Obesity in Down Syndrome

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Objectives

- What are the **long-term consequences** of Obesity in Down Syndrome?

- What are some **barriers** to weight loss in Down Syndrome?

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Disclosures

- Financial: None

- Artificial Intelligence: Used during literature search only

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Case

- **19-year-old Male** with Trisomy 21 came to establish care
- Non-verbal / avoiding eye contact
- Refused vitals
- But watching videos on phone laughing / giggling
- Mom worried about multiple concerns but main was **weight**
  - **Eats all day** especially snacks at night
    - **Breaks open locks** on pantry & fridge

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Case – Medical History

- **BMI 50.7**
- Psych: **Autism, ADHD, Oppositional Defiance, Apraxia**
- Pulm: **OSA not on CPAP**, Chronic Rhinitis
- GI: Celiac Disease, IBS
- Derm: **Hidradenitis**, Seborrheic Dermatitis, Lymphedema
- Endo: **Dyslipidemia**

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Case – Weight Loss Barriers

- **Significant oppositional / behavioral issues**
  - Went through multiple psychiatric medication trials
    - Now on **Lisdexafetamine** & **Quetiapine**
      - Problem: Quetiapine → **Drug induced weight gain**
      - Unfortunate: Lisdexafetamine → No appetite / binging suppression
    - **Phentermine** & **Bupriopion-Naltrexone not options**

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Case – Weight Loss Barriers

- Limited food options given **diarrhea / intolerance**
  - Only likes snacks
    - **Orlistat** & **Bariatric Surgery not options**

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Case – Weight Loss Barriers

- History of refusing vitals, labs, imaging, exams, etc.
  - **Last labs 4 years ago**
  - Only able to do them during sedated dental exams
    - Unable to find adult dentists who do special needs
  - **Injectable GLP-1 agonists not options**

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Now what?

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Scale of Problem

- **> 50% Children Overweight** (> 25% Obese)
- **> 80 % Adults Overweight** (> 50% Obese)
  - **> 60% Adults with Intellectual Disabilities & Autism**
  - **Females higher risk**
  - No difference per race
- **Increased association of DM and OSA in adults <u>although</u> not correlated with comorbidities in children**

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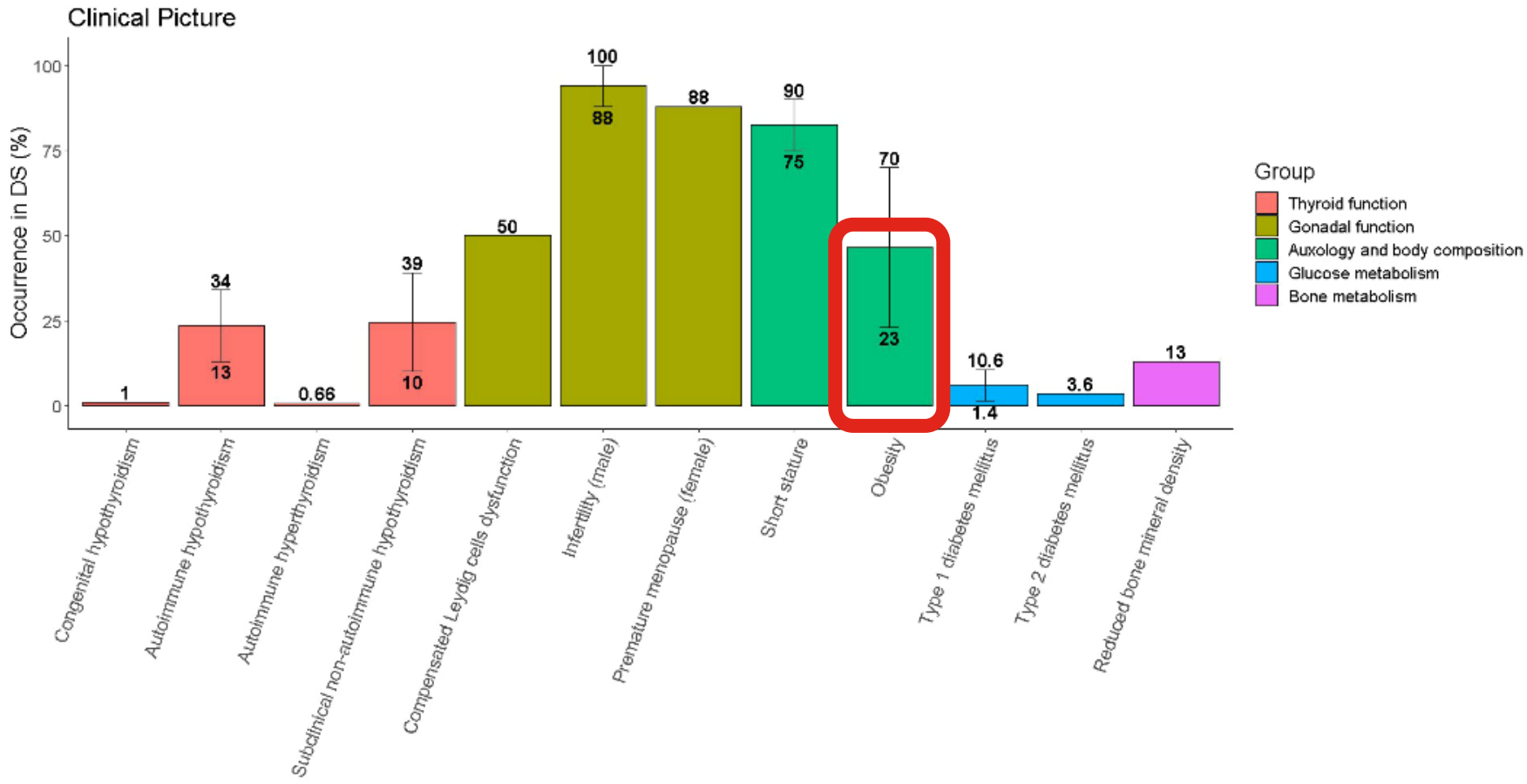

FIGURE 1

Occurrence of endocrine disorders among children and adolescents with Down syndrome (DS). Single disorders are grouped with reference to the organ involved. Whenever literature reports different prevalence for the same disorder the median value was represented by the height of the bar, while the range was represented by the vertical line connecting the lowest and the greatest occurrence.

Pathophysiology

- **Mitochondrial Dysfunction** (directly related to trisomy)
  - **Lower Metabolic Rate** (unrelated to body mass)
  - **Leptin Resistance / Deficiency** (appetite suppressant)
  - **Brown Adipose Tissue Dysfunction**
  - **Hypothyroidism** (subclinical and clinical [~50% adults])
  - **Insulin Signaling Defects**

