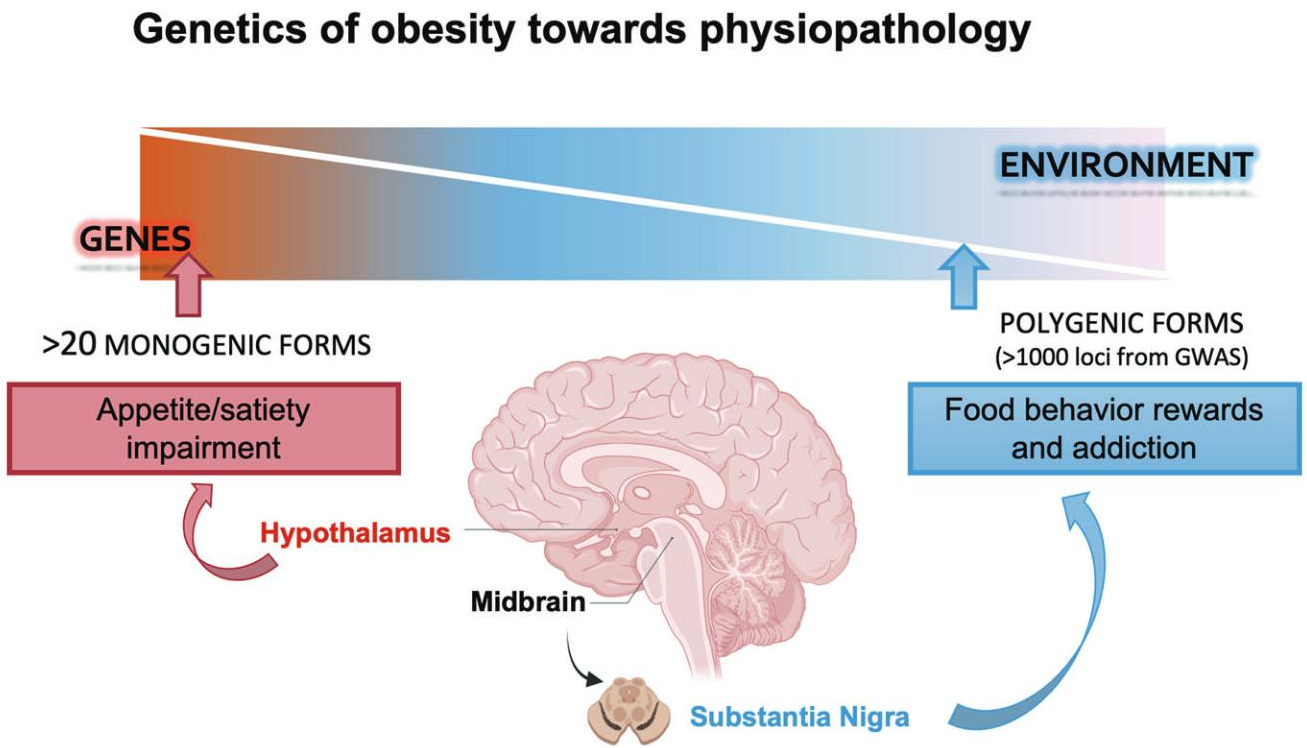


Fig. 2 Comparative overview of brain regulation of energy balance in monogenic versus polygenic obesity. Monogenic obesity is characterized by disruptions in the hypothalamic circuits responsible for appetite control, leading to hyperphagia. Contrastingly, polygenic obesity implicates brain regions such as the substantia nigra and the insula, which are associated with addiction and reward processing.

