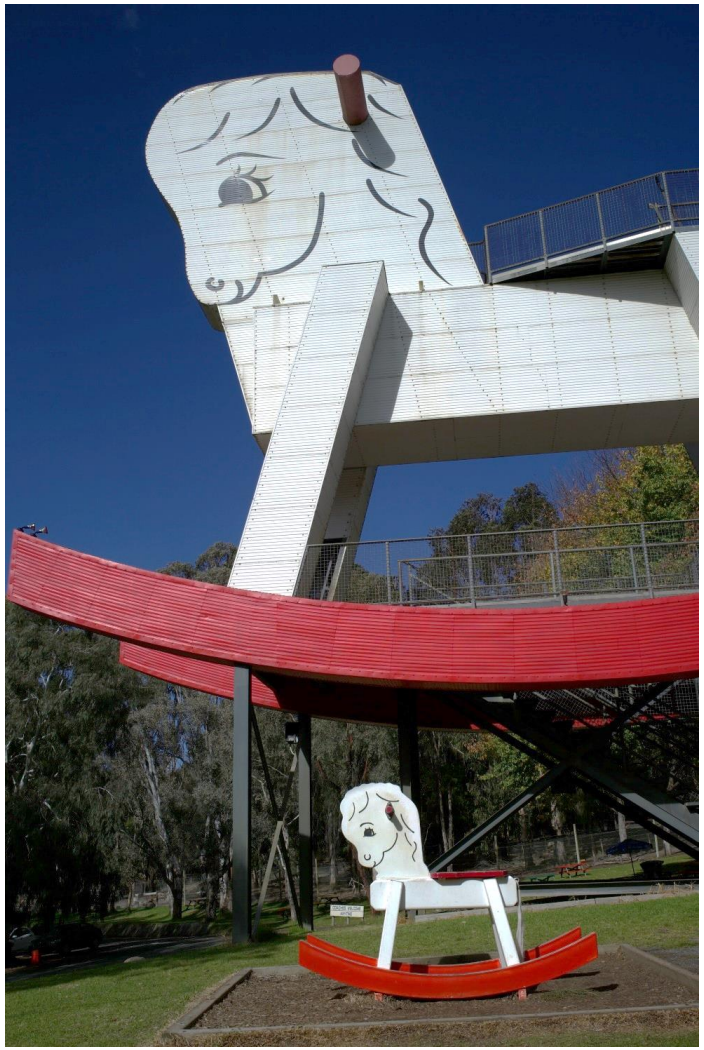


Diabetes and Geriatric Giants

The 17th AHKDN Annual Symposium

Dr James Luk

MBBS(HK), MSc(Experimental Medicine)(UBC), FRCP(Lond), FRCP(Edin), FRCP(Glasg), FRCP(Irel), FHKCP, FHKAM(Medicine)

Consultant QMH and FYKH
Hon Clinical Associate Professor HKU
Past President, the Hong Kong Geriatrics Society

Declaration of Financial Interests or Relationships

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Rundown

- Case sharing
- Burden of DM in older population in HK
- What are Geriatric Giants?
- DM + cognitive impairment
- DM + depression
- DM + sarcopenia and frailty
- DM + falls and fractures
- DM + polypharmacy
- Take home message

Madam Y

- F89
- Education – primary school level
- Live with son who needs to go to work
- Daytime alone
- Known DM, HT, hyperlipidemia for 30 yrs Fu private Dr
- Recently noticed cognitive impairment, started Aricept 5 mg nocte and mirtazapine 15 mg nocte for 3 months by private Dr

Drug list:

- Glimeperide 2 mg daily
- Metformin 1 g bd
- Glargine 20 unit nocte
- Amlodipine 10 mg daily
- Telmisartan 40 mg daily
- Crestor 10 mg daily
- Ezetimibe 10 mg daily
- Aricept (donepezil) 5 mg nocte
- Mirtazapine 15 mg nocte

Notice recurrent episode of lethargy, confusion and unresponsiveness over 3 months

Repeated falls at home due to weakness of legs

Increased frailty with decreased IADL ability, just managed the BADL

Fluctuation in food intake

With progressive cognitive decline reported by caregivers

Son noticed that if he gave her Coca Cola, she will be less confused and lethargic

Son performed hstix once for her when lethargic – Hstix = 3

Attended memory clinic new case

- MoCA 10/30 <7th percentile
  - Disorientation to time, place,
  - Impaired delay recall
  - Poor spatial orientation
- Not depressed (GDS 3/15)
- Moderately Frail – CFS 5/9
- BMI 18
- Loss of calf muscle
- No BPSD

- Blood tests: GFR 45
- TFT, B12 Folate normal
- VDRL -ve
- HBA1c 6%
- 25(OH)D = 25 nmol/L (N ≥ 30 nmo/L)*
- CTB cerebral atrophy, small vessel disease

** Luk JKH, Chan DKY, AJGG 2024*

Working diagnoses

- Recurrent hypoglycemia due to aggressive glycemia control
  - HBA1c 6%
  - Glimepiride (renal clearance, prolonged half-life)
  - Mismatch insulin dosage and oral intake
- Alzheimer's disease*
  - Worsening of dementia due to repeated hypoglycemia which exacerbated neuronal damage in a vulnerable brain
- Polypharmacy
- Falls
- Frailty and sarcopenia**
- Low BMI
- Vitamin D deficiency

**Lam K, Chan WSY, Luk JKH, Leung AYM. Assessment and diagnosis of dementia: a review for primary healthcare professionals. HK Med J 2019*

***Luk JKH, Chan DKY. Frailty and sarcopenia—from theory to practice HK Med J 2022*

Management

Discontinue glimerpiride
Off glargine, change to insulin degludec (Tresiba) 8 units nocte and further titrate
Switch to DDP-4 inhibitor (sitagliptin) which has less hypoglycemia
Reduce metformin to 500 mg bd
New target – 7.5%
Caregiver education to recognize hypoglycemia atypical presentation in elderly
Off Aricept, replace with memantine 5 mg daily and titrate up
Replace vitamin D2 1000 IU daily

Management

Refer GDH for rehabilitation (balance exercise, sarcopenic program with resistance exercise)

DM monitoring in GDH with titration of insulin

Dietitian consultation – DM and sarcopenic diet

Reassess 16 weeks with HBA1c recheck

At 16 weeks FU

Appetite improved

HBA1c raised to 7.4%

No further hypoglycemic episode

No more falls

Less lethargic, reduced agitation

Cognitive function slightly improved

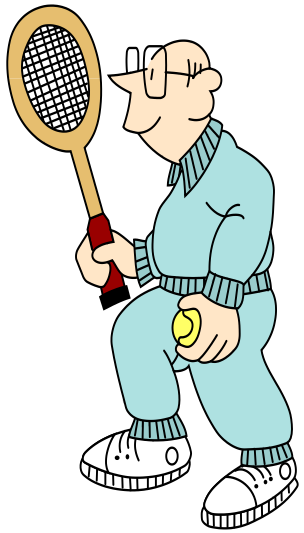
Increased functional state and walking speed

DM Burden in Older People (CHP 2025)

- 8.5% people in HK have DM
- Prevalence range from 2% in <35 to >20% age >65
- Major cause of morbidity and mortality in Hong Kong



Issues of older people



- Multiple comorbidities, psychological and social problems
- Frailty and sarcopenia
- Nutrition and swallowing problems
- Functional and physiological capacities diminished
- Atypical presentation of illnesses e.g. presented as delirium, falls
- EoL issues including Advance Medical Directive (AMD)
- Cognitive dysfunction pronounced
- Polypharmacy and adverse drug complications common
- Lack of evidence-based medicine for age >75

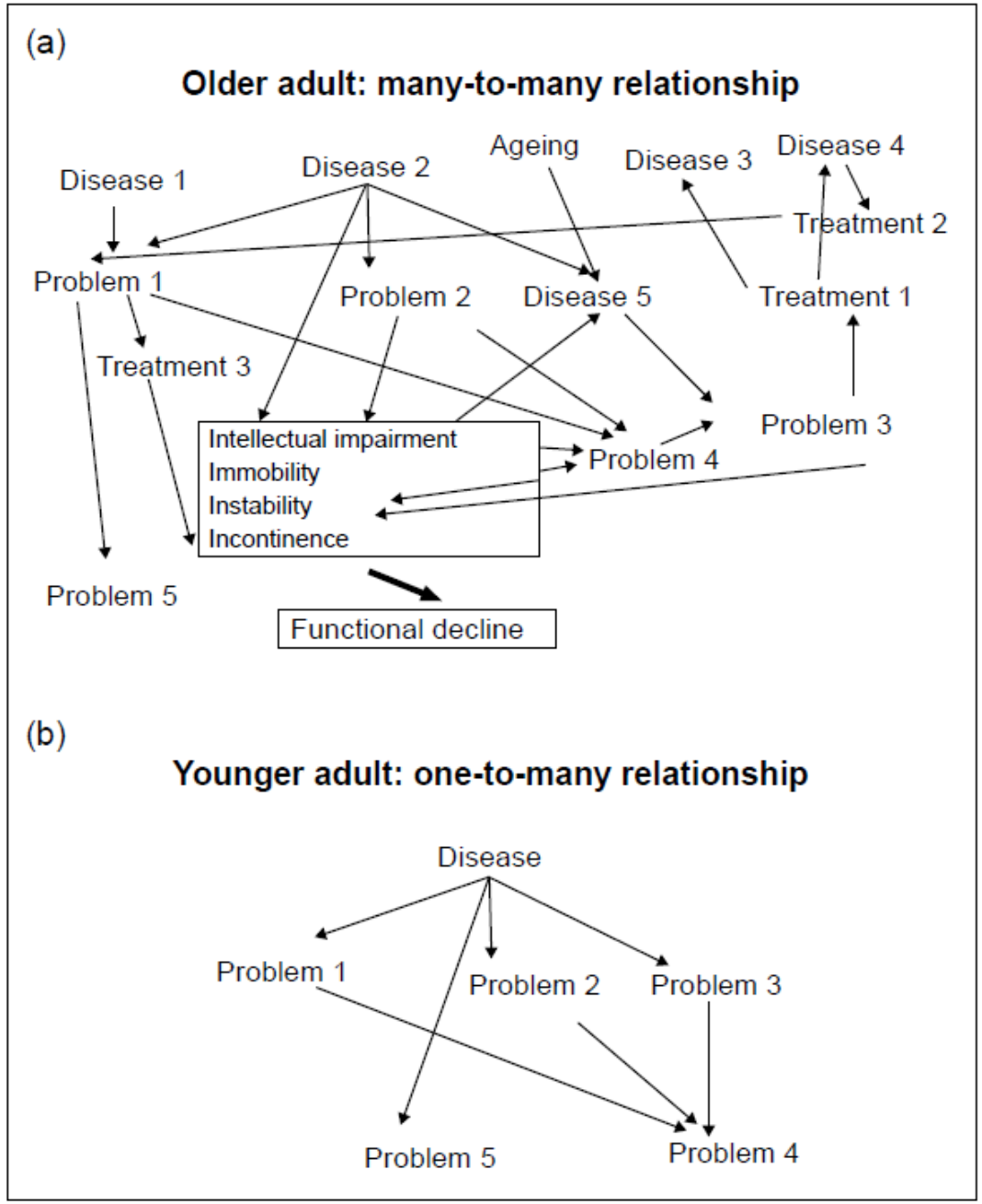


Figure 1.8 The complexity of illness in (a) the older adult compared with (b) the younger adult

Table 1.1 Geriatric syndromes: their social risk factors and common features[29-33]