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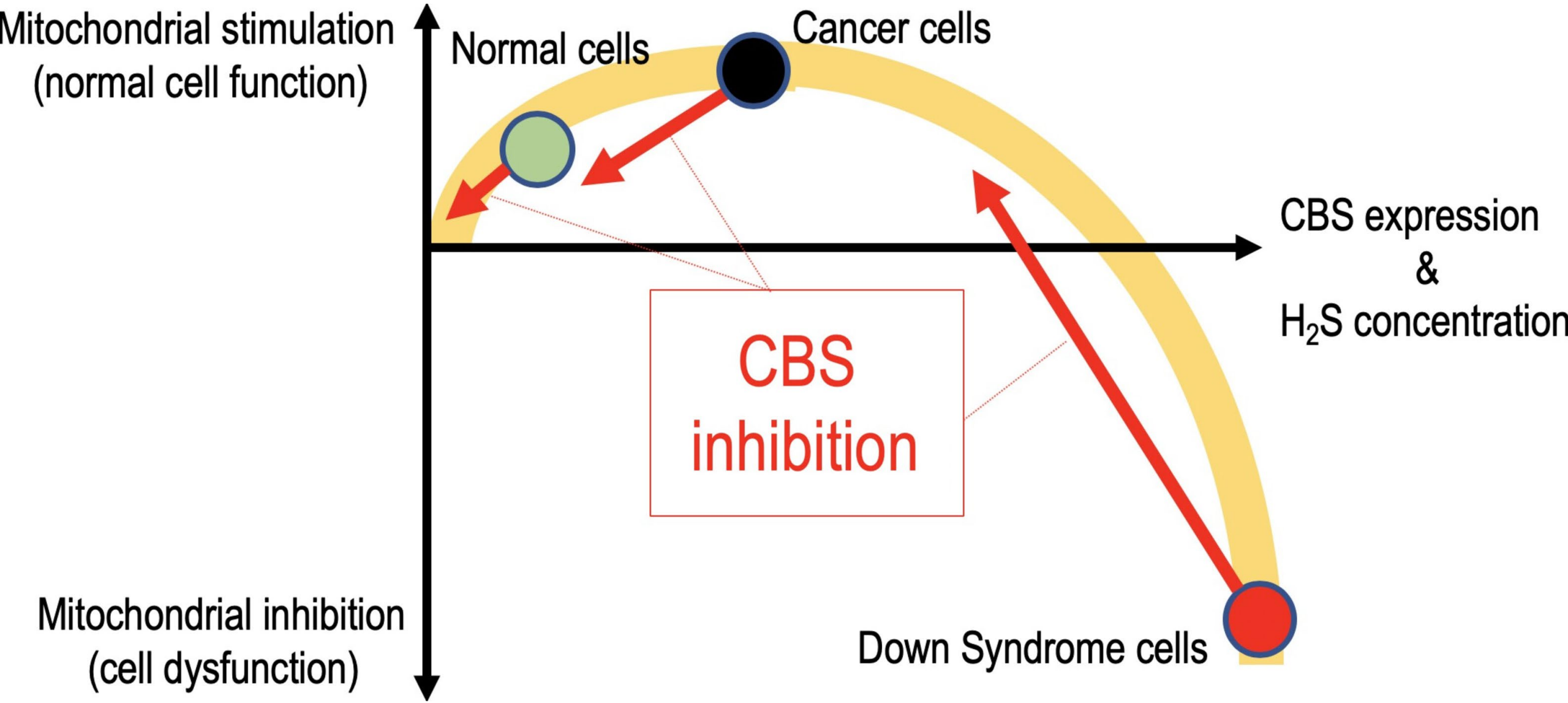
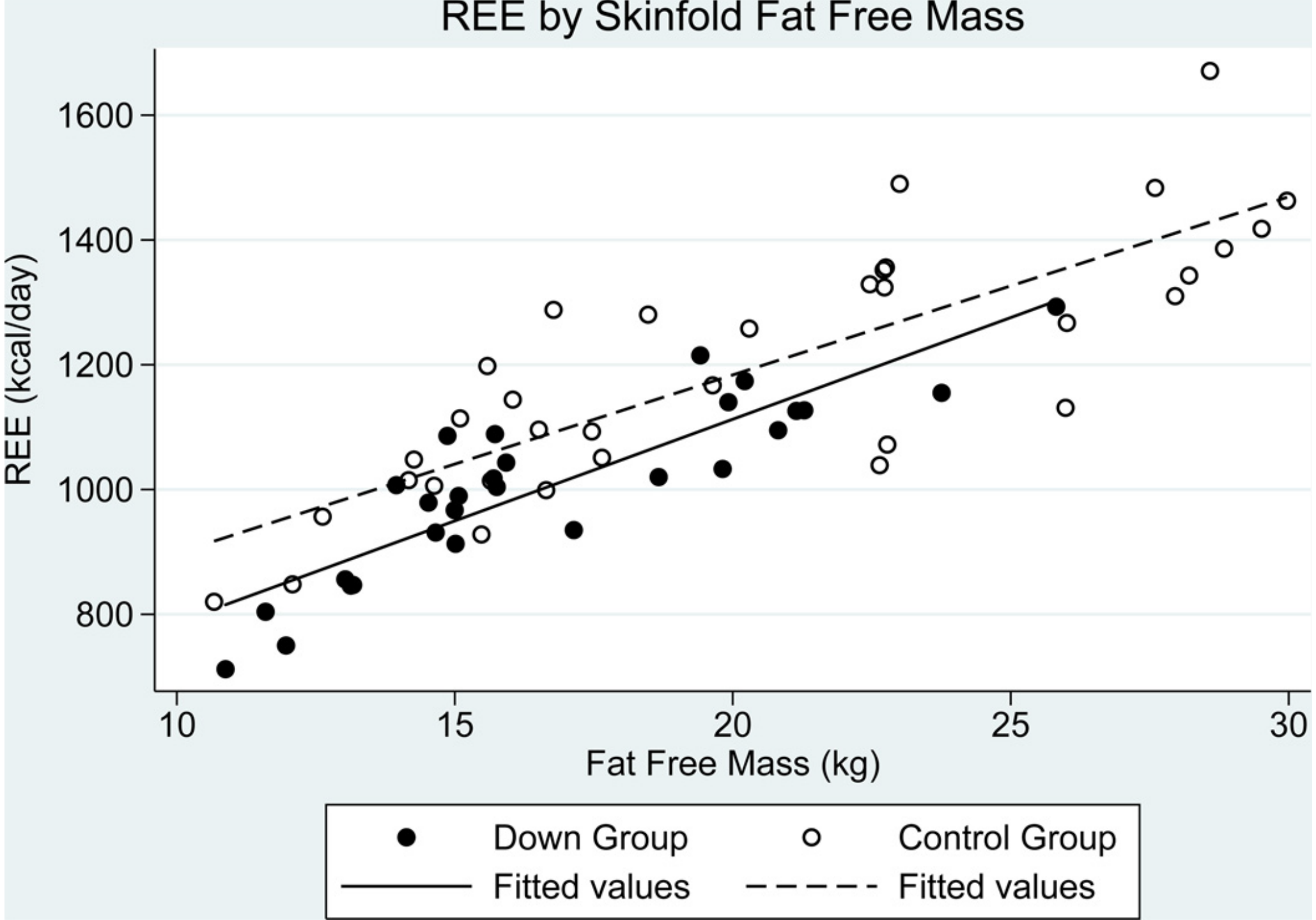
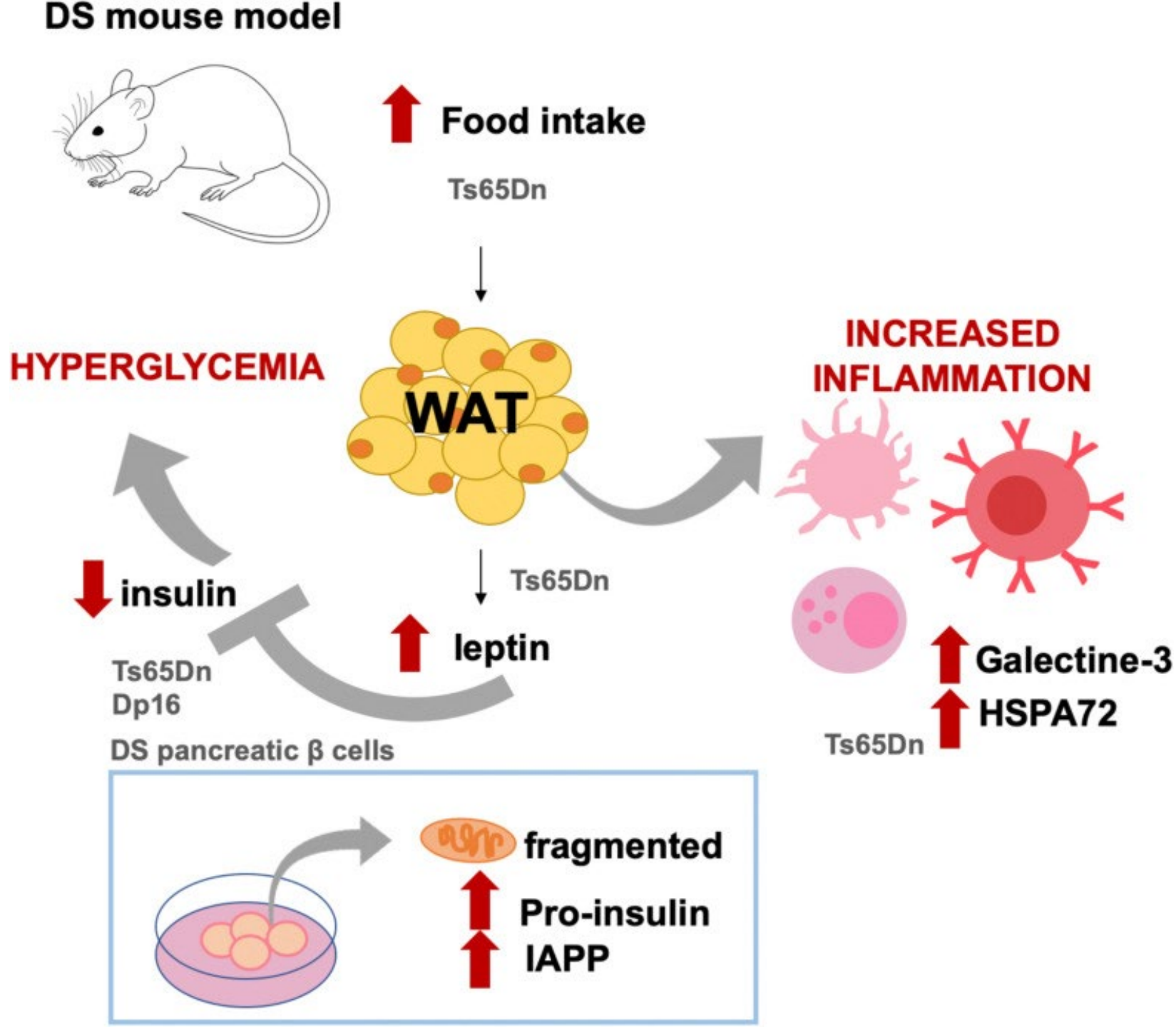

Mitochondrial stimulation
(normal cell function)
Normal cells
Cancer cells
CBS expression
&
H_2S concentration
CBS
inhibition
Mitochondrial inhibition
(cell dysfunction)
Down Syndrome cells


REE by Skinfold Fat Free Mass
REE (kcal/day)
1600
1400
1200
1000
800
10
15
20
25
30
Fat Free Mass (kg)
Down Group
Control Group
Fitted values
Fitted values


DS mouse model
Food intake
Ts65Dn
HYPERGLYCEMIA
WAT
INCREASED INFLAMMATION
Ts65Dn
insulin
leptin
Ts65Dn
Dp16
Galectine-3
HSPA72
Ts65Dn
DS pancreatic β cells
fragmented
Pro-insulin
IAPP

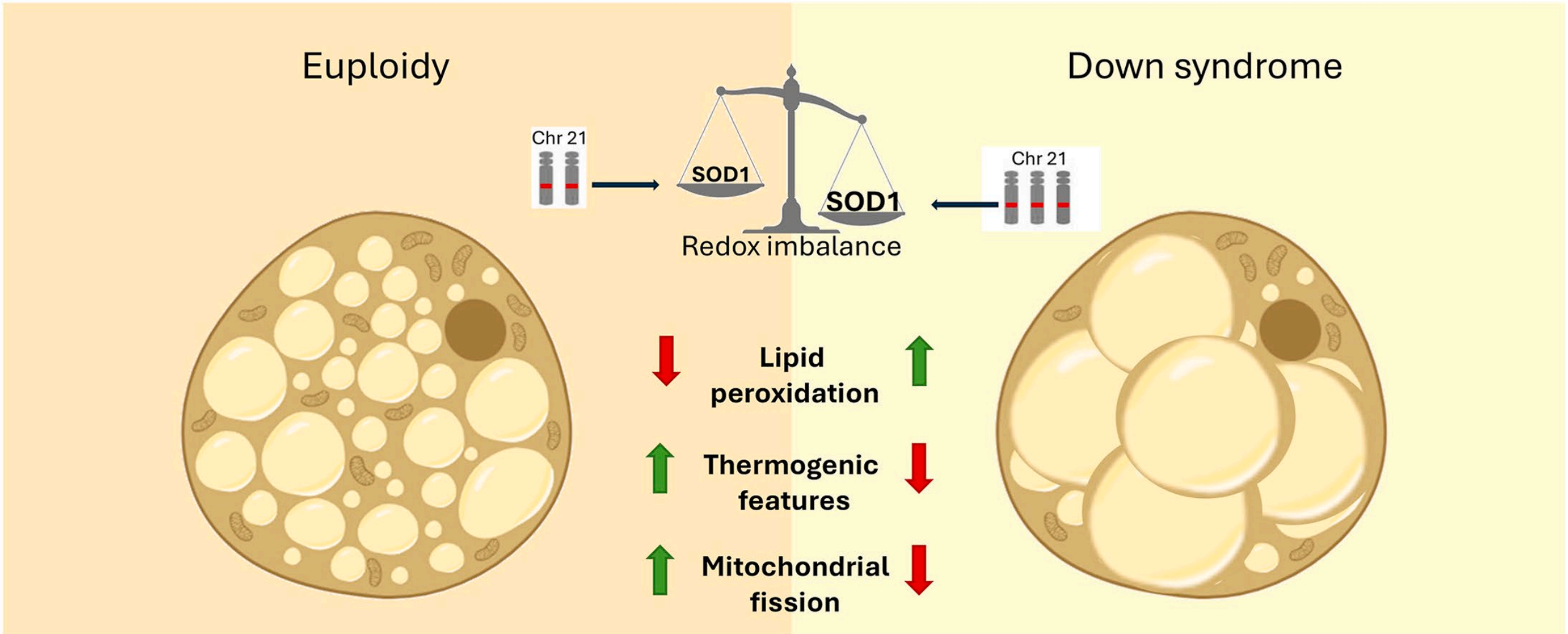

Euploidy
Down syndrome
Chr 21
SOD1
SOD1
Chr 21
Redox imbalance
Lipid peroxidation
Thermogenic features
Mitochondrial fission

Table II. Serum levels of adipocytokines in study subpopulation

Variables	Nonobese children with DS (n = 40)	Obese children with DS (n = 44)	*P*
Leptin, ng/mL	8.88 ± 6.71	21.44 ± 9.49	**<.001**
Adiponectin, μg/mL	7.03 ± 0.80	5.75 ± 0.79	**<.001**
TNF-α, pg/mL	76.23 ± 22.02	105.78 ± 67.41	**.01**
IL-6, pg/mL	144.76 ± 56.57	154.86 ± 55.39	>.05

Data are mean ± SD. $P < .05$ was considered significant.
Bold indicates the values reached significant level.