Saeed et al., Molecular Psychiatry, epub 2024

Monogenic vs. polygenic obesity

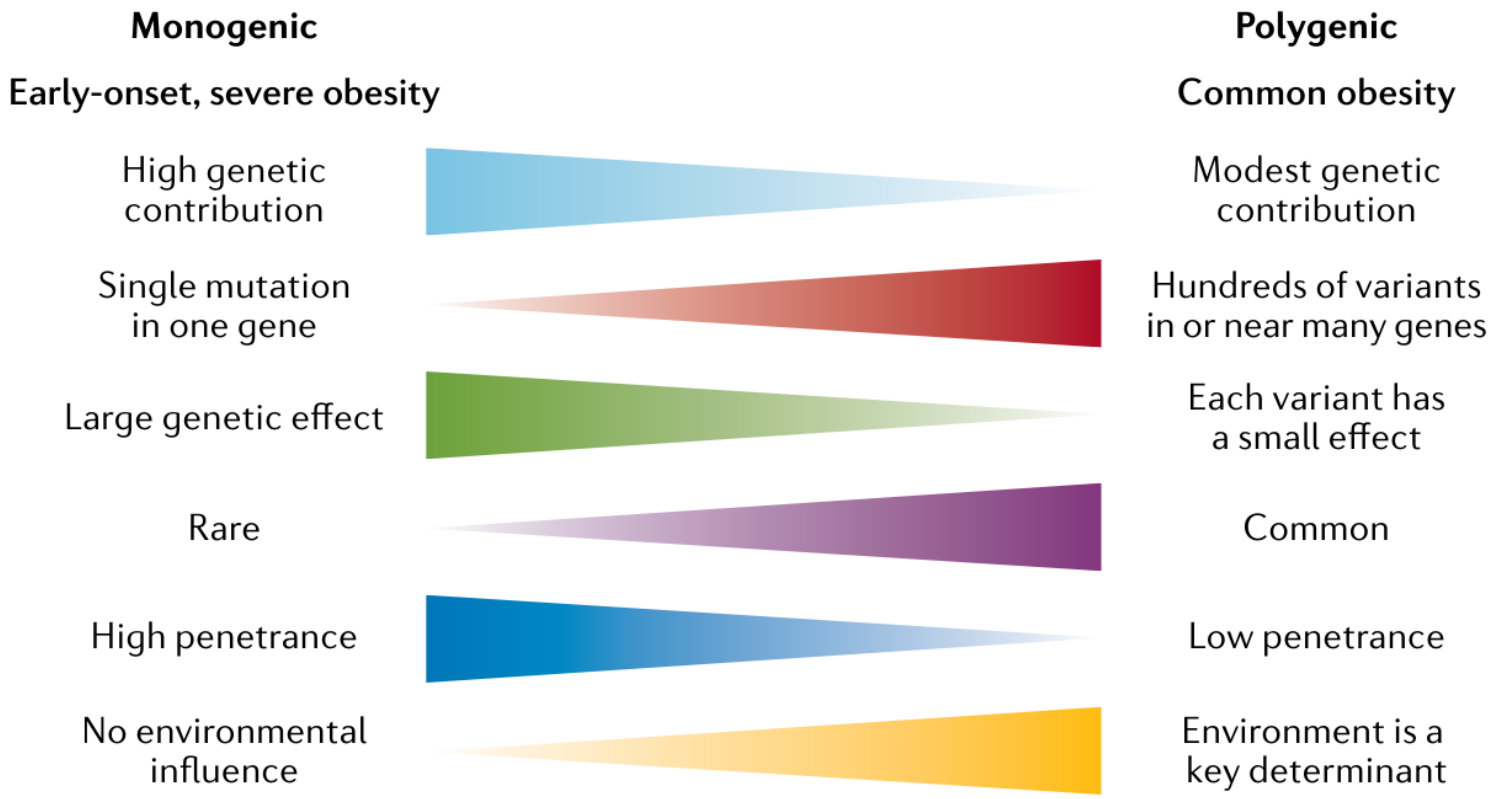
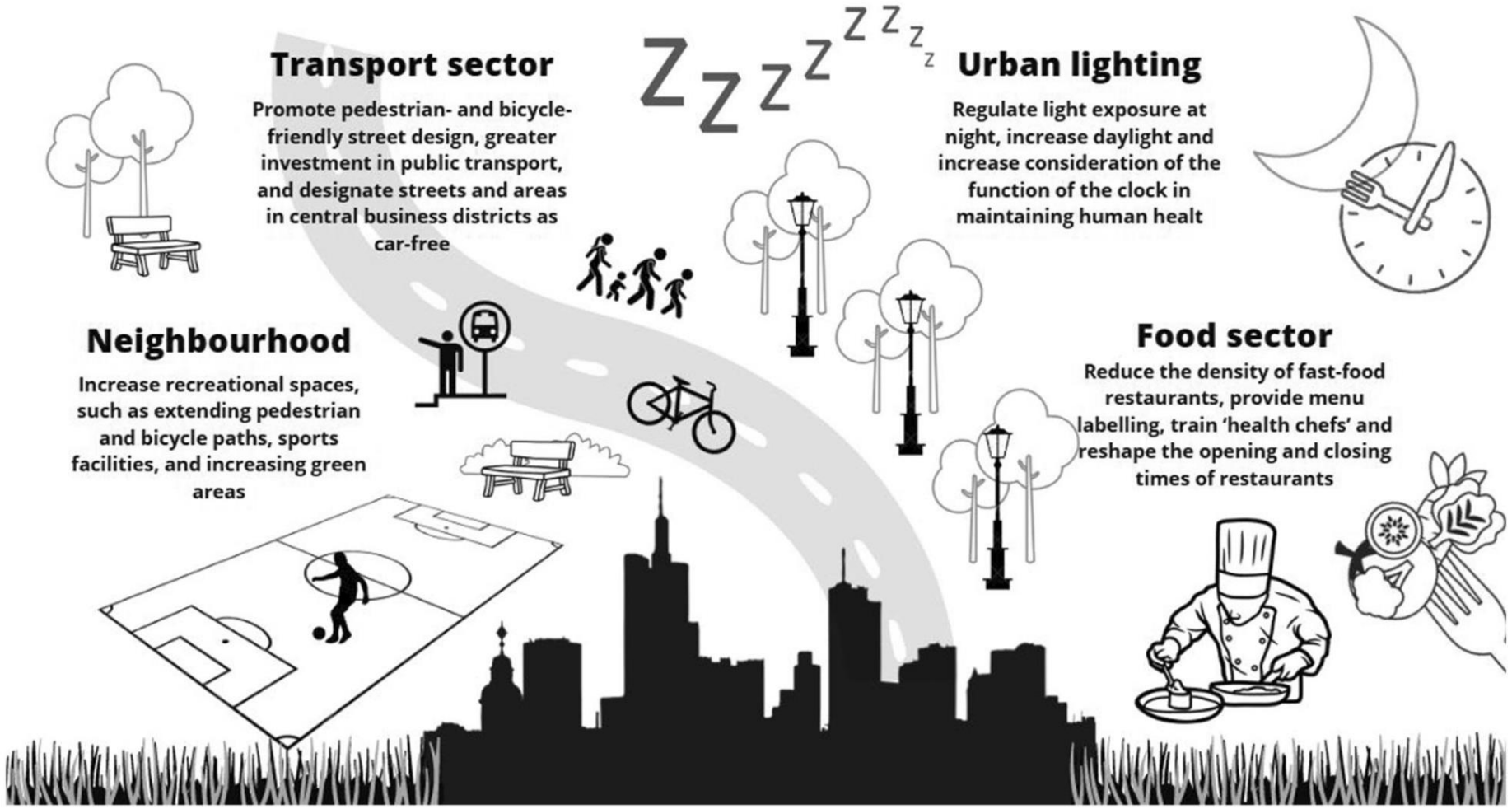


Fig. 2 | **Key features of monogenic and polygenic forms of obesity.**

Environment: Instructions to build weight friendly cities



Verde et al., Diabetes Metab Res Rev 2024, e3476

From an obesity perspective …

Volksabstimmung vom 24. November 2024

Am 24. November 2024 stimmen die Schweizer Stimmberechtigten über 4 Vorlagen ab.

Ausbau Nationalstrassen

NO

Untermiete

Kündigung wegen Eigenbedarfs

Einheitliche Finanzierung der Gesundheitsleistungen

YES

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Thank you