Geriatric syndrome	Social risk factor	Common feature
Original geriatric giants[29] Prof Bernard Isaacs • Immobility • Instability (falls and fractures) • Incontinence • Intellectual impairment (cognitive dysfunction, delirium, dementia)	• Isolation • Ignorance • Impecunity (poverty) • Informal care with inadequate support	• Gigantic number • Gigantic impact (loss of independence) • Complex (multiple causes, no simple care) • Inter-related and interacting • Ignored (inverse care law)
Subsequent additions[30-33] • Iatrogenesis • Impaired vision / hearing • Immune deficiency • Ill-treatment (inadequate care, elder abuse) • Irritable colon • Insomnia • Impotence • Frailty • Sarcopenia (muscle dysfunction) • Failure to thrive (malnutrition, anorexia, weight loss) • Depression		

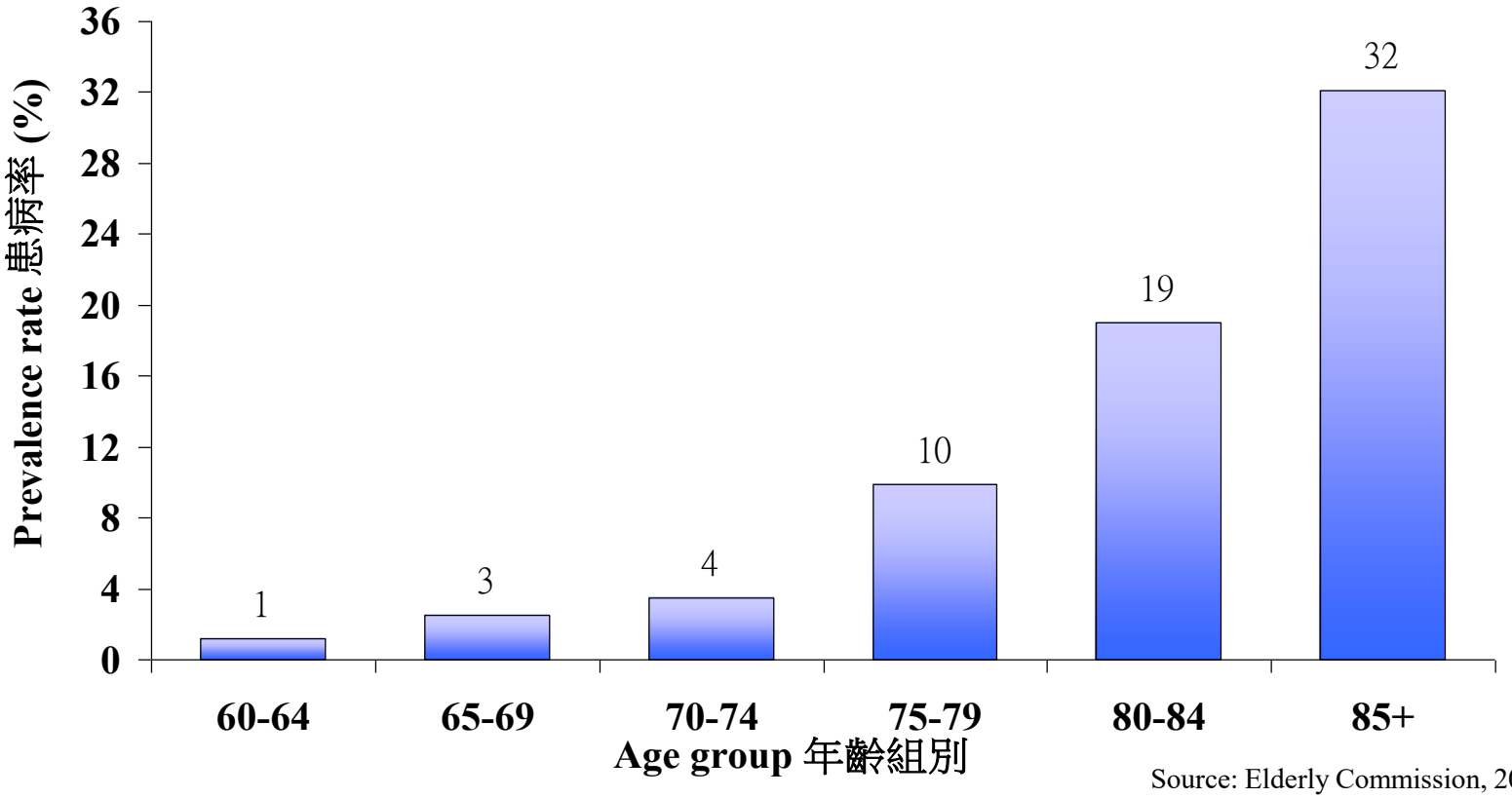
Elderly Abuse

EOL

DM and Cognitive Function

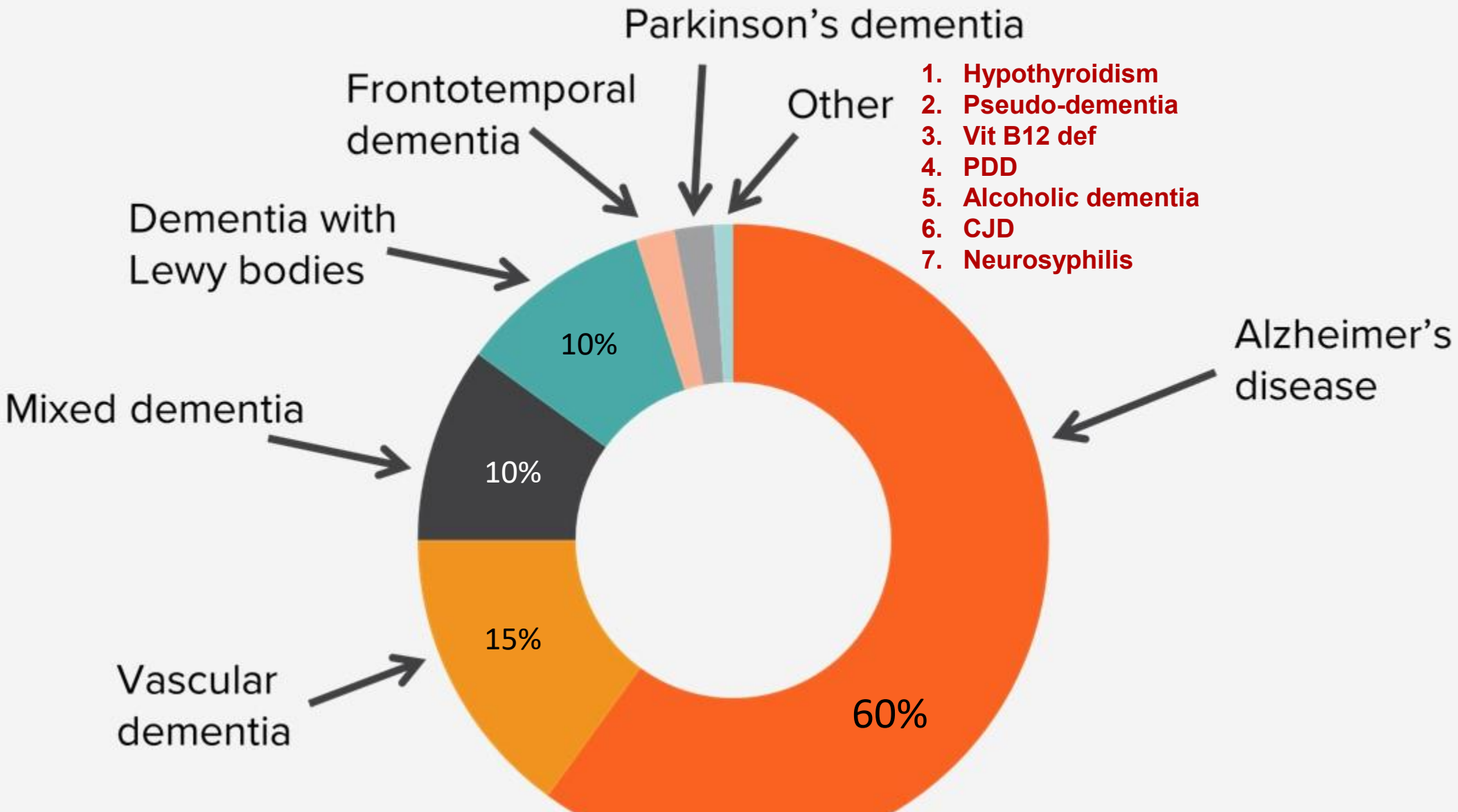
Dementia Prevalence Increases with Age

Prevalence rate of dementia among community-dwelling Hong Kong population, by age group, 2005-2006



Source: Elderly Commission, 2006

TYPES OF DEMENTIA



Pathogenesis of AD

- **β** amyloid plaques (extracellular)
- Neurofibrillary tangles (pTau) (intracellular)



Loss of neuronal synapses, neuronal death and cognitive impairment

Risk factors of Alzheimer's Disease

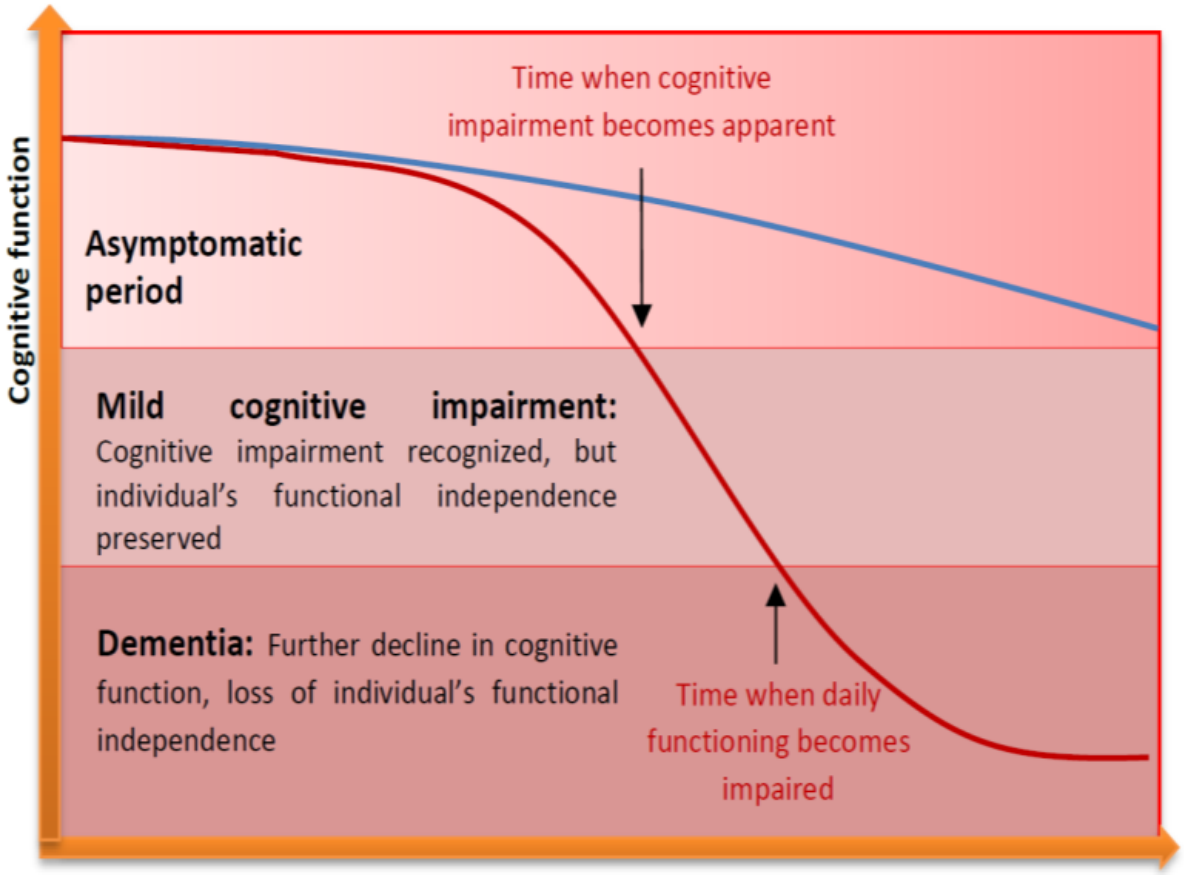
Non-modifiable risk factors		**Advancing age** **Family History** **Genetics** **Gender**
Modifiable risk factors	*Lifestyle factors*	**Smoking** **Alcohol** **Physical inactivity** **Low participation of cognitive activities** **Social isolation**
	Vascular risk factors	**Hypertension** **Diabetes mellitus** **Overweight & obesity** **Stroke**
	Other factors	**Depression** **Drugs** **Low education attainment** **Head injury**