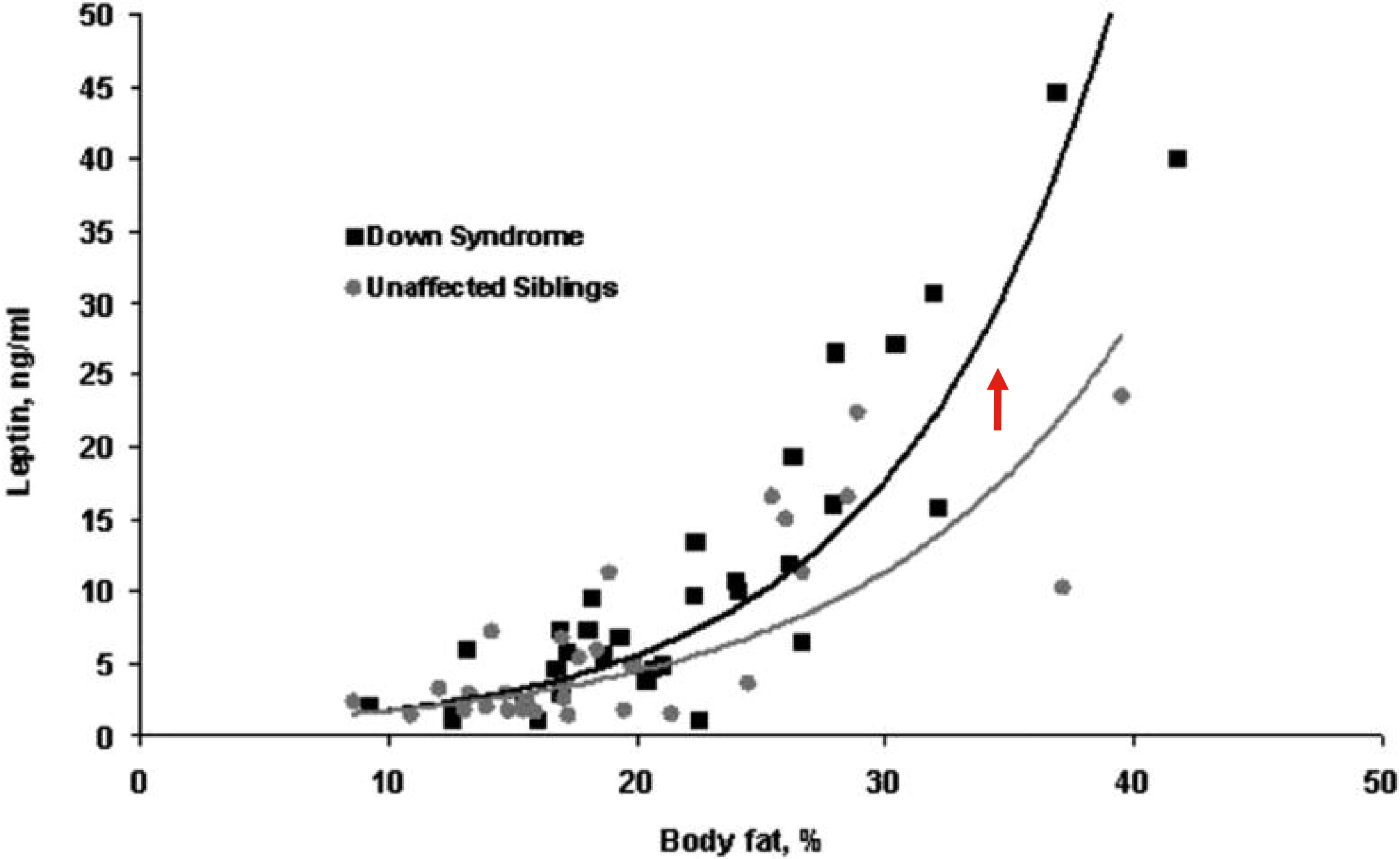

Down Syndrome
Unaffected Siblings
Leptin, ng/ml
Body fat, %
0
5
10
15
20
25
30
35
40
45
50
0
10
20
30
40
50

Table 3. Statistical comparison between mean values of serum leptin level of different studied groups.

Variable	Group							
	Group I DS with studied sibs No=20		Group II DS-without studied sibs No=20		Group III Sibs of group I No=20		Group IV Healthy controls No=20	
	Range	M±SD	Range	M±SD	Range	M±SD	Range	M±SD
Leptin (ng/ml)	10–39	21.2±7.2	10–39	20.3±8.1	2.4–8	5.2±1.6	2.5–10	5.2±2.05

Group I V II		Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV	
t	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
0.354	0.7	9.64	0.0001**	9.5	0.0001**	8.103	0.0001**	8.011	0.0001**	0.025	0.9

N.B. Student "*t*" test was used for statistical comparison.

P value>0.05=statistically non significant. *P* value<0.01**=statistically highly significant.

M: mean; SD: standard deviation.

Table 5. Statistical comparison between mean values of serum TSH levels of different studied groups.

Variable	Group							
	Group I DS with studied sibs No=20		Group II DS-without studied sibs No=20		Group III Sibs of group I No=20		Group IV Healthy controls No=20	
	Range	M±SD	Range	M±SD	Range	M±SD	Range	M±SD
TSH (ulU/ml)	2.9–5	4.2±0.7	2.1–5	4.1±0.85	1.3–3.6	2.3±0.77	1.3–3.9	2.8±0.76

Group I VS II		Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV	
t	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
0.34	0.7	8.23	0.0001**	6.26	0.0001**	7.164	0.0001**	5.36	0.0001**	1.92	0.06

N.B. Student "*t*" test was used for statistical comparison.

P value>0.05=statistically non significant. *P* value<0.01**=statistically highly significant.

M: mean; SD: standard deviation.

TSH: thyroid stimulating hormone.

Table 6. Statistical comparison between mean values of serum FT4 (pmol/l) level of different studied groups.

Variable	Group							
	Group I DS with studied sibs No=20		Group II DS-without studied sibs No=20		Group III Sibs of group I No=20		Group IV Healthy controls No=20	
	Range	M±SD	Range	M±SD	Range	M±SD	Range	M±SD
FT4 (pmol/l)	10.5–17.7	13.3±1.9	9.8–19.3	14.29±2.5	10.5–16.2	12.5±1.5	12.1–17.6	14.21±1.5

Group I VS II		Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV	
t	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
1.29	0.2	1.537	0.132	1.53	0.134	2.688	0.01*	0.122	0.9	3.514	0.001**

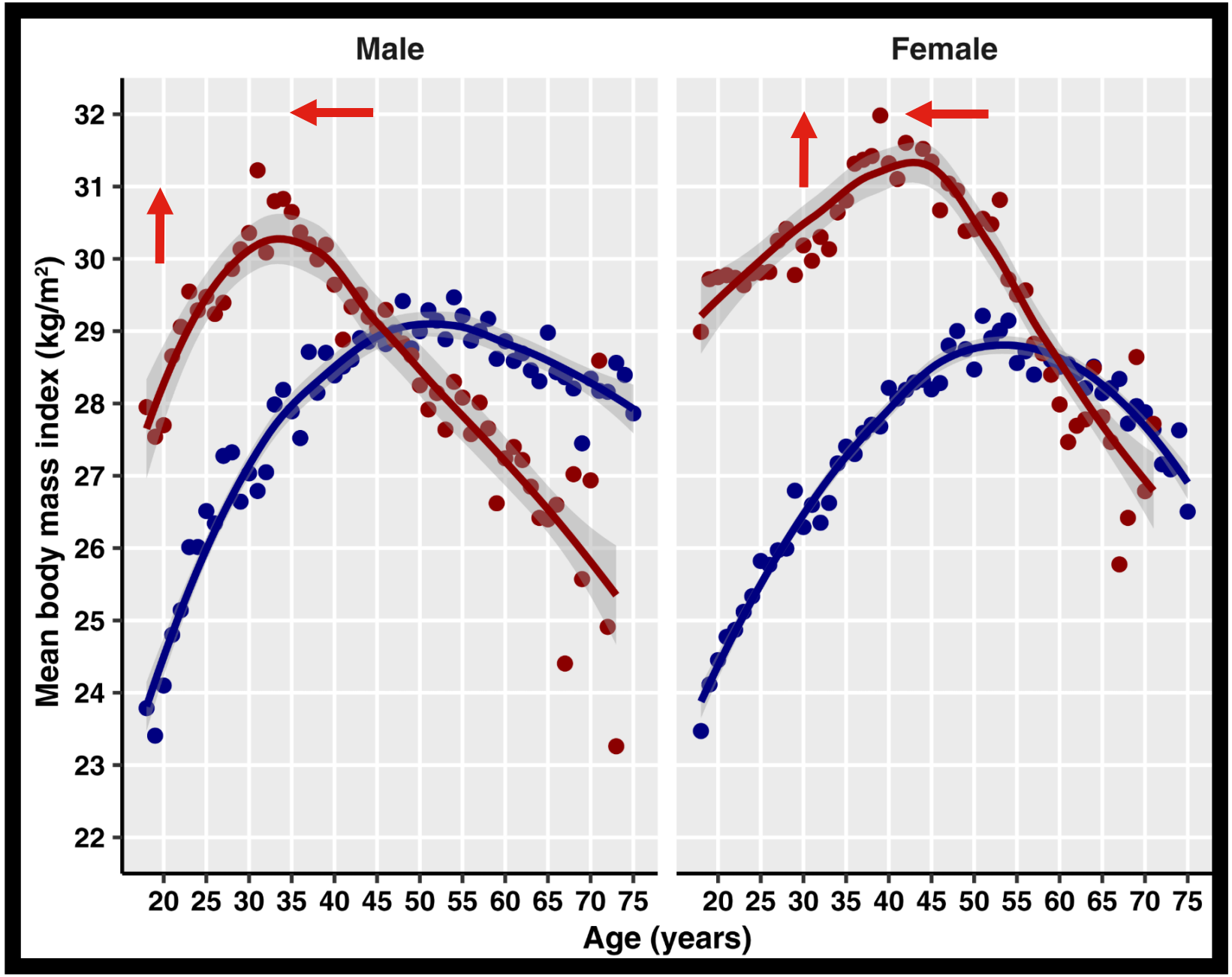
N.B. Student "*t*" test was used for statistical comparison.

P value>0.05=statistically non significant. *P* value<0.05*=statistically significant.

P value<0.01**=statistically highly significant. M: mean; SD: standard deviation.

FT4: free thyroxin.

Figure 2



Mean BMI by single year of age and sex for patients with DS (red) and control patients (blue).