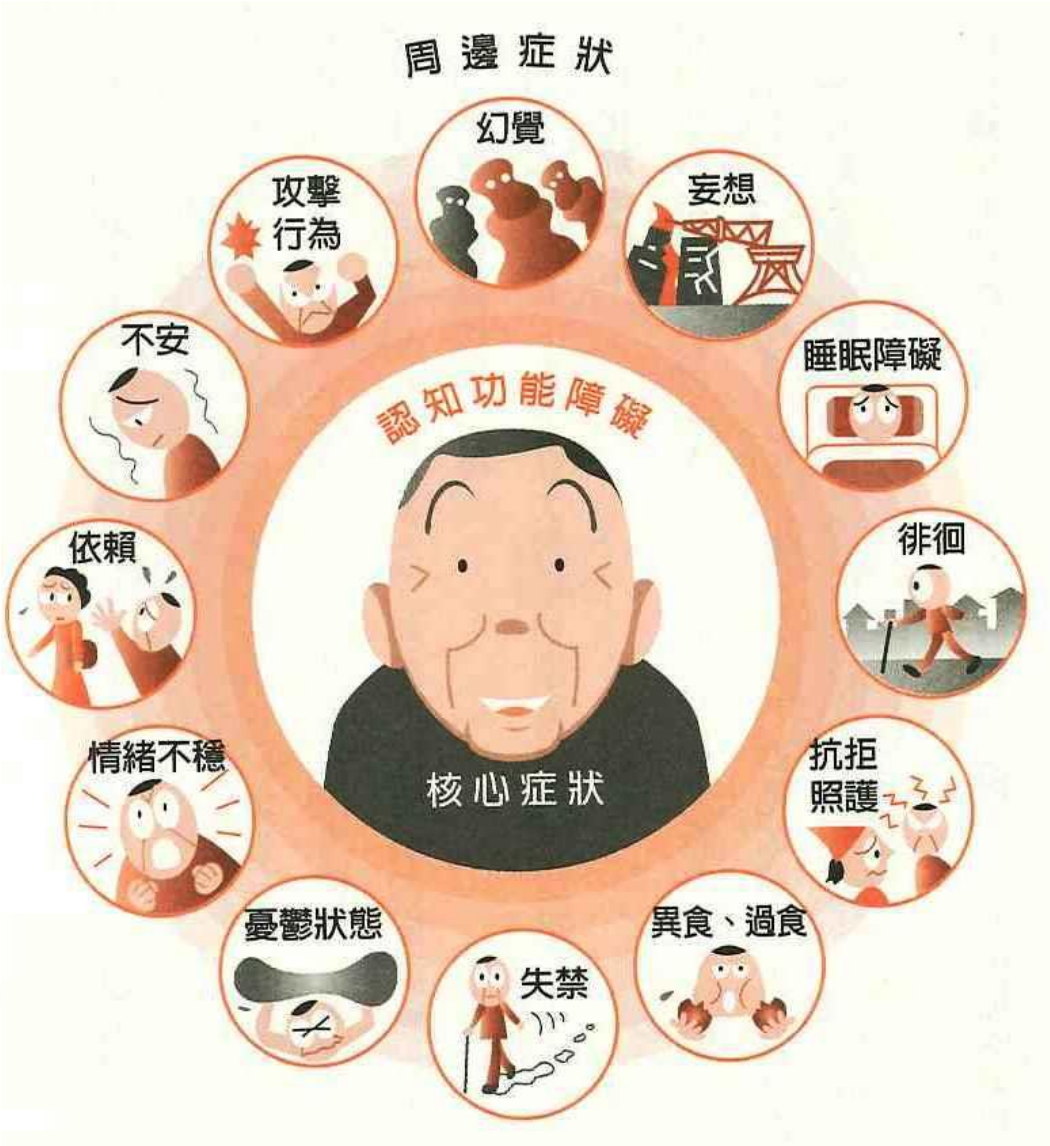
APOE4 allele

Presenillin 1 gene and 2 gene mutation (young onset adult)

Down Syndrome







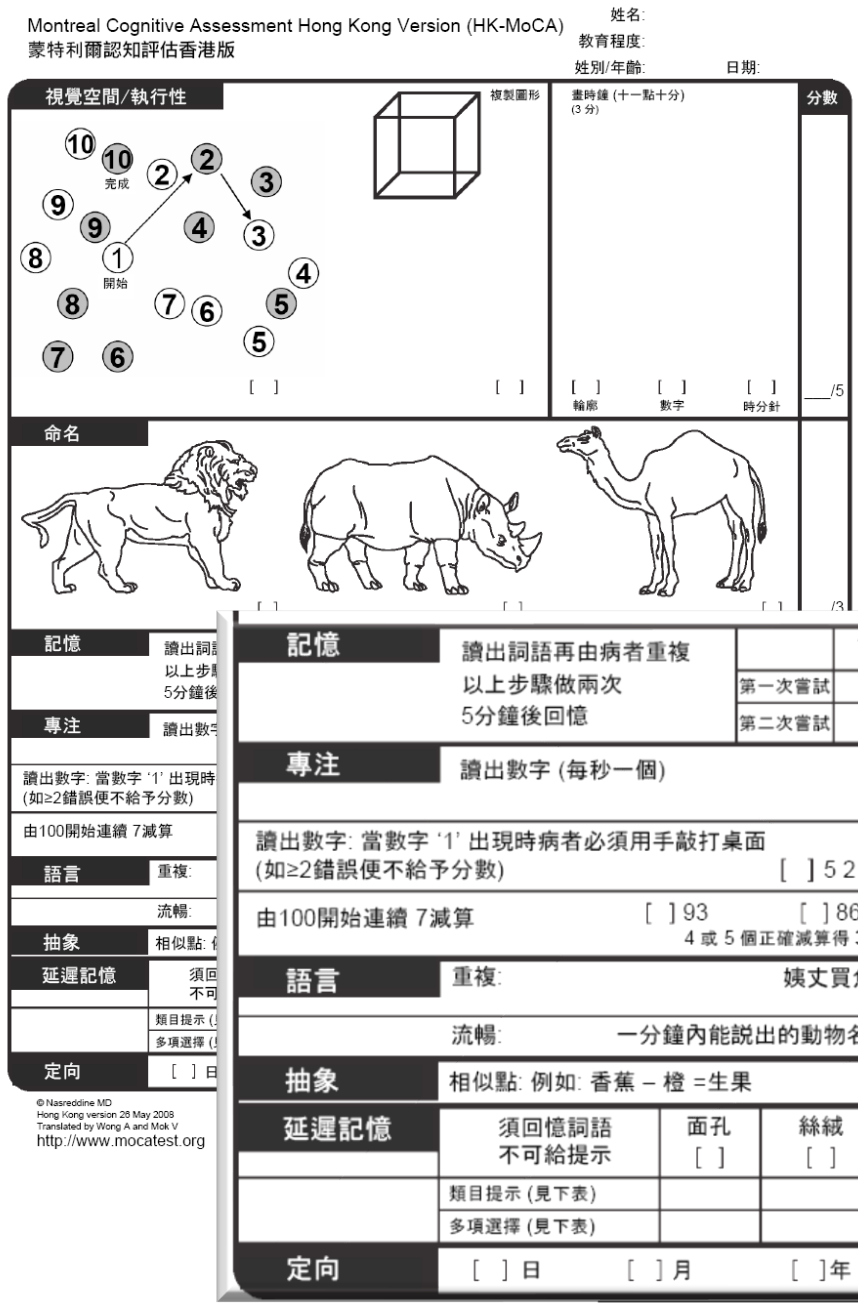
Huge burden to society and health system

Screening tests

AMT

HK - MoCA

Clock drawing



Montreal Cognitive Assessment Hong Kong Version (HK-MoCA)
蒙特利爾認知評估香港版

姓名:
教育程度:
姓別/年齡: 日期:

視覺空間/執行性 | 複製圖形 | 畫時鐘 (十一點十分) (3 分) | 分數 /5

命名 /3

記憶 | 讀出詞語再由病者重複 以上步驟做兩次 5分鐘後回憶

專注 | 讀出數字: 當數字 '1' 出現時 (如≥2錯誤便不給予分數)

由100開始連續 7減算

語言 | 重複: | 流暢:

抽象 | 相似點:

延遲記憶 | 須回 不可 | 類目提示 | 多項選擇

定向 | [ ] 日

© Nasreddine MD
Hong Kong version 28 May 2008
Translated by Wong A and Mok V
http://www.mocatest.org

MoCA ©

記憶	讀出詞語再由病者重複 以上步驟做兩次 5分鐘後回憶		面孔	絲絨	教堂	雛菊	紅色	不用計分
		第一次嘗試						
		第二次嘗試						
專注	讀出數字 (每秒一個)			病者須把數字向前重複[ ] 2 1 8 5 4 病者須把數字向後重複[ ] 7 4 2				___/2
讀出數字: 當數字 '1' 出現時病者必須用手敲打桌面 (如≥2錯誤便不給予分數)				[ ] 5 2 1 3 7 4 1 1 8 0 6 2 1 5 1 7 4 5 1 1 1 4 1 7 0 5 1 1 2				___/1
由100開始連續 7減算			[ ] 93	[ ] 86	[ ] 79	[ ] 72	[ ] 65 4 或 5 個正確減算得 **3** 分, 2 或 3 個正確得 **2** 分, 1個正確得 **1** 分, 沒有正確得 **0** 分	___/3
語言	重複:			姨丈買魚腸[ ] 西詩四十四歲[ ]				___/2
	流暢:		一分鐘內能說出的動物名稱的數目			[ ] (N ≥ 11 個名稱)		___/1
抽象	相似點: 例如: 香蕉 – 橙 =生果			[ ] 火車 – 單車		[ ] 手錶 – 間尺		___/2
延遲記憶	須回憶詞語 不可給提示		面孔 [ ]	絲絨 [ ]	教堂 [ ]	雛菊 [ ]	紅色 [ ]	分數只給予沒有提示的正確回憶	___/5
	類目提示 (見下表)							
	多項選擇 (見下表)							
定向	[ ] 日	[ ] 月	[ ] 年	[ ] 星期	[ ] 地點	[ ] 地區			___/6

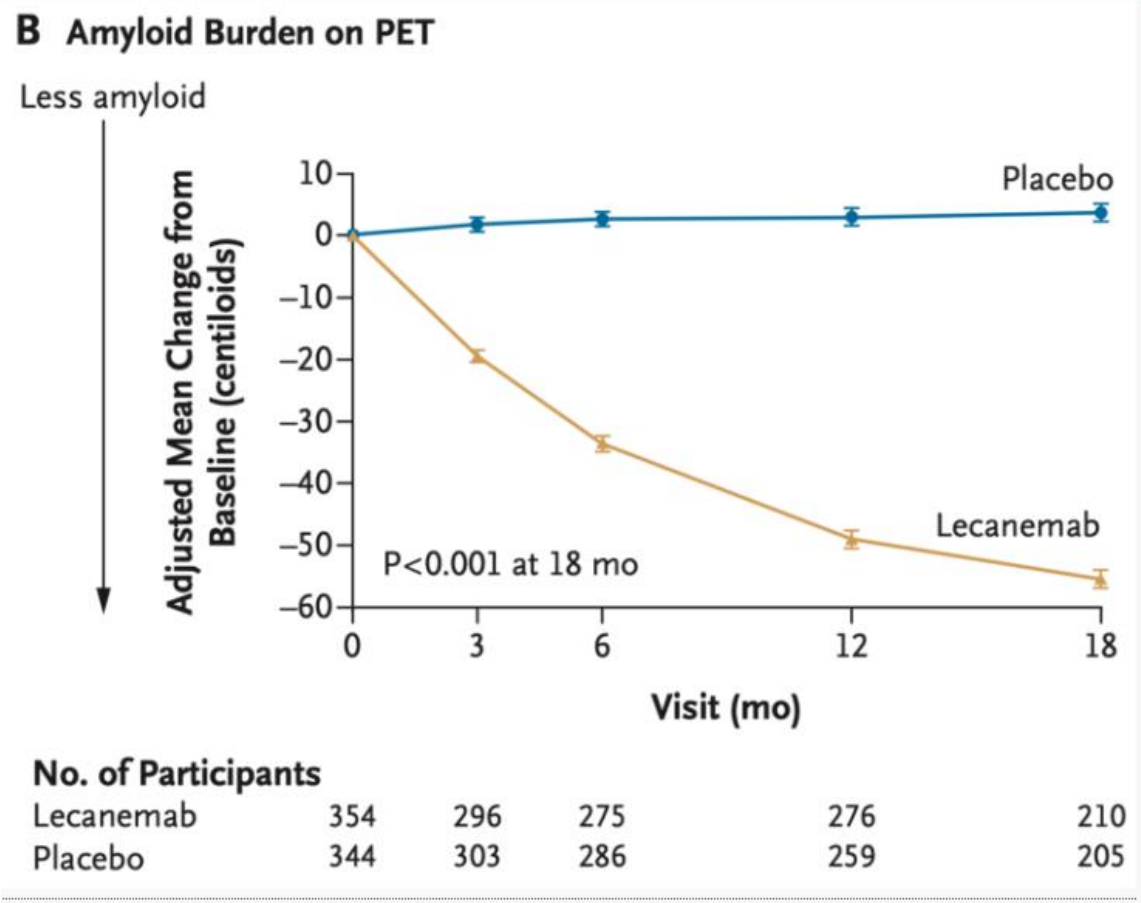
New plasma biomarkers : p Tau 217

- Plasma p Tau 217 able to differentiate AD from other neurodegenerative disorders

- It also predicts the development of AD in future amongst asymptomatic and MCI patients

Lecanemab

Lecanemab removes amyloid from the brain



Lecanemab

Lecanemab slows cognitive decline in patients with Alzheimer's disease

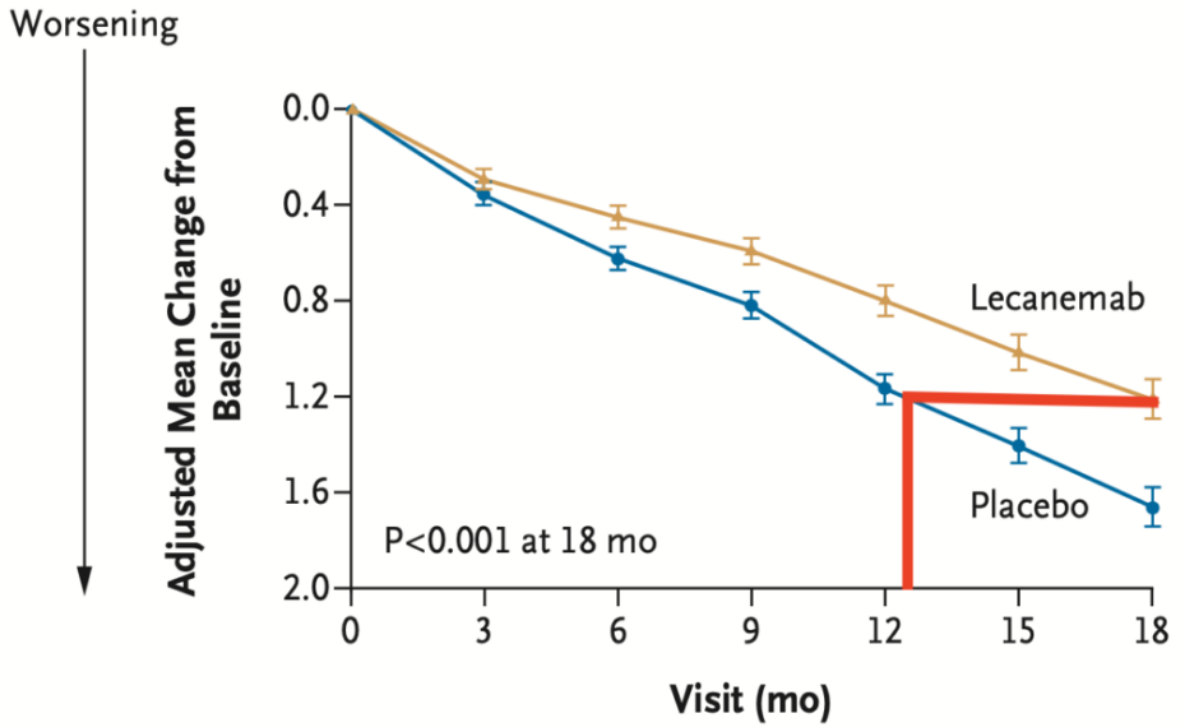
CDR-SB Score (Clinical Dementia Rating-Sum of the Boxes scale)

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3
	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

30% slowing of cognitive decline translating into 5 to 6 months of life in a better cognitive state (buy time)

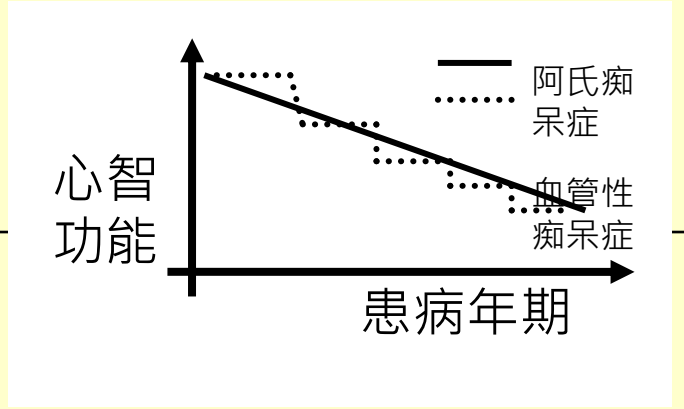


No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Vascular Cognitive Impairment (VCI)

Categories	Pathologies
Subcortical大腦皮質下 ~ 50-70%	Small vessel disease
Cortical 大腦皮質 ~ 10-20%	Large vessel infarcts
Strategic重要地方 ~ 5-10%	e.g. thalamic lesions, inferior medial temporal lobe, association areas (e.g. angular gyrus)
Others ~ 5-10%	hemorrhagic stroke,
Mixed Dementia 混合性癡呆 ~ 40% of dementia	Concurrent dementing illness, e.g. AD



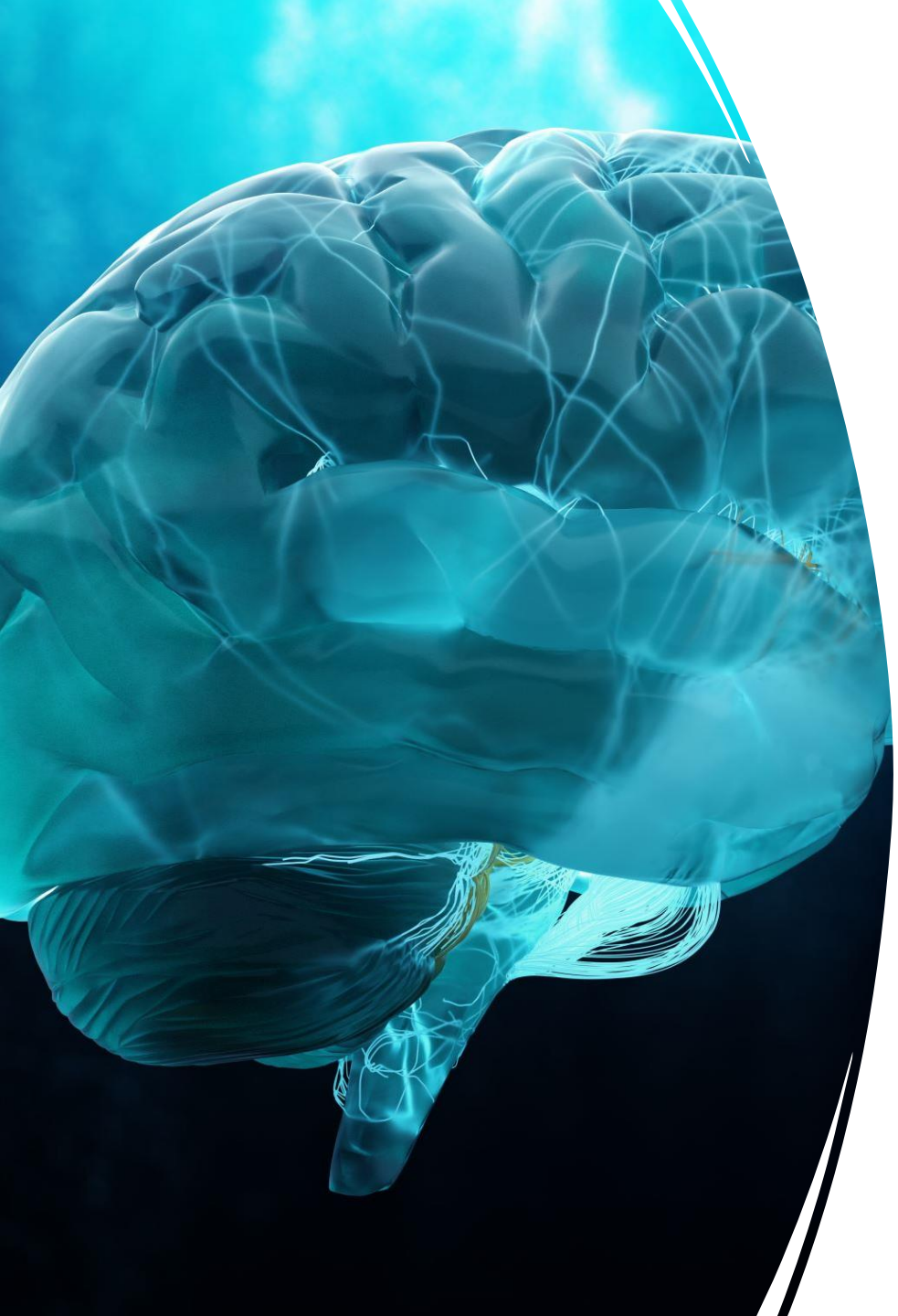
Dementia and DM

Cognitive dysfunction
Patients with diabetes are at increased risk for dementia.