Caveat

- **BMI after age 40 actually downtrends**
  - **Driven by Alzheimer's**
    - **Coincides with amyloid deposition**
    - Amyloid deposition affects Hypothalamus, Metabolism, Feeding
    - ~ 0.23 kg/m2 drop per year
      - **> 1 kg/m2 yearly drop = 35% higher risk of Alzheimer** in general population

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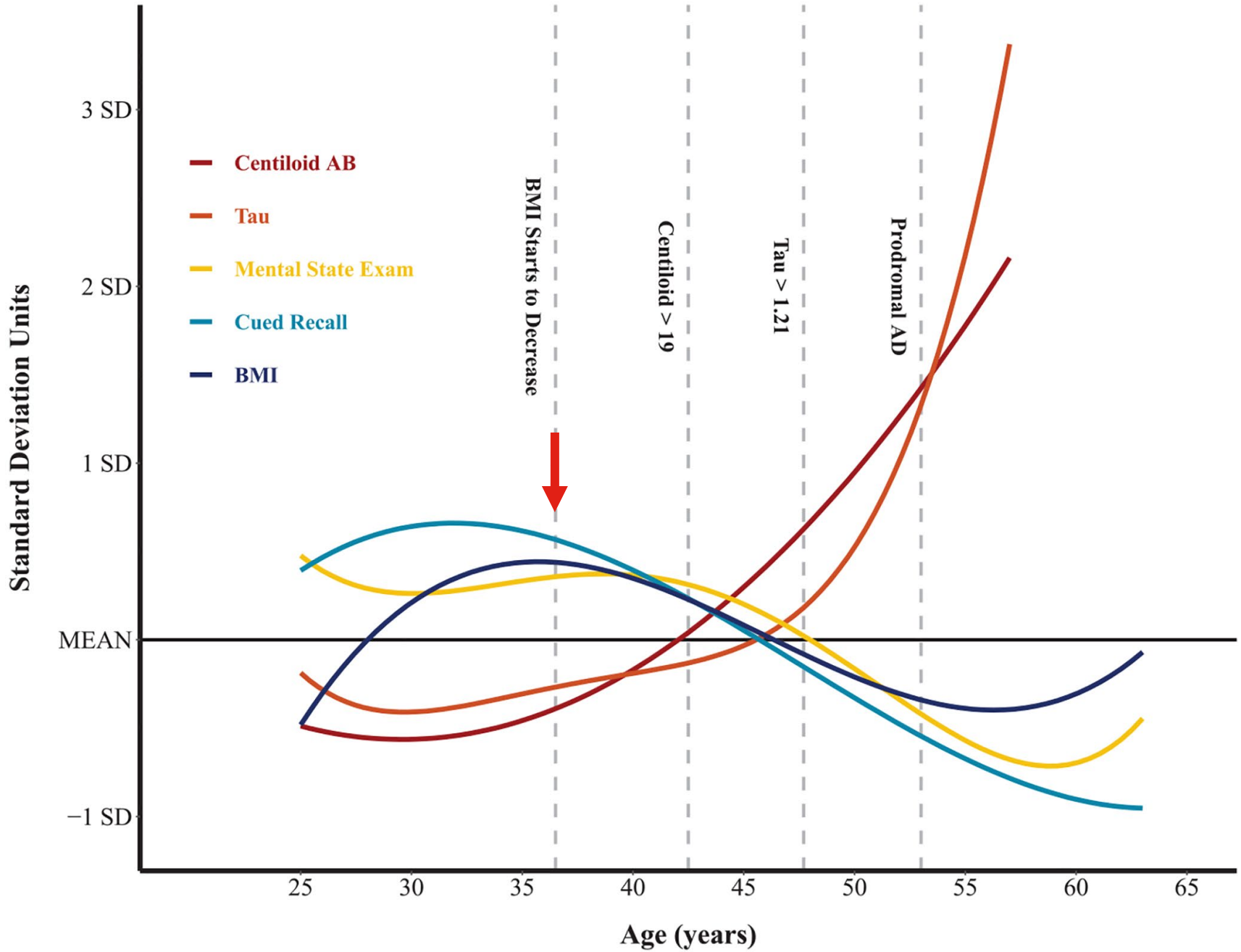
Standard Deviation Units
3 SD
2 SD
1 SD
MEAN
−1 SD
Centiloid AB
Tau
Mental State Exam
Cued Recall
BMI
BMI Starts to Decrease
Centiloid > 19
Tau > 1.21
Prodromal AD
25
30
35
40
45
50
55
60
65
Age (years)

Longterm Consequences

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Metabolic Syndrome

- At same BMI as general population:
  - **Higher fat mass**
  - **Lower lean mass**
  - Higher fasting glucose
  - **Insulin resistance**
  - **Higher triglycerides**
  - Lower HDL

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Table 2. Statistical comparison between mean values of body fat% of different studied groups.

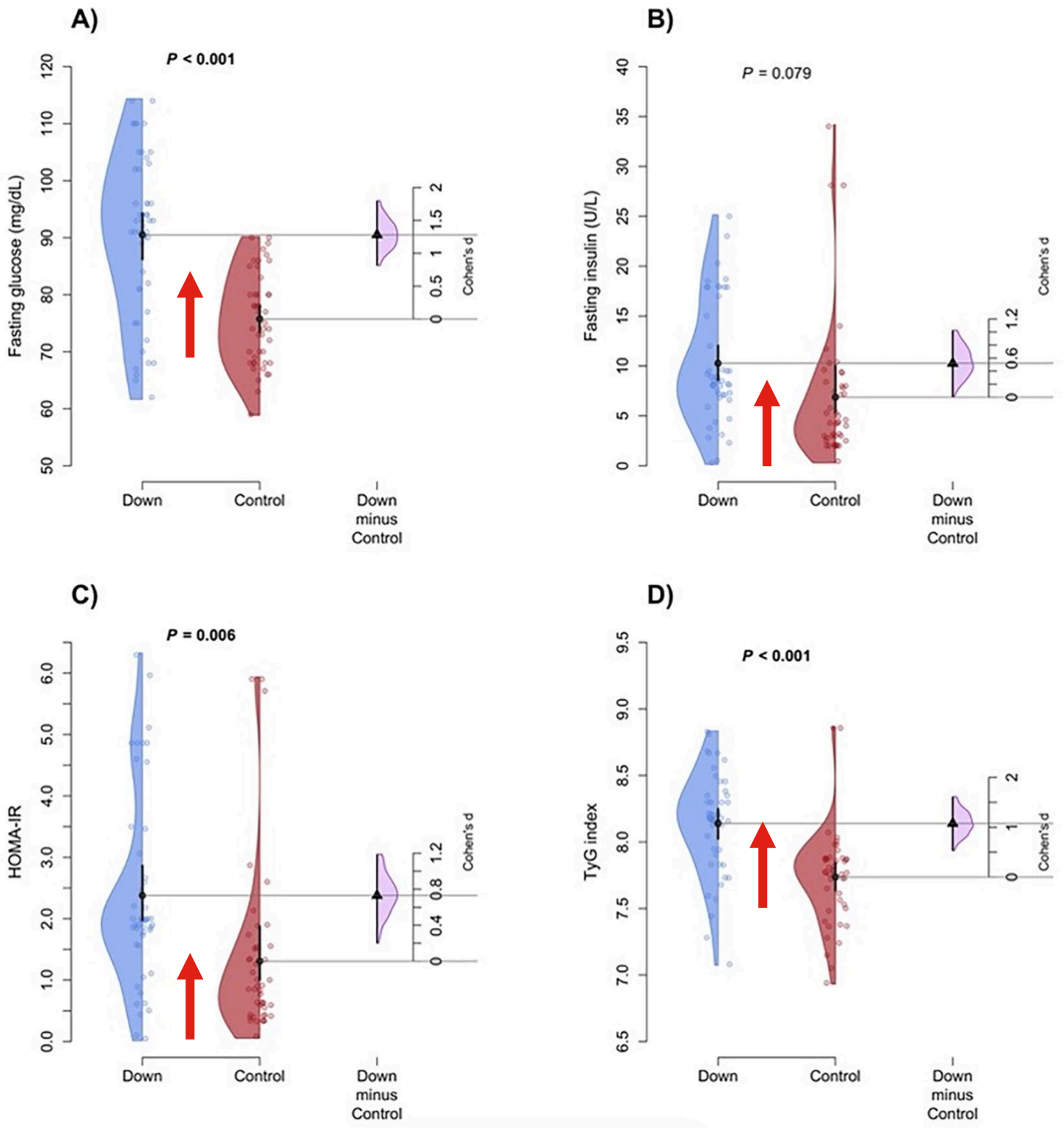
Variable	Group							
	Group I DS with studied sibs No=20		Group II DS-without studied sibs No=20		Group III Sibs of group I No=20		Group IV Healthy controls No=20	
	Range	M±SD	Range	M±SD	Range	M±SD	Range	M±SD
Body fat%	17.6–29.8	24.5±3.6	17.3–29.5	23.5±3.5	15.4–22.8	20.2±2.5	13.3–23	17.5±3.0

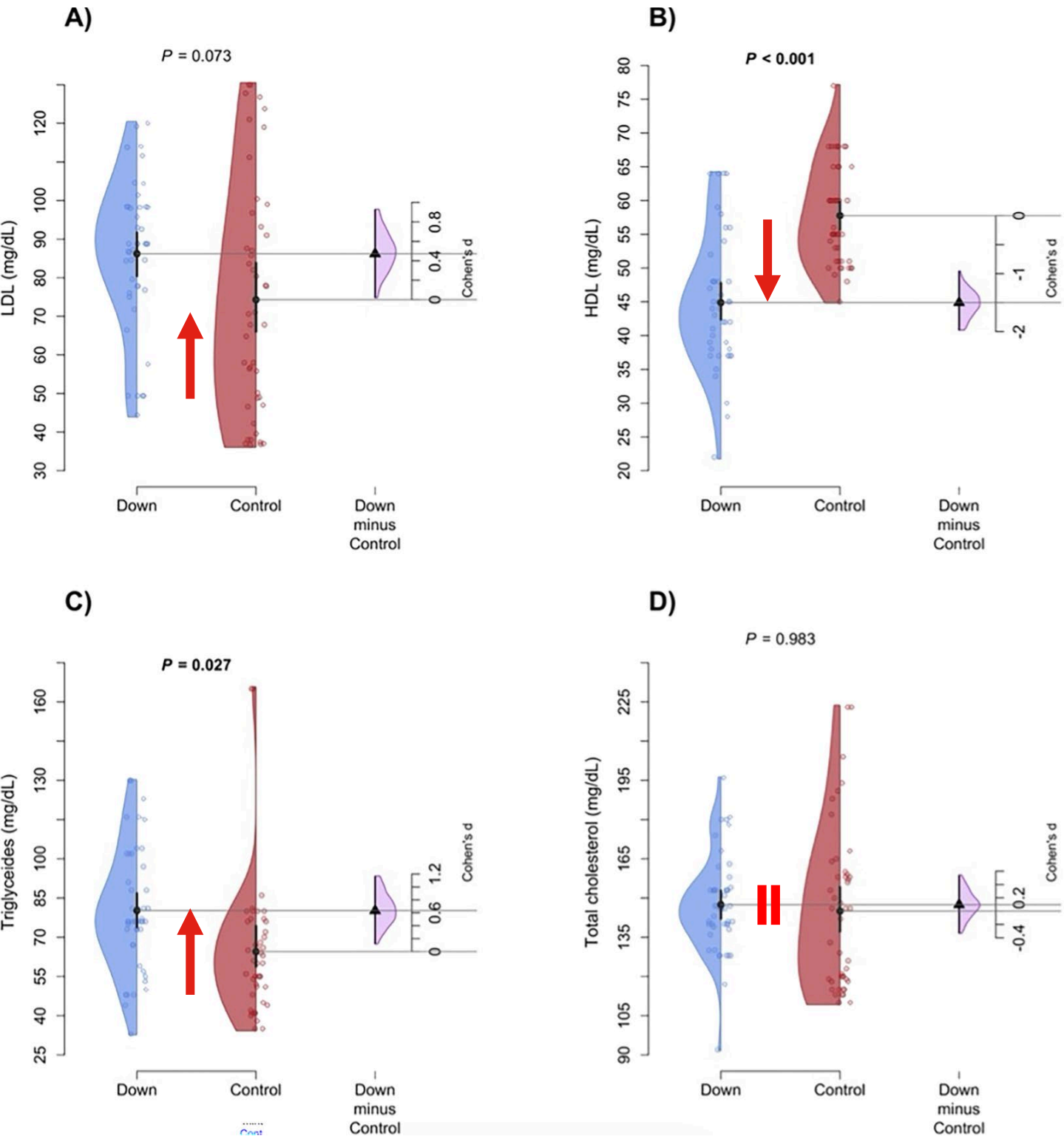
Group I VS II		Group I VS III		Group I VS IV		Group II VS III		Group II VS IV		Group III VS IV	
t	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*	*t*	*P*
0.81	0.4	4.314	0.0001**	6.54	0.0001**	3.451	0.001**	5.769	.0001**	2.96	0.005**

N.B. Student "*t*" test was used for statistical comparison.