1.5x risk of decline in cognitive function

1.5x risk Alzheimer's disease

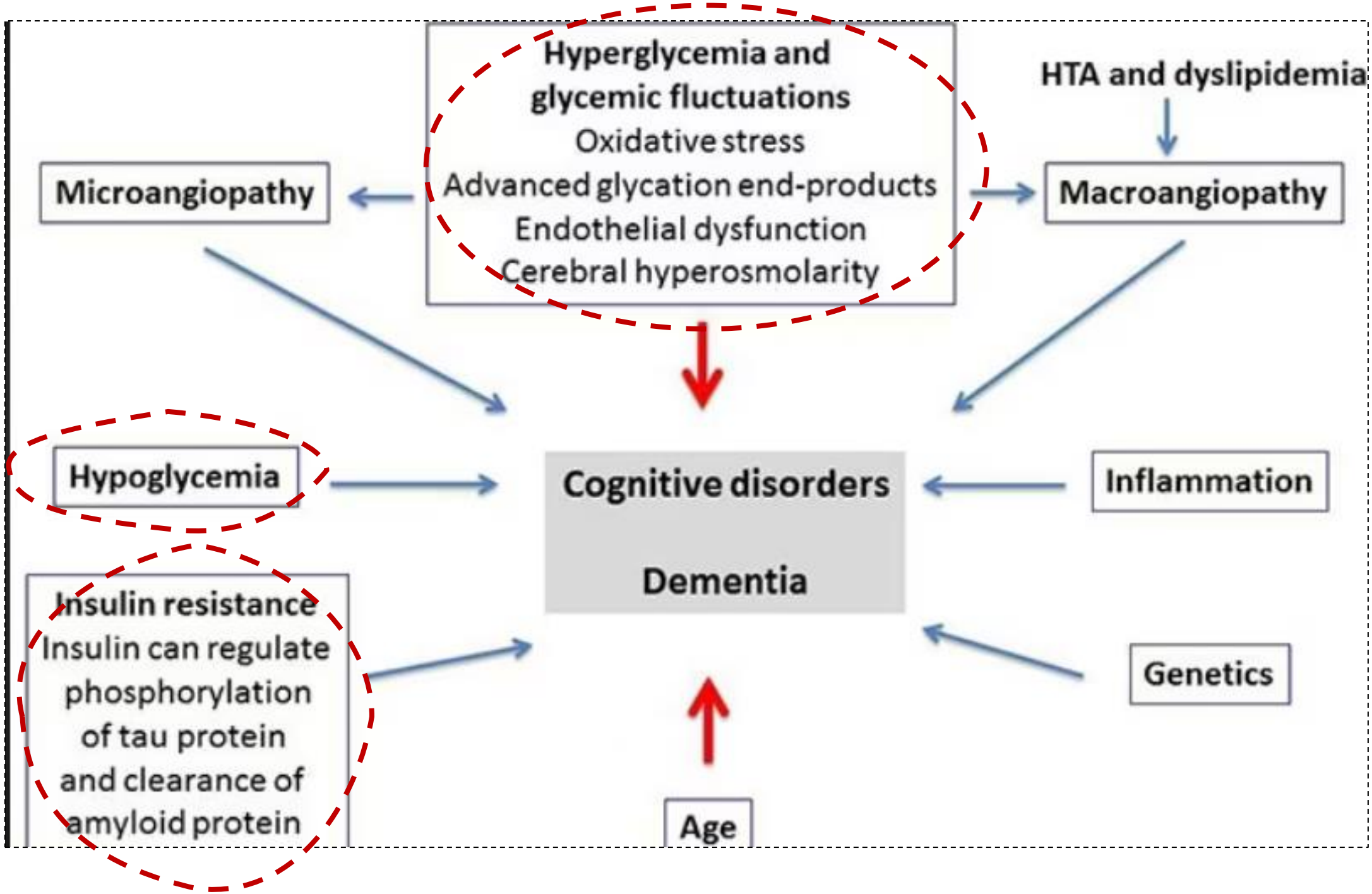
2.5x risk for vascular dementia



Proposed mechanism of the relationship between DM and cognitive dysfunction

- ***Hyperglycemia*** leads to oxidative stress, inflammation, endothelial dysfunction
- Insulin resistance in the brain leads to amyloid deposition and tau phosphorylation

- Repeated ***hypoglycemia*** leads to brain cell lost and cognitive dysfunction


Hyperglycemia and glycemic fluctuations
Oxidative stress
Advanced glycation end-products
Endothelial dysfunction
Cerebral hyperosmolarity
HTA and dyslipidemia
Microangiopathy
Macroangiopathy
Hypoglycemia
Cognitive disorders
Dementia
Inflammation
Insulin resistance
Insulin can regulate phosphorylation of tau protein and clearance of amyloid protein
Genetics
Age

International Journal of
Molecular Sciences

MDPI

Review

Alzheimer's Disease as Type 3 Diabetes: Common Pathophysiological Mechanisms between Alzheimer's Disease and Type 2 Diabetes

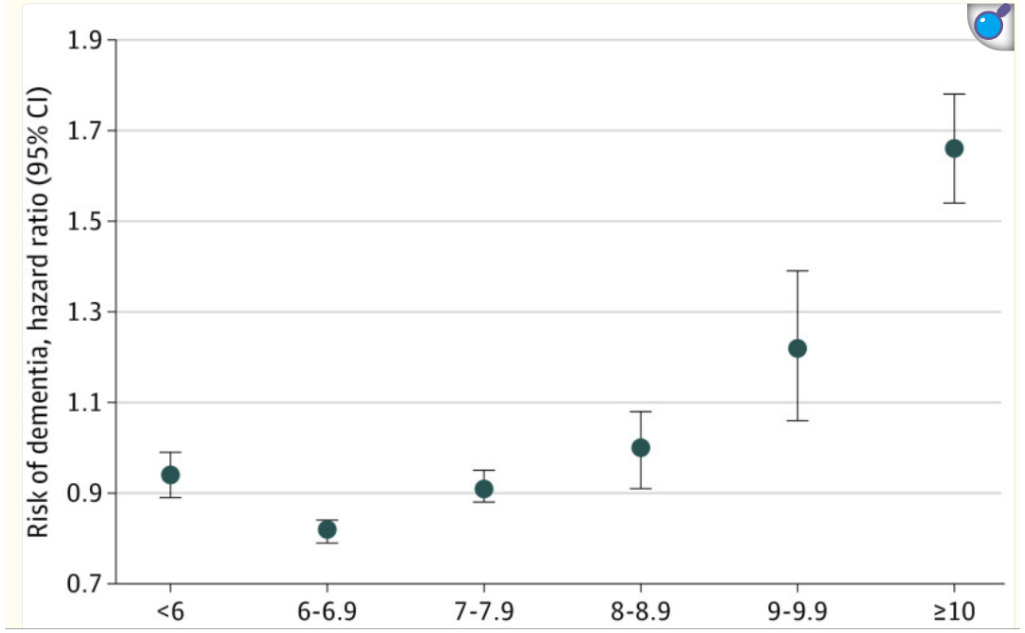
Michalis Michailidis [1], Despina Moraitou [1], Despina A. Tata [1], Kallirhoe Kalinderi [2], Theodora Papamitsou [3]

- AD and DM share similar pathology: insulin resistance, neuroinflammation, oxidative stress, mitochondrial dysfunction and metabolic syndrome.
- Beta-amyloid and tau protein accumulate in DM and AD brains.
- Studies suggesting AD as a metabolic disease in the brain **(type 3 diabetes).**

J or U -shaped association

- Observational studies support a J-shaped association between HBA1C and dementia incidence
  - A HBA1c level of around 7% seems to be associated with a lower dementia risk

Figure 1. Dementia Hazard by Majority Glycated Hemoglobin (HbA_{1c}) Exposure.



JAMA Neurol. 2023 Apr 17;80(6):597–604. doi: 10.1001/jamaneurol.2023.0697

Glycemic Control Over Multiple Decades and Dementia Risk in People With Type 2 Diabetes

Chris Moran [1,2,3,4,✉], Mary E Lacy [5,6], Rachel A Whitmer [5,7], Ai-Lin Tsai [5], Charles P Quesenberry [5], Andrew J Karte[r] [5], Alyce S Adams [5,8], Paola Gilsanz [5,9]

Huang *et al.*
Diabetology & Metabolic Syndrome (2022) 14:31
https://doi.org/10.1186/s13098-022-00799-9

Diabetology &
Metabolic Syndrome

REVIEW Open Access

Association between hypoglycemia and dementia in patients with diabetes: a systematic review and meta-analysis of 1.4 million patients

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Whitmer 2009	0.3646	0.0722	13.5%	1.44 [1.25, 1.66]	2009
Yaffe 2013	0.7372	0.3761	2.8%	2.09 [1.00, 4.37]	2013
Haroon 2015	0.5481	0.0335	15.3%	1.73 [1.62, 1.85]	2015
Chin 2016	0.9892	0.4654	1.9%	2.69 [1.08, 6.70]	2016
Cukierman-Yaffe 2018	0.1906	0.151	9.0%	1.21 [0.90, 1.63]	2018
Lee 2019	0.8242	0.1871	7.3%	2.28 [1.58, 3.29]	2019
Kim 2020	0.2263	0.0371	15.1%	1.25 [1.17, 1.35]	2020
Whitmer 2021	0.5068	0.2146	6.2%	1.66 [1.09, 2.53]	2021
Zheng 2021	0.2624	0.0324	15.3%	1.30 [1.22, 1.39]	2021
Li 2021	0.0862	0.0701	13.6%	1.09 [0.95, 1.25]	2021
Total (95% CI)			**100.0%**	**1.44 [1.26, 1.65]**	

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 78.28$, df = 9 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 5.34$ ($P < 0.00001$)

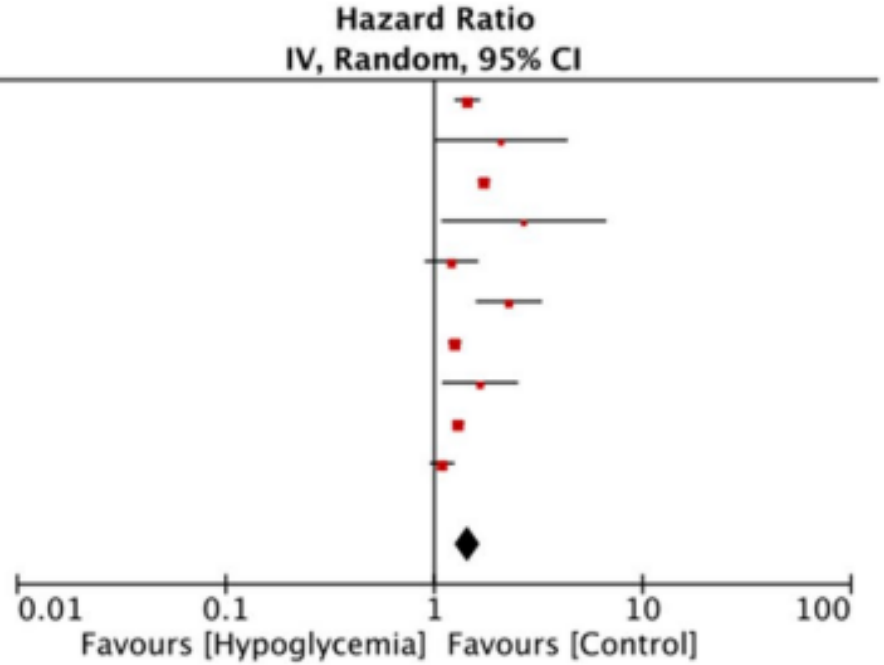


Fig. 2 Meta-analysis of the association between hypoglycemic episodes and risk of dementia in DM patients

Hypoglycemia and Dementia Risk in Older Patients with Type 2 Diabetes Mellitus: A Propensity-Score Matched Analysis of a Population-Based Cohort Study

Young-Gun Kim[1,2,*], Dong Gyu Park[3,*], So Young Moon[4], Ja Young Jeon[5], Hae Jin Kim[5], Dae Jung Kim[5], Kwan-Woo Lee[5], Seung Jin Han[5]

Table 2. The risk of dementia in patients with hypoglycemia compared to patients without hypoglycemia

Variable	Number	Events	HR	95% CI	*P* value
All-cause dementia	11,932	2,934	1.254	1.166–1.349	<0.001
Alzheimer's disease	11,932	2,186	1.264	1.162–1.375	<0.001
Vascular dementia	11,932	721	1.286	1.110–1.490	<0.001

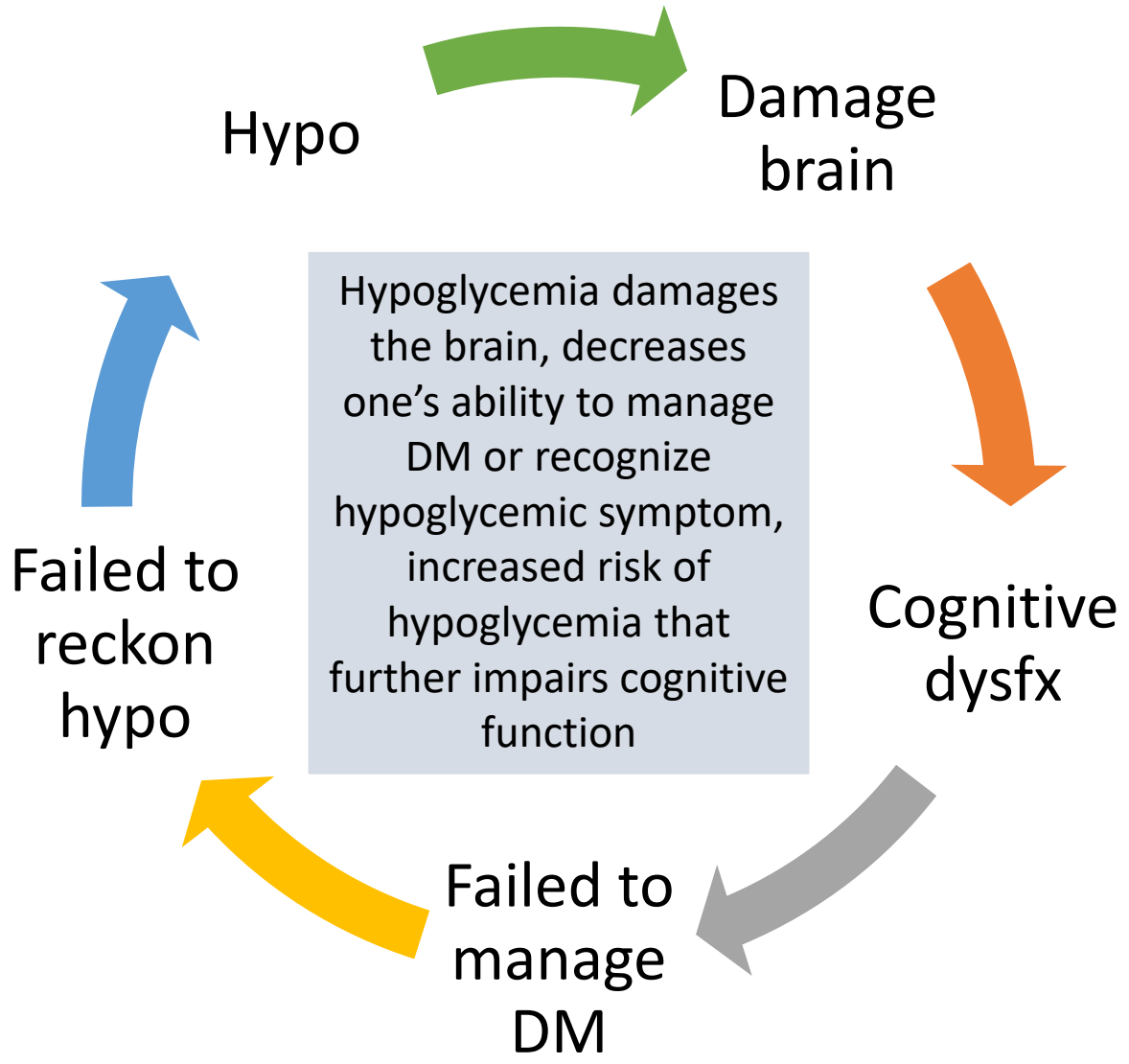
HR, hazard ratio; CI, confidence interval.

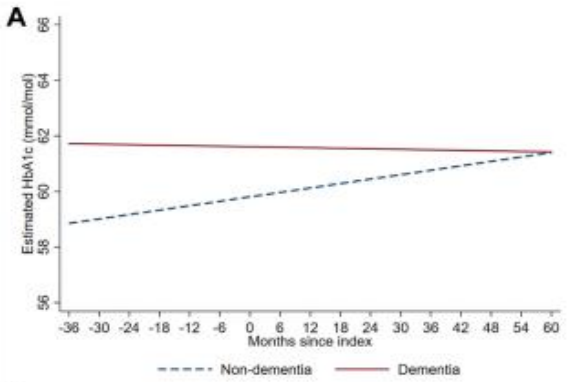
Table 3. The risk of dementia according to number of hypoglycemic episodes in patients with and without previous hypoglycemic episode

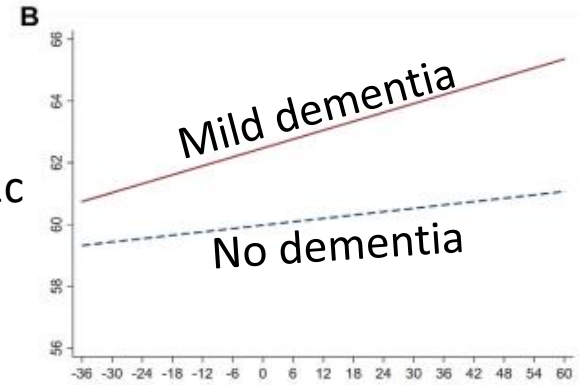
No. of previous hypoglycemic episodes	Number	Events	HR	95% CI	*P* value
1	4,622	1,159	1.170	1.043–1.313	0.008
2–3	2,946	550	1.201	1.016–1.421	0.032
>3	4,354	256	1.358	1.060–1.740	0.016

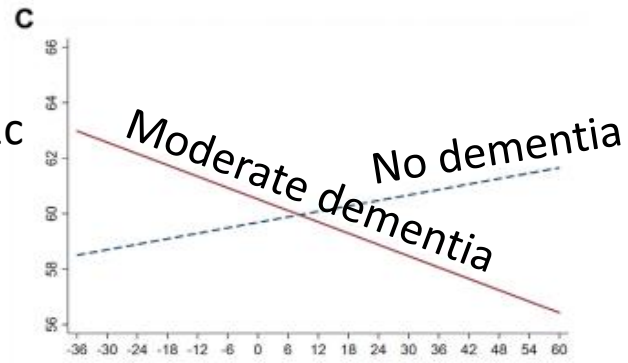
HR, hazard ratio; CI, confidence interval.

Vicious cycle of hypoglycemia









JAMDA 23 (2022) 1555–1563

ELSEVIER

JAMDA

journal homepage: www.jamda.com

Original Study

The Impact of Dementia on Diabetes Control: An Evaluation of HbA_{1c} Trajectories and Care Outcomes in Linked Primary and Specialist Care Data

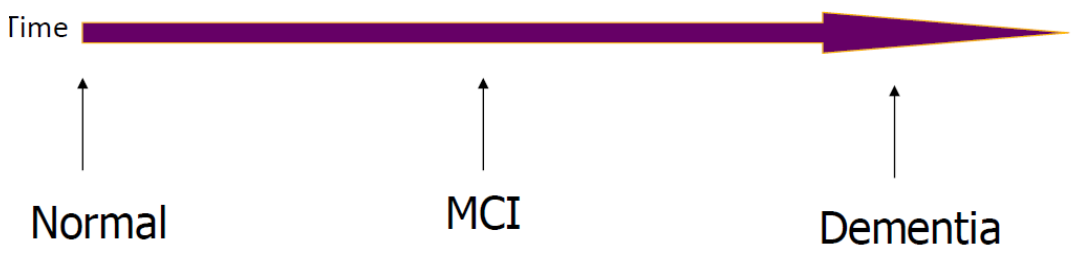
Usha Gungabissoon PhD [a,b,*], Matthew Broadbent MA(Hons) [c], Gayan Perera PhD [a], Mark Ashworth DM [d], Nicholas Galwey PhD [e], Robert Stewart MD [a,c]

Challenges in diabetes self management and poor glycemic control as a cause of cognitive decline, could contribute to the steeper increase in HbA1c in those with mild dementia.

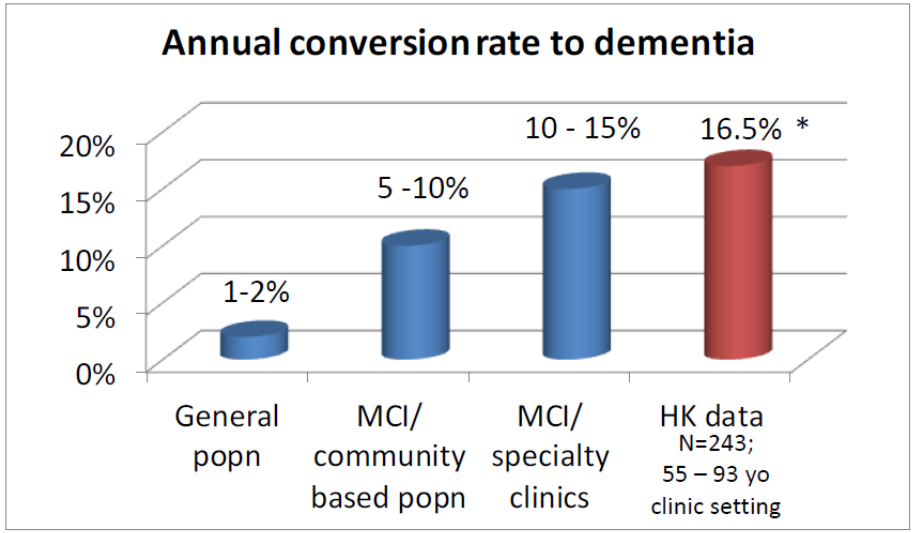
In contrast, declining HbA1c trajectory in those with moderate-severe dementia may be due to weight loss and/or frailty, which are more common in dementia, particularly in its later stages.