P value>0.05=statistically non significant. *P* value<0.05=statistically significant.

P value<0.01**=statistically highly significant.


A)
P < 0.001
Fasting glucose (mg/dL)
50
60
70
80
90
100
110
120
Cohen's d
0
0.5
1
1.5
2
Down
Control
Down minus Control
B)
P = 0.079
Fasting insulin (U/L)
0
5
10
15
20
25
30
35
40
Cohen's d
0
0.6
1.2
Down
Control
Down minus Control
C)
P = 0.006
HOMA-IR
0.0
1.0
2.0
3.0
4.0
5.0
6.0
Cohen's d
0
0.4
0.8
1.2
Down
Control
Down minus Control
D)
P < 0.001
TyG index
6.5
7.0
7.5
8.0
8.5
9.0
9.5
Cohen's d
0
1
2
Down
Control
Down minus Control


A)
P = 0.073
LDL (mg/dL)
30 40 50 60 70 80 90 100 120
0 0.4 0.8
Cohen's d
Down
Control
Down minus Control
B)
P < 0.001
HDL (mg/dL)
20 25 30 35 40 45 50 55 60 65 70 75 80
0 -1 -2
Cohen's d
Down
Control
Down minus Control
C)
P = 0.027
Triglyceides (mg/dL)
25 40 55 70 85 100 130 160
0 0.6 1.2
Cohen's d
Down
Control
Down minus Control
D)
P = 0.983
Total cholesterol (mg/dL)
90 105 135 165 195 225
-0.4 0.2
Cohen's d
Down
Control
Down minus Control

Diabetes

- **4 times more likely** (at age <30)
  - Reverses later ages especially after 45
- **Diagnosed 15 years earlier** (Median age 38 vs 53)
  - Need **screening earlier: Every 2 years after 21** if overweight
    - **Either Fasting Glucose or A1c (but should get both)**
      - **A1c actually lower in DS suspected from macrocytosis and higher RBC turnover**
  - But **better metabolic control** than general population:
    - **Less insulin use** and **organ damage** (ex: retinopathy, nephropathy, neuropathy)

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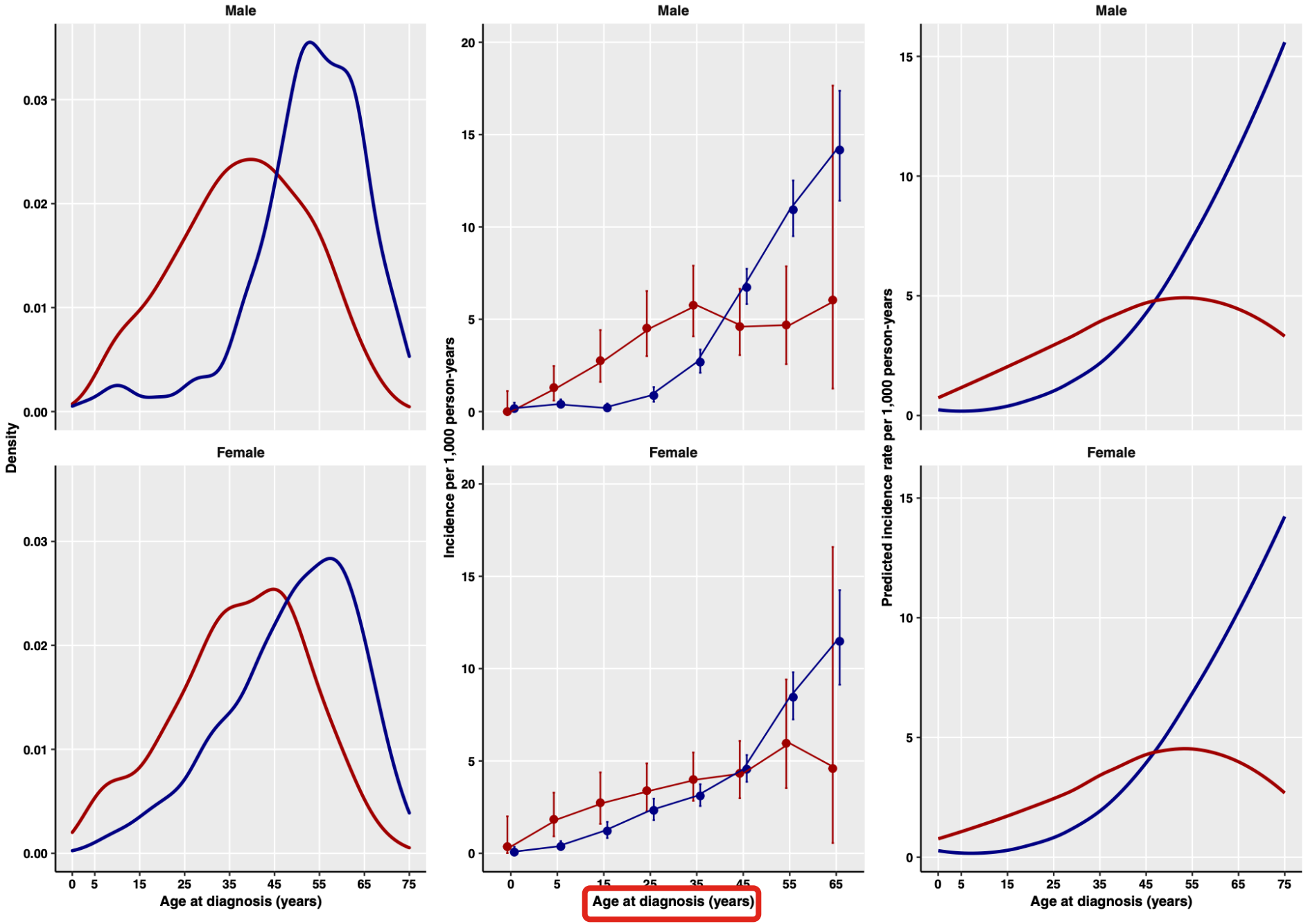

Figure 1—Distribution of age at diagnosis of diabetes by sex for patients with DS (red) and control patients (blue). Left: Density plot of incident cases. Middle: Age-specific incidence rates (95% CIs). Right: Predicted incidence by age from regression model.

Type 2 Diabetes

- **Type 2 is 10 times higher** in ages 5-14 years
  - Remains higher till 45 years then is **lower risk after 54 years**
- **Strongly correlated with BMI** (similar to non-DS patients)
  - **Incidence per 1000** person years:
    - **7.58 in Obese** (vs. 16.89 in control patients)
    - 3.90 in Overweight (vs. 7.12 in control patients)
    - 1.93 in Normal weight (vs. 2.24 in control patients)

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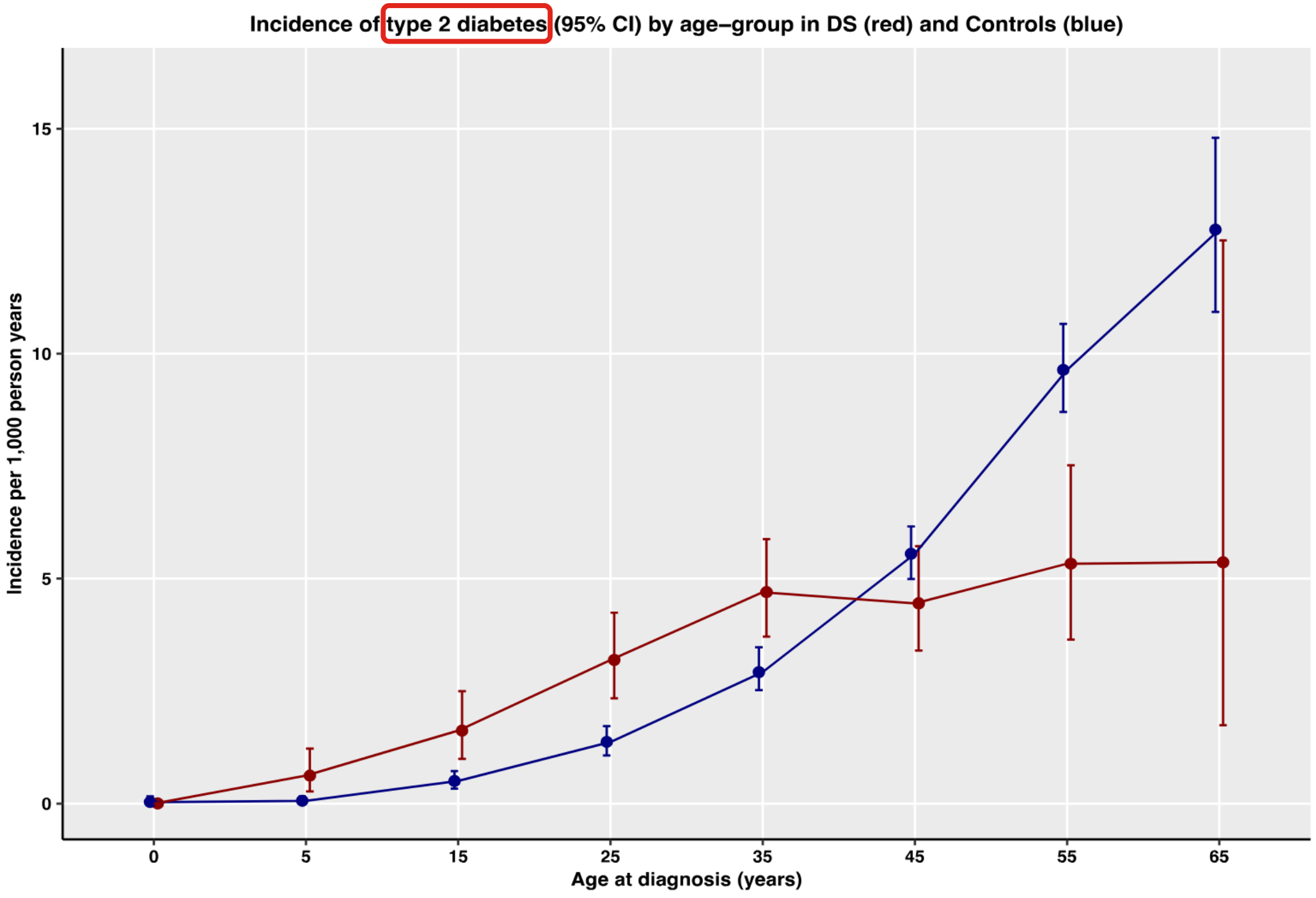
Incidence of type 2 diabetes (95% CI) by age–group in DS (red) and Controls (blue)
Incidence per 1,000 person years
15
10
5
0
0
5
15
25
35
45
55
65
Age at diagnosis (years)

Note about Type 1 Diabetes

- **Type 1 is 3 times higher** especially in **adolescence**
  - **But Type 1 DOES NOT correlate with BMI**
- Down Syndrome recognized as **immunodeficient state**
  - Higher rates of Auto-immune / antibodies (ex: **Hashimoto, Celiac, T1DM**, etc.)