Mild Cognitive Impairment (MCI)

- An intermediate state of cognitive function between changes seen in aging and those fulfilling the criteria fo dementia



MCI -> Dementia
Annual conversion rate



Research Article

Mild Cognitive Impairment and Depressive Symptoms in Elderly Patients with Diabetes: Prevalence, Risk Factors, and Comorbidity

Malgorzata Gorska-Ciebiada,[1] Malgorzata Saryusz-Wolska,[1] Maciej Ciebiada,[2] and Jerzy Loba[1]

- A meta-analysis of longitudinal studies showed that DM increased the risk of MCI by 21%.
- Data from large population studies suggest that chronic hyperglycemia is a risk for cognitive impairment in DM

Continuous glucose monitoring (CGM)

- Patient benefits include improvement in A1C, reductions in hypoglycemia and glycemic variability, and greater treatment satisfaction and improved sense of mental well-being
- Real time data can be transferred to nurses and doctors
- Warn patient if hypoglycemia occurs with alarm
- Enable easier adjustment of insulin
- Drawbacks – cost (HKD >550 for a sensor – 15 days)

Continuous Glucose Monitoring in Comorbid Dementia and Diabetes: The Evidence So Far

Journal of Diabetes Science and Technology
1–7
© 2024 Diabetes Technology Society

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/19322968241301058
journals.sagepub.com/home/dst
Sage

Busra Donat Ergin, MSc[1], Kieran Gadsby-Davis, MSc[1], Katharina Mattishent, MD, PhD[1,2], Ketan Dhatariya, MD[1,2], Nikki Garner, PhD[1,2], and Michael Hornberger, PhD[1]

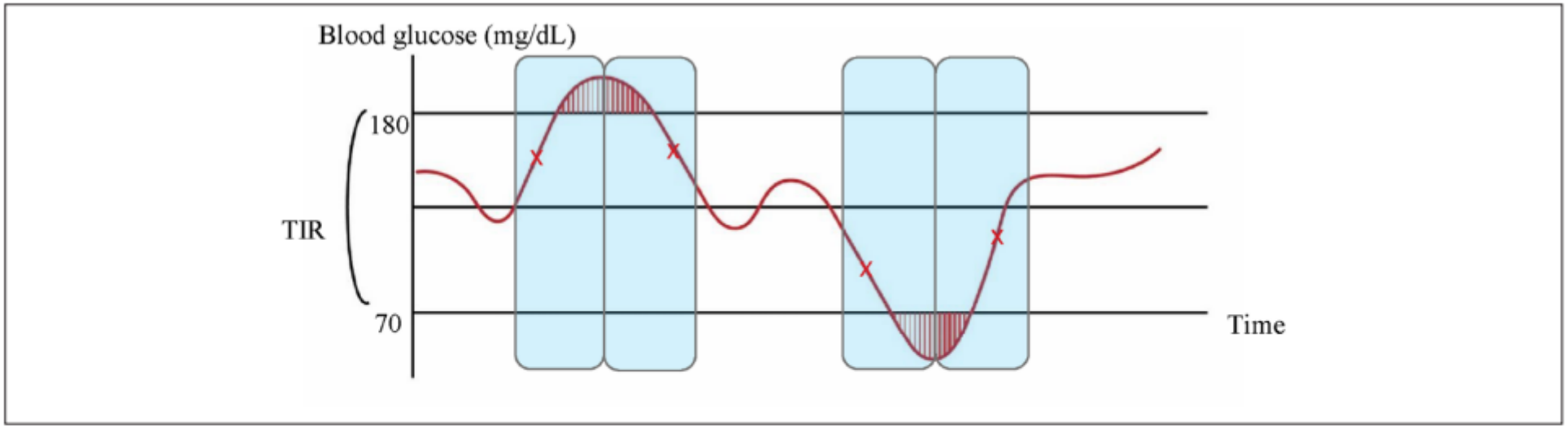


Figure 1. The blood glucose fluctuations with the time both captured by finger pricks and for CGM alarms/alerts. Diagram illustrating differences in glucose fluctuations via finger prick measurements or CGM. The red shaded area shows the dysglycemia. The red "x" refers the finger prick measurements., TIR = time in range, time spent in targeted blood glucose (70-180 mg/dL). The blue-shaded area shows the time that CGM receiver or smartphone sends alarms/alerts when it detects the interstitial glucose is upgoing/descending trend in a short time. The CGM can send notifications when the interstitial glucose of the user is increasing or decreasing rapidly (it also provides the speed with two modes) even if they are in euglycemia.

Table 1. Benefits and Challenges of Using Continuous Glucose Monitoring Sensors Among Individuals With Cognitive Impairment in Hospital Setting and After Hospitalization.

Opportunities	Possible outcomes
Benefits	• Captures dysglycemia, including nocturnal hypoglycemia. • Improves CGM-derived glucose metrics including time in range. • Provides real-time insight into glycemic levels to health care professionals. • May mitigate adverse hospital outcomes, such as length of stay, readmission, or mortality.
Challenges	• Additional training for patients and health care staff required on how to use, manage, and monitor CGM. • Frequent alarms/alerts can lead "alarm/alert fatigue," and patients may remove CGM sensors. • Cost for the health care system, if CGM is not covered and no current training exists.

This table defines some benefits, opportunities, and challenges of CGM use in individuals with cognitive impairment in hospital setting.[44,58,78,79]
Abbreviation: CGM, continuous glucose monitoring.

CGM and Dementia



Community-based studies in T2DM-dementia using CGM show potential for better management of T2DM



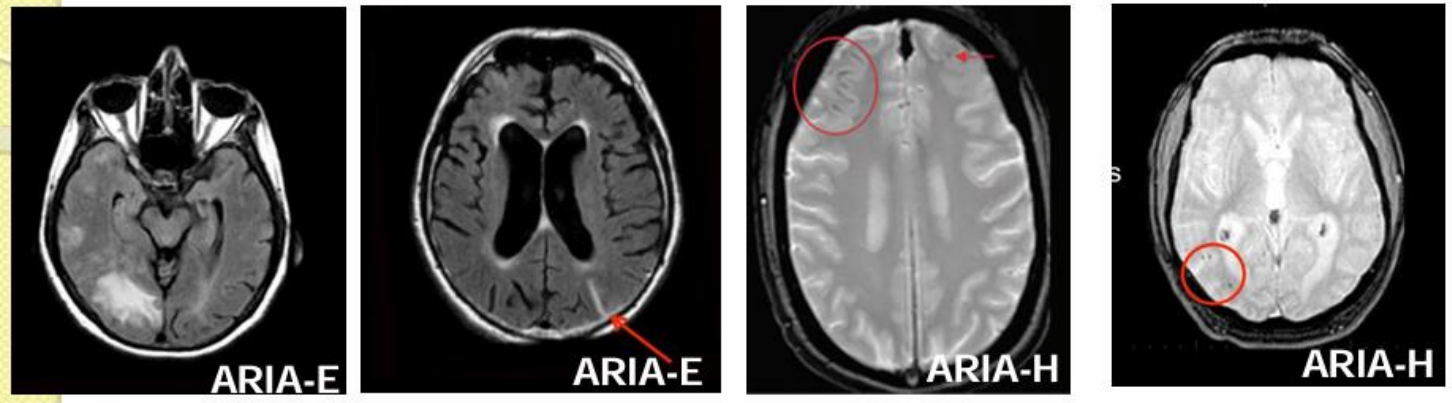
The CGM has a significant potential impact to reduce cognitive impairment and dementia risk via improving diabetes management.



More studies are needed

Amyloid-related imaging abnormalities (ARIA) in Lecanemab treatment

ARIA-E and ARIA-H



ARIA-E = cerebral ***vasogenic edema*** or ***sulcal effusions/ exudates***
ARIA-H = cerebral ***microhemorrhages*** or ***superficial hemosiderosis***

- Risk factors
  - Dose-dependent
  - APOEε4-dependent

DM has been studied as a Risk factor for ARIA but no Conclusion yet

van Dyck CH, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9-21.



DM and lecanemab treatment for AD

- No contraindication if patient has DM
- However, indirectly, DM can have higher chance of ***stroke, TIA*** which are contraindications for lecanemab
- DM patients have higher chance of ***coronary heart disease and AF*** (patient on anticoagulant is contraindicated for lecanemab treatment)
- DM not risk factor for ARIA E or ARIA H (ApoE 4 is the risk factor)

Implications in clinical practice

- Assessment for cognitive impairment is recommended in older adults with DM
  - In particular, those with repeated hypoglycemia, wide glucose excursions, and deterioration in glycemic control can be tell tale signs of cognitive impairment
- Annual assessment of cognitive function is also suggested

DIABETES AND THE ENDOCRINE PANCREAS I: EDITED BY MATTHEW FREEBY

Type 2 diabetes mellitus and cognitive functio understanding the connections

Dao, Lisa[a]; Choi, Sarah[b]; Freeby, Matthew[a]

Author Information

Current Opinion in Endocrinology & Diabetes and Obesity 30(1):p 7-13, February 2023. | *DOI:* 10.1097/MED.0000000000000783

DM and depression

Depression – a never-ending spiral

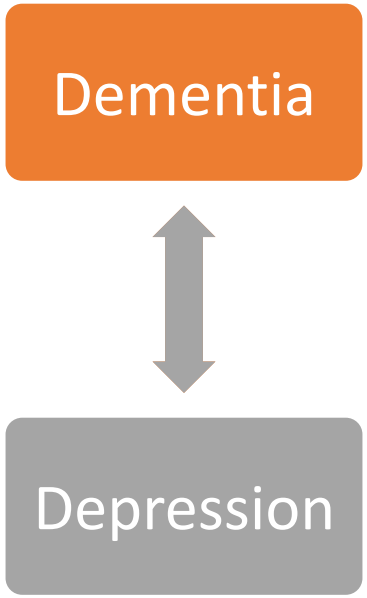
Bidirectional association between DM and depression

DM as a risk factor for depression

- Depression more common in patients with DM

Depression as a risk factor for DM

- Depression increased the risk of DM by 60%



Epidemiology

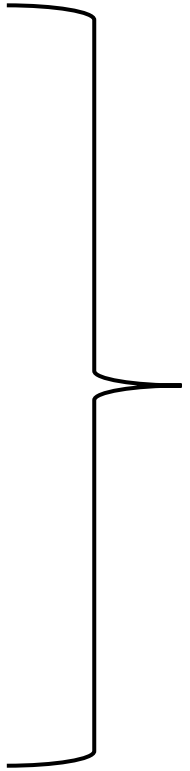
The prevalence of depression was significantly **higher in patients with DM** compared with those without (17.6 vs. 9.8%). (Badescu SV et al. J Med Life 2016)

The prevalence of depression was **higher in females** with diabetes (27%) compared with males (18%) (Anderson RJ et al Diabetes Care 2001)

Depression is associated 1.5- to 2.6-fold **increase of mortality** among individuals with DM (Sartorius N. 2018)

Share of common pathophysiology mechanisms between DM and depression (Badescu SV et al. J Medicine and Life 2016)