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Note about Type 1 Diabetes

- Genes on Chromosome 21:
  - **Inhibit pancreatic β-cells**
    - Dual-specificity tyrosine phosphorylation regulated kinase 1A (*DYRK1A*)
    - Regulator of calcineurin 1 (*RCAN1*)
  - **Regulate immune system (T-cells)**
    - Autoimmune regulatory protein (AIRE)

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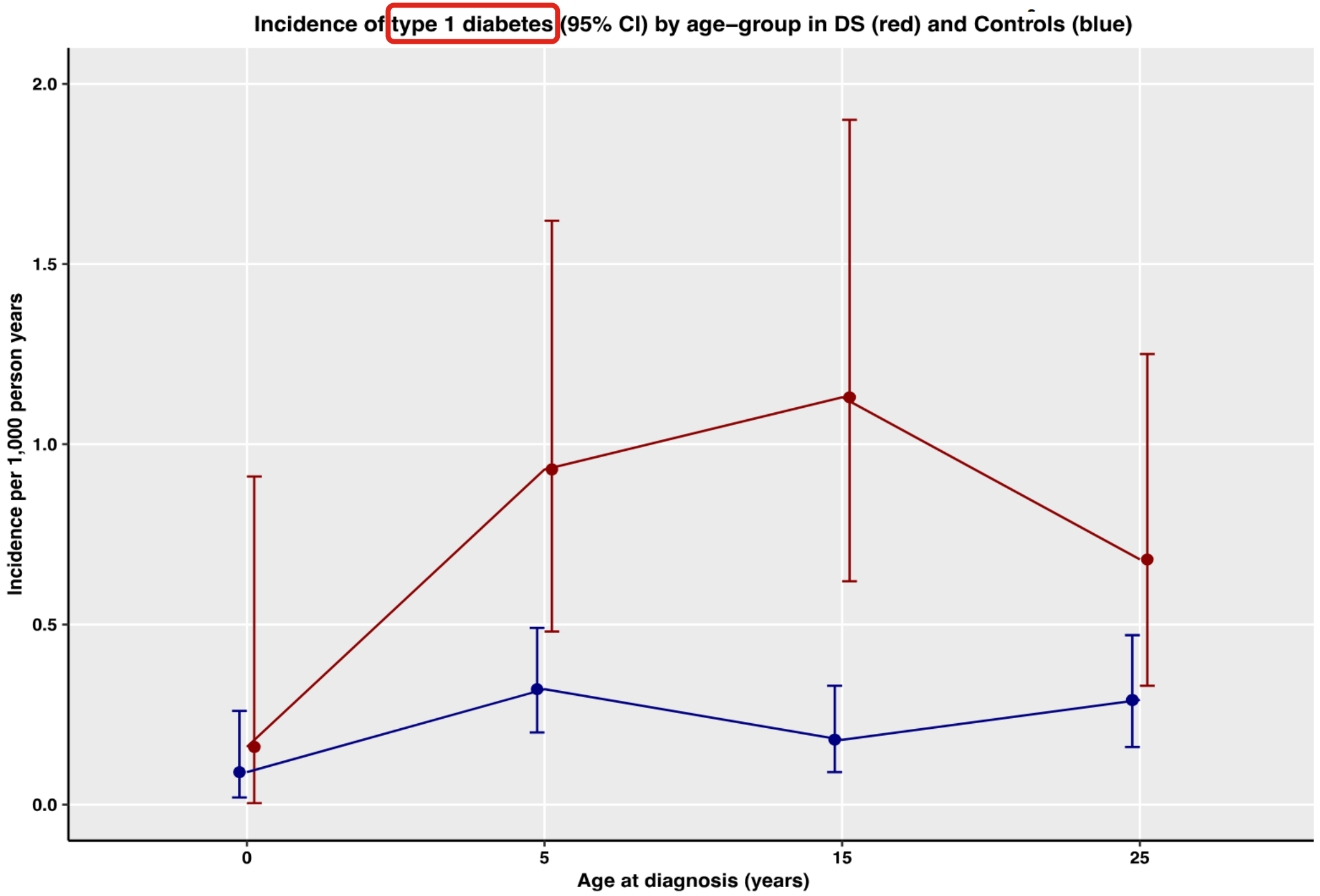
Incidence of type 1 diabetes (95% CI) by age–group in DS (red) and Controls (blue)
Incidence per 1,000 person years
2.0
1.5
1.0
0.5
0.0
0
5
15
25
Age at diagnosis (years)

Fatty Liver Disease

- Both from Obesity and DS specific paths
  - In 45% non-obese and in **82% overweight children with DS**
    - Versus 5.7% and **33% in other European** children
- Compared to controls **there is increased liver enzymes**

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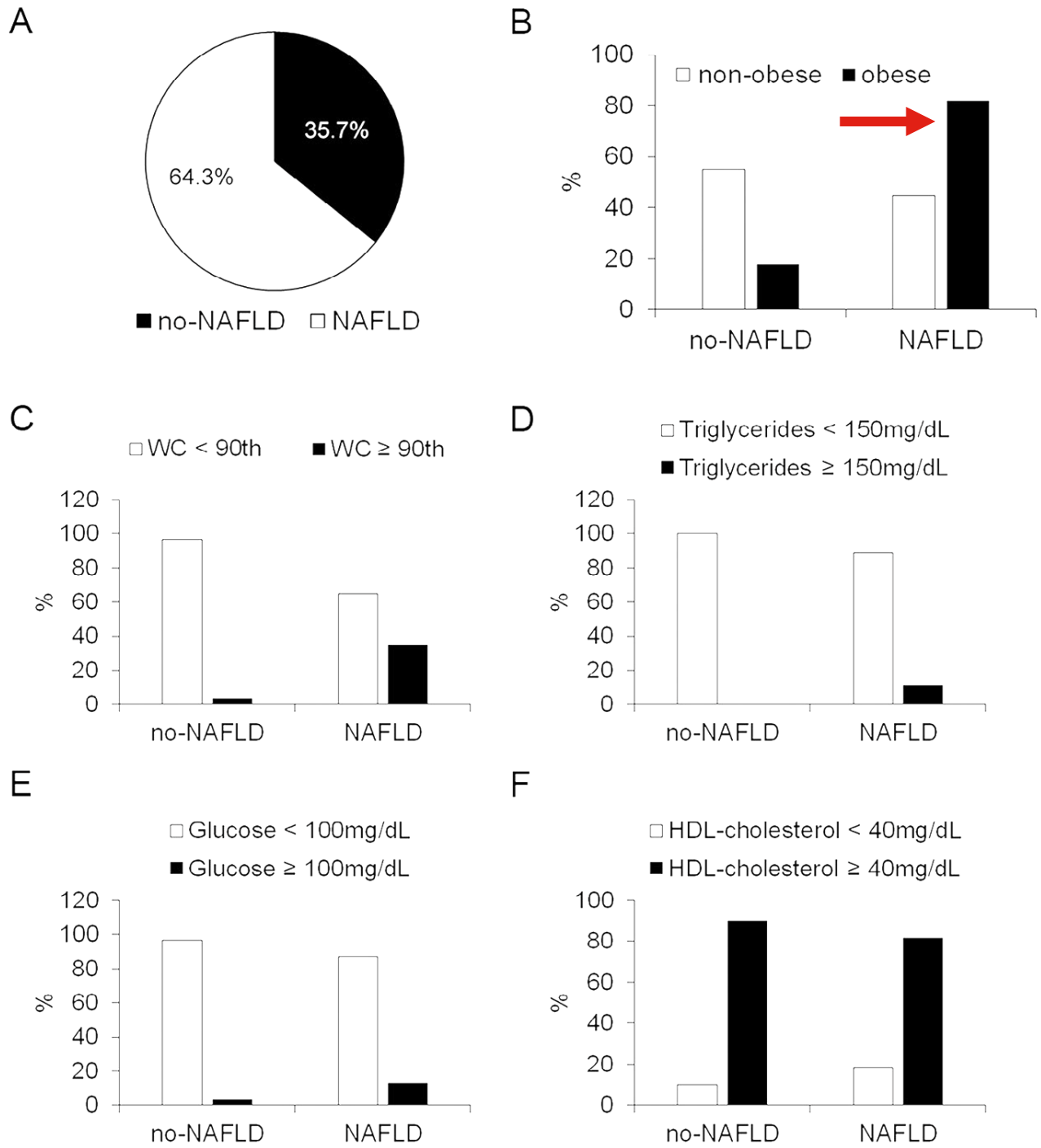
	Down (n=48)	Controls (n=47)	Down-controls		
	Mean (95% CI)	Mean (95% CI)	Mean difference (95% CI)	p-Value	Cohen's d
Liver enzymes					
Aspartate aminotransferase, U/L	33.4 (30.7, 36.0)	23.7 (21.3, 26.1)	9.62 (5.99, 13.26)	**<0.001**	1.528
γ-Glutamyltransferase, U/L	14.3 (12.4, 16.2)	11.6 (10.2, 13.0)	2.68 (0.82, 4.54)	**0.006**	0.774
Alanine aminotransferase, U/L	21.7 (18.9, 24.5)	13.6 (11.9, 15.3)	8.1 (4.78, 11.41)	**<0.001**	1.390
AST-ALT ratio	1.70 (1.53, 1.86)	1.93 (1.57, 2.28)	−0.23 (−0.63, 0.17)	0.251	0.383


A
35.7%
64.3%
no-NAFLD
NAFLD
B
non-obese
obese
%
100
80
60
40
20
0
no-NAFLD
NAFLD
C
WC < 90th
WC ≥ 90th
%
120
100
80
60
40
20
0
no-NAFLD
NAFLD
D
Triglycerides < 150mg/dL
Triglycerides ≥ 150mg/dL
%
120
100
80
60
40
20
0
no-NAFLD
NAFLD
E
Glucose < 100mg/dL
Glucose ≥ 100mg/dL
%
120
100
80
60
40
20
0
no-NAFLD
NAFLD
F
HDL-cholesterol < 40mg/dL
HDL-cholesterol ≥ 40mg/dL
%
100
80
60
40
20
0
no-NAFLD
NAFLD

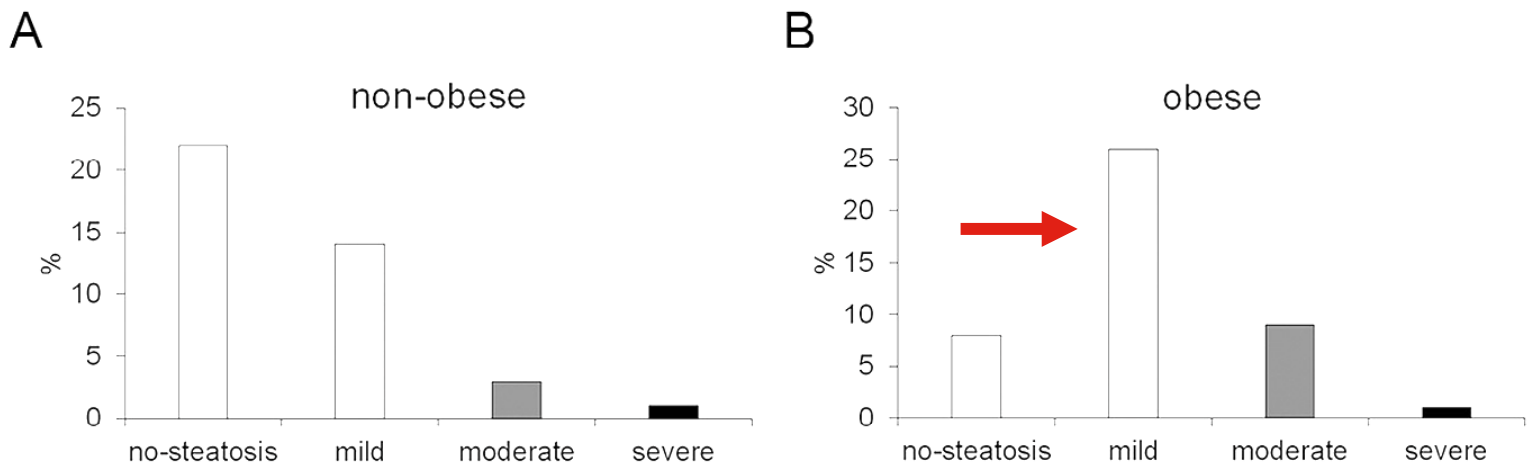


Figure 4. Severity of NAFLD in Italian children with DS. Stratification of severity of steatosis assessed by ultrasound scan in **A,** nonobese and **B,** obese/overweight (obese) subjects with DS.

Metabolic Syndrome Implications

- Associated with **higher risk of death from coronary heart disease, hypertension and diabetes**
- **HOWEVER**, ASCVD events were **mostly cerebrovascular**
- Coronary / **myocardial infarctions were actually lower**
  - Theory: Chronically **lower blood pressure is protective**
    - **Absence of "stiff arteries"** despite ASCVD risk factors as above
      - Although BP went up with BMI – still lower than general population trend

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Table 4. Risk of cardiovascular events in patients with Down Syndrome. (Data are n [%] patients unless otherwise indicated).

	DS (n = 4,081)	Non-DS (n = 16,324)	Model 1 Risk Ratio (95% CI)	Model 2 Risk Ratio (95% CI)
Cerebrovascular event	**88 (2.2)**	**129 (0.8)**	**2.70 (2.08–3.53)*****	**1.95 (1.49–2.56)*****
Stroke	77 (1.9)	105 (0.6)	2.91 (2.18–3.88)***	2.09 (1.55–2.80)***
Ischemic stroke	36 (0.9)	38 (0.2)	3.76 (2.39–5.92)***	2.59 (1.63–4.11)***
Hemorrhagic stroke	25 (0.6)	30 (0.2)	3.31 (1.95–5.60)***	2.67 (1.56–4.57)***
Coronary event	**55 (1.3)**	**290 (1.8)**	**0.74 (0.57–0.98)***	**0.47 (0.35–0.62)*****
MI	44 (1.1)	259 (1.6)	0.67 (0.49–0.91)**	0.42 (0.30–0.57)***

DS = Down Syndrome; MI = myocardial infarction; TIA = transient ischemic attack.

Cerebrovascular events include stroke (ischemic, hemorrhagic or unspecified) or transient ischemic attack.

Coronary events include myocardial infarction or angina.

Model 1: adjusted for sex

Model 2: adjusted for sex and overall cardiovascular risk

(Overall cardiovascular risk is represented by a variable that includes the presence of any of congenital heart disease, cardiac arrhythmia, pulmonary hypertension, hypertension, diabetes mellitus, sleep apnea, smoking or Moyamoya disease)

* P<0.05

** P<0.01

*** P<0.001

Table 2. *Cardiovascular outcomes in DS as compared to non-DS.*

	N	aHR (95% CI)
Intracerebral hemorrhage	62	5.03 (3.67–6.88)[a]
Subarachnoid hemorrhage	11	1.20 (0.59–2.44)[a]
Any hemorrhagic stroke[b]	71	5.14 (3.84–6.89)[a]
Ischemic stroke	121	4.41 (3.53–5.52)
Stroke NOS	21	6.30 (3.59–11.06)[a]
Any stroke[c]	199	4.18 (3.50–4.98)[a]
Acute myocardial infarction	32	0.85 (0.56–1.29)
Any coronary artery surgery	5	0.13 (0.05–0.63)[a]

TABLE II. Differences Between Groups in Hemodynamic Parameters and Surrogate Markers of Atherosclerosis

	Adults With DS	Controls	Adjusted Effect	*P* Value
Hemodynamic variables				
SBP, mm Hg	113.3±12.9	125.4±12.9	−11.4 [−16.8 to −6.1]	<.01[a]
DBP, mm Hg	70.3±9.0	76.8±9.9	−5.1 [−8.9 to −1.2]	<.01[a]
AoSBP, mm Hg	101.3±12.5	113.5±14.2	−8.5 [−13.6 to −3.4]	<.01[a]
AoDBP, mm Hg	71.0±9.2	78.3±10.3	−5.8 [−9.7 to −1.8]	<.01[a]
Subclinical vascular disease				
PWV	5.9±1.3	6.9±2.0	−0.93 [−1.2 to −0.6]	<.01[a]
cIMT	0.514±0.115	0.500±0.09	0.04 [−0.0009 to 0.1]	.06

Abbreviations: AoDBP, aortic estimated diastolic blood pressure; AoSBP, aortic estimated systolic blood pressure; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; DS, Down syndrome; PWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure. Data are expressed as mean±standard error or as number (percentage).

[a]Significant at $P<.05$ after adjustment for age and sex.

Sleep Apnea

- **~90% of children & adults (~45% Severe)**
  - Versus 2-5% general pediatric population
- **Severe OSA** / **Lower SaO2** more **likely if Obese** or **Older**
- **AAP: All children must be screened by age 4 with sleep study**

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Sleep Apnea

- **Anatomical** Reasons:
  - Midface hypoplasia, Macroglossia, Mandible shortening, Hypotonia
  - 50% have **Tonsillar Hypertrophy** (but **not correlated with OSA**)
    - **After Adenotonsillectomy 80% have persistent OSA**
      - 2/3 have pharyngomalacia while 50% have laryngomalacia

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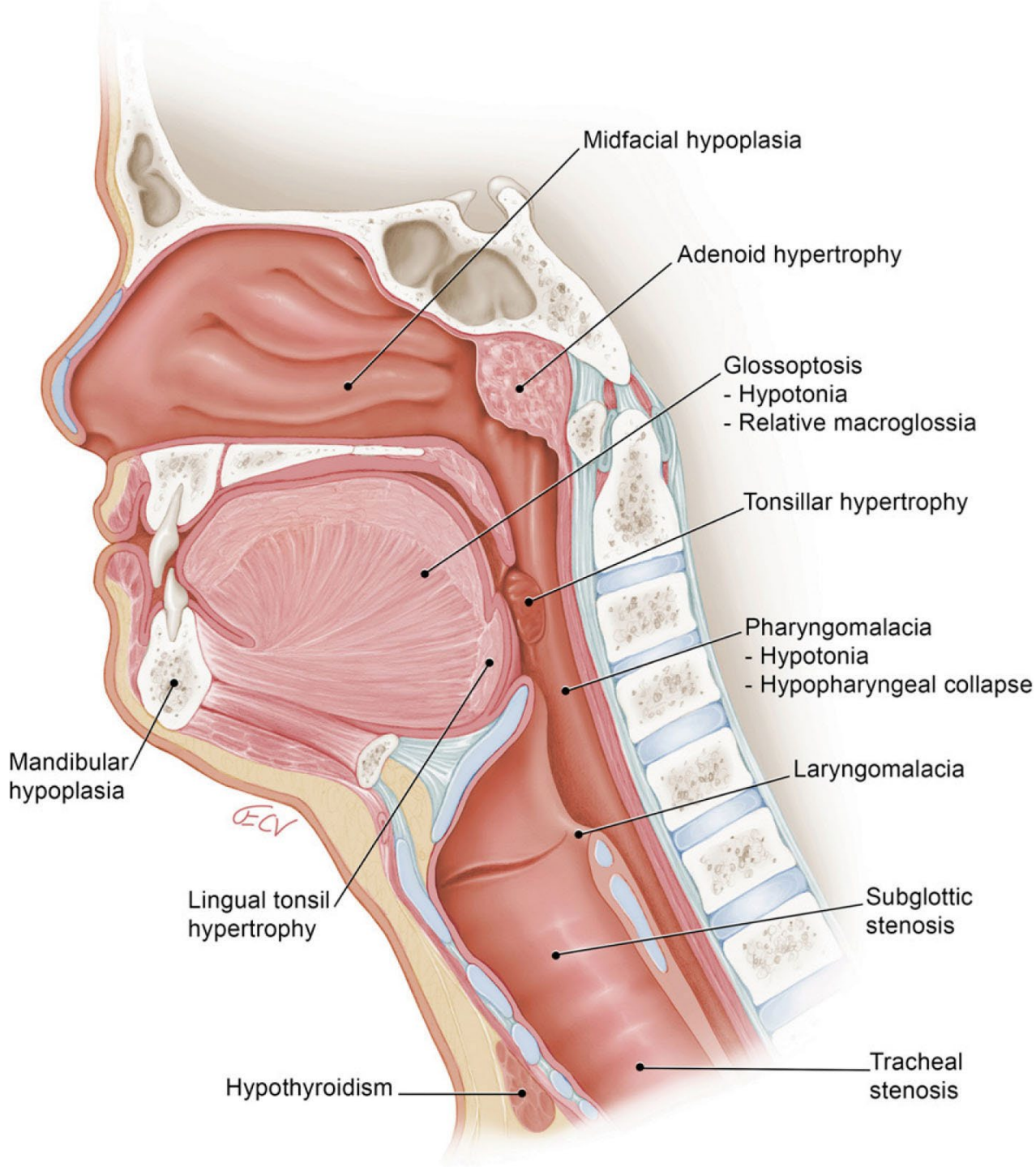
Midfacial hypoplasia
Adenoid hypertrophy
Glossoptosis
- Hypotonia
- Relative macroglossia
Tonsillar hypertrophy
Pharyngomalacia
- Hypotonia
- Hypopharyngeal collapse
Laryngomalacia
Subglottic stenosis
Tracheal stenosis
Hypothyroidism
Lingual tonsil hypertrophy
Mandibular hypoplasia
ECV

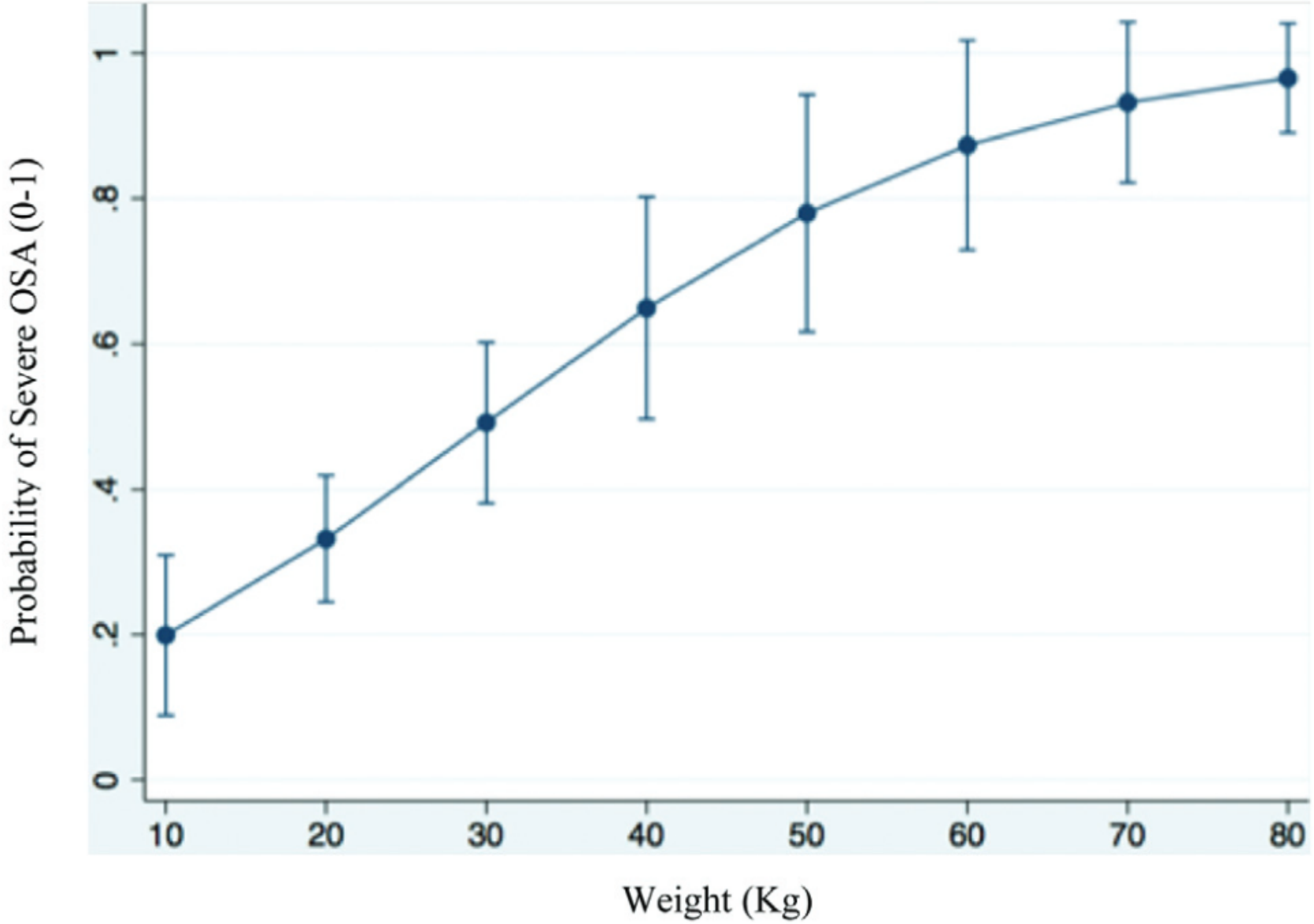

Figure 2. Risk of severe obstructive sleep apnea (OSA; apnea-hypopnea index $\geq$10) by weight among children with Down syndrome. Error bars indicate 95% CI

TABLE 3. Common Symptoms and Sequelae of OSA in Children with DS

Cardiovascular	Neurocognitive Manifestations	Other
Pulmonary hypertension	Poor school performance	Failure to thrive
Congestive heart failure	Inattention	Snoring
	Executive dysfunction	Fatigue
	Decreased memory	Restless sleep
	Behavioral disruptions	Gastroesophageal reflux
		Polycythemia
		Hypercapnia

See Table 1 legend for expansion of abbreviation.

TABLE 2. Common Symptoms and Sequelae of OSA in Adults With DS

Cardiovascular	Neurocognitive Manifestations	Other
Coronary artery disease	Excessive daytime sleepiness	Snoring
Arrhythmias	Executive dysfunction	Nocturia
Congestive heart failure	Impaired attention	Restless sleep
Pulmonary hypertension	Decreased memory	Early morning headache
Cerebral vascular accident	Mood dysregulation/depressive symptoms	Fatigue
		Gastroesophageal reflux
		Polycythemia
		Hypercapnia

See Table 1 legend for expansion of abbreviation.

Cognitive Impairment

- Decreased slow wave sleep seen in DS
- Patients with **OSA performed worse on verbal IQ, memory and executive function**
  - Rating of OSA / sleep disruption correlated with worse executive function
  - Presence of Snoring correlated with **disruptive school behavior**
  - OSA associated with **ADHD** and **Visual-Perceptual skill deficiencies**
  - Oxidative stress **implicated in pathogenesis of Alzheimer's**

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Dementia

- Almost **all have "neuropath" evidence** of Alzheimer by 40
  - 95 times higher risk vs general population
  - 90% lifetime incidence
  - 70% present in deaths after 35 years
- **Pre-existing Obesity strongly associated** with symptoms
  - Early **Brain Insulin Resistance precedes** dementia path
  - **Leptin elevation associated** with dementia
  - **Metabolic Syndrome not correlated** although markers still worsens with age despite reversal of BMI

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Challenges in Losing Weight

- Limited literature (so far) on DS specific interventions
- Limited structured programs
- **Lower exercise capacity / higher energy cost**
- Physician Knowledge Gaps
- **Caregiver Dependence / Stress (cooking / feeding)**
- Communication Barriers (non-verbal, delayed, etc.)

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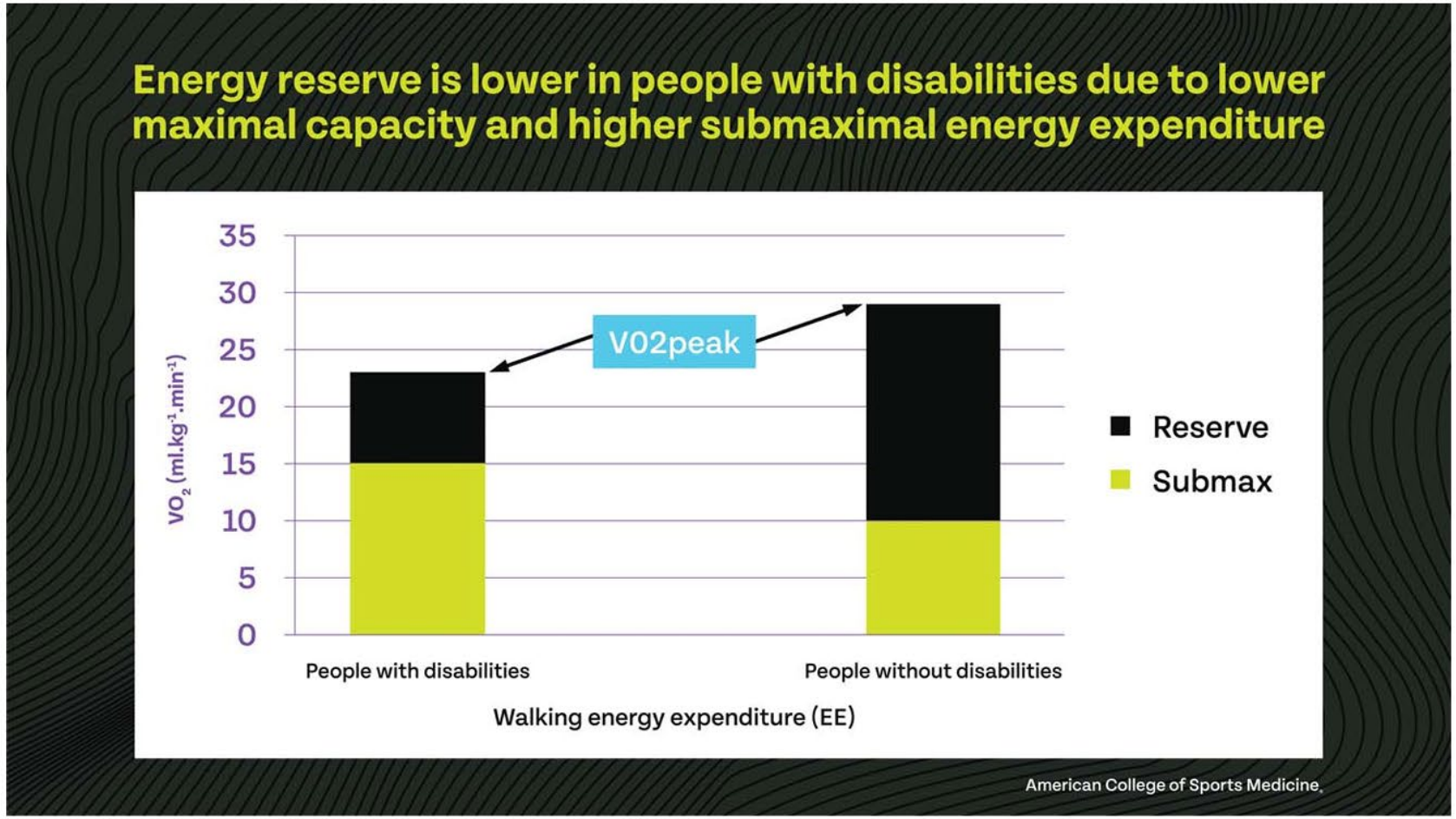

FIGURE 1—Metabolic and cardiorespiratory reserve in people with disabilities. This is a conceptual figure based on data from several studies (25–29,35,40,42,45,46,51–55). In general, people with disabilities have lower maximal capacity than people without disabilities. It is also well established that most people with developmental and physical disabilities spend more energy walking or running (if they can) or moving in general (for the same movement as people without disabilities) than people without disabilities. Thus, submaximal $\dot{V}O_2$ is higher in people with disabilities than in people without disabilities.

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