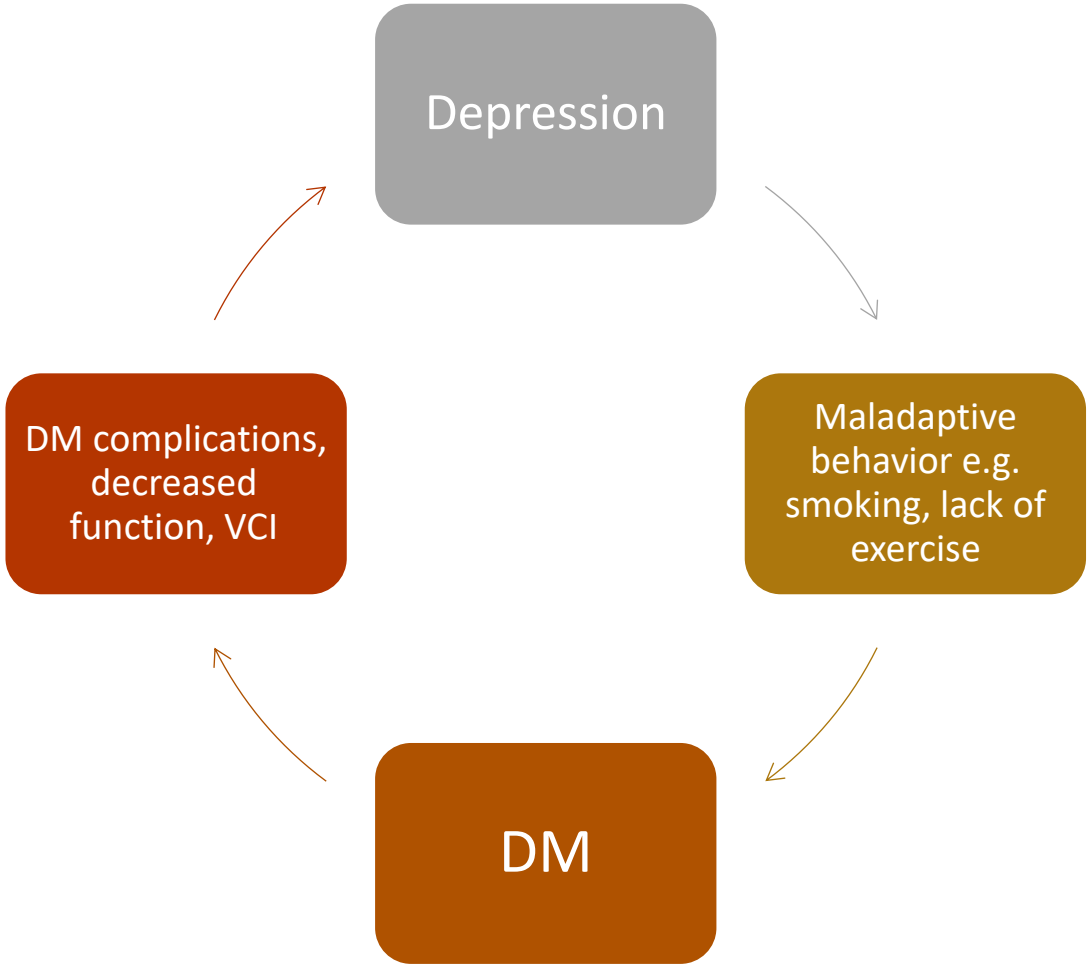
- **Genetic factors**
- **Low socioeconomic status**
- **Maladaptive behavior**, poor sleep, lack of exercise, poor diet, obesity
- **Chronic stress** – increase level of cortisol, adrenalin and nor-adrenalin; induces immune dysfunction



DM

Depression

Complex bidirectional relationship between depression and type 2 DM (viscous cycle)



The consequences of DM with depression

(Markowitz S et al Psychosomatics 2011)

Patient with DM who are depressed have increased:
Mortality
Cardiac events
Hospitalization
DM related complications
Functional impairment
Health care cost

Implications in clinical practice

- Having depression increases the risk of DM.
- Having depression decreases individuals' ability to successfully self-manage DM and increases likelihood for poor DM outcomes.

- Screen all DM older patients for depression
- Treat depression with priority –
  - Depressive symptoms improve in 2 to 4 weeks
  - Facilitate better glycemic control (patient more compliant to DM treatments)
  - Avoiding downstream adverse outcomes

(Patrak F et al. Lancet Diabetes Endocrinol 2015)

老人憂鬱量表

以下列舉的問題是人們對一些事物的感受。在過去一星期內，你是否曾有以下的感受，如有的話，請圈『是』，若無的話，請圈『否』。

1.	你基本上對自己的生活感到滿意嗎？	是 / 否
2.	你是否已放棄了很多以往的活動和嗜好？	是 / 否
3.	你是否覺得生活空虛？	是 / 否
4.	你是否常常感到煩悶？	是 / 否
5.	你是否很多時感到心情愉快呢？	是 / 否
6.	你是否害怕將會有不好的事情發生在你身上呢？	是 / 否
7.	你是否大部份時間感到快樂呢？	是 / 否
8.	你是否常常感到無助？(即是沒有人能幫助自己)	是 / 否
9.	你是否寧願晚上留在家裡，而不愛出外做些有新意的事情？(譬如：和家人到一新開張酒樓吃晚飯)	是 / 否
10.	你是否覺得你比大多數人有多些記憶的問題？	是 / 否
11.	你認為現在活著是一件好事嗎？	是 / 否
12.	你是否覺得自己現在一無是處呢？	是 / 否
13.	你是否感到精力充沛？	是 / 否
14.	你是否覺得自己的處境無望？	是 / 否
15.	你覺得大部份人的境況比自己好嗎？	是 / 否

總分 _____

- 92% sensitivity
- 89% specificity

Geriatric Depression Scale-15

Sheikh JI, Yesavage JA. Clin Gerontol 1986; 5: 165-173

Management- holistic approach

A comprehensive approach will improve patients' physical and psychological well-being

Physician role

- Education of patients (cognitive dysfunction)**
- Psychological intervention (cognitive dysfunction)**
- Prescription of medications
  - SSRI, bupropion
- Systematic follow-up
- Appropriate use of specialists and resources

Social interventions (poor social support in older people)**

** obstacles in older people

psychoanalytic psychotherapy

DM and Sarcopenia
肌少症

Luk JKH, Chan DKY. Frailty and sarcopenia—from theory to practice HKMJ 2022

Definitions - European Working Group on Sarcopenia in Older People (EWGSOP)

A syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and high mortality.

This definition supported by Asian Working Group on Sarcopenia (AWGS)

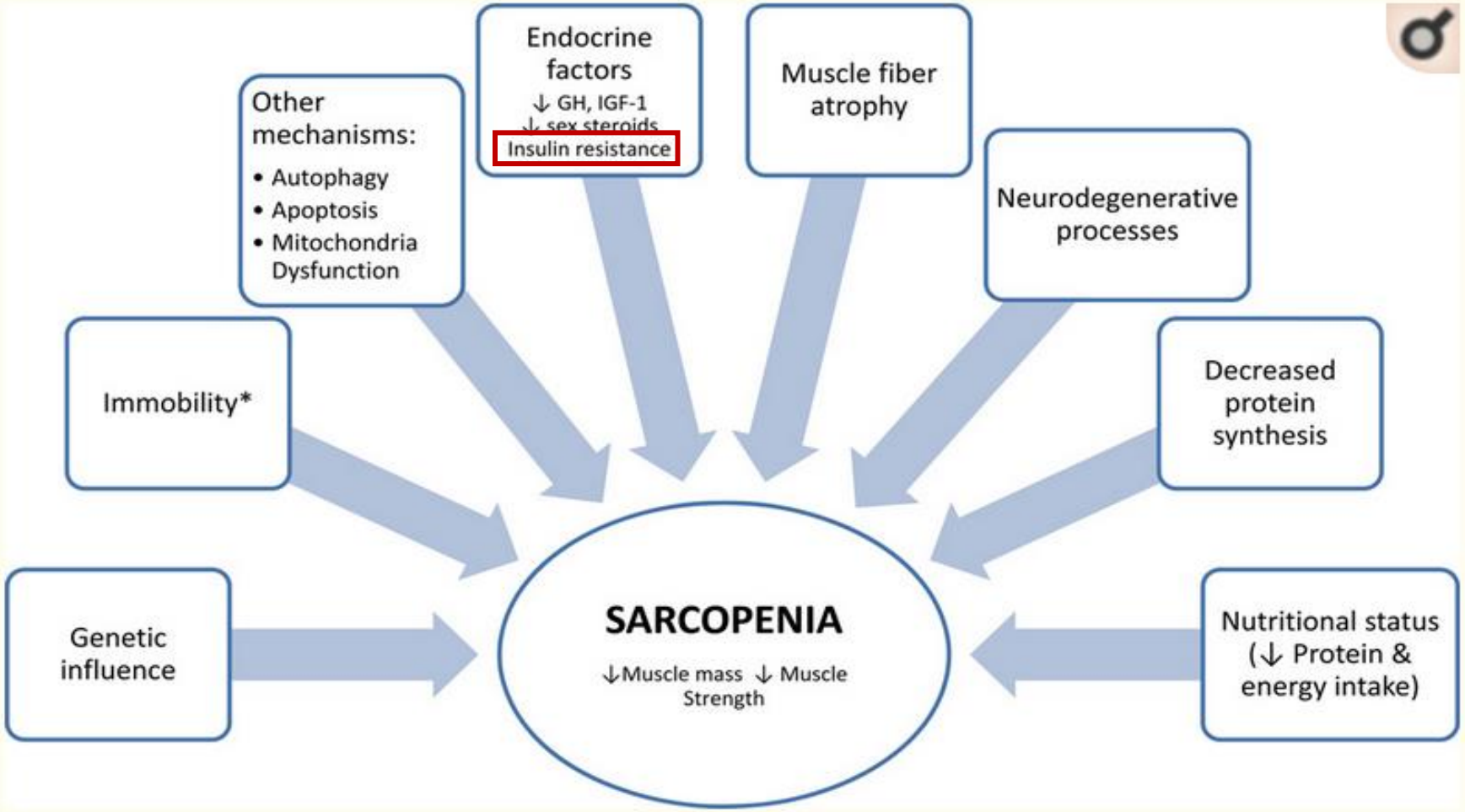


Figure 2

Pathophysiology of sarcopenia

GH= growth hormone, IGF-1= insulin-like growth factor-1. *Immobility may also be considered part of disuse atrophy rather than sarcopenia

J Am Med Dir Assoc. 2020 Mar;21(3):300-307.e2. doi: 10.1016/j.jamda.2019.12.012. Epub 2020 Feb 4.

Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment.

Chen LK[1], Woo J[2], Assantachai P[3], Auyeung TW[4], Chou MY[5], Iijima K[6], Jang HC[7], Kang L[8], Kim M[9], Kim S[10], Kojima T[11], Kuzuya M[12], Lee JSW[4], Lee SY[13], Lee WJ[14], Lee Y[15], Liang CK[5], Lim JY[16], Lim WS[17], Peng LN[18], Sugimoto K[19], Tanaka T[20], Won CW[10], Yamada M[21], Zhang T[22], Akishita M[11], Arai H[23].

- Low muscle strength
  - Handgrip strength <28 kg for men and <18 kg for women;
- Low physical performance
  - 6-m walk <1.0 m/s, Short Physical Performance Battery score ≤9, or 5-time chair stand test ≥12 seconds.
- Muscle mass (skeletal mass index)
  - DXA, <7.0 kg/m^2 in men and <5.4 kg/m^2 in women; Bioimpedance, <7.0 kg/m^2 in men and <5.7 kg/m^2 in women.

Epidemiology of sarcopenia (prevalence)

Australia (EWGSOP criteria) ≥65	6.4% in men, 9.3% in women
China (AWGS criteria) ≥65	26.2% in men, 33.6% in women
Hong Kong (EWGSOP criteria) ≥65	9%

Pathophysiology



Imbalance between muscle protein anabolism and catabolism leading to overall loss of skeletal muscle



Reduce type II fibre with transition of type II (*Fast-twitch muscle fibres)* to type I fibre (*Slow-twitch muscle fibres*)



Intramuscular and intermuscular fat infiltration (myosteatosis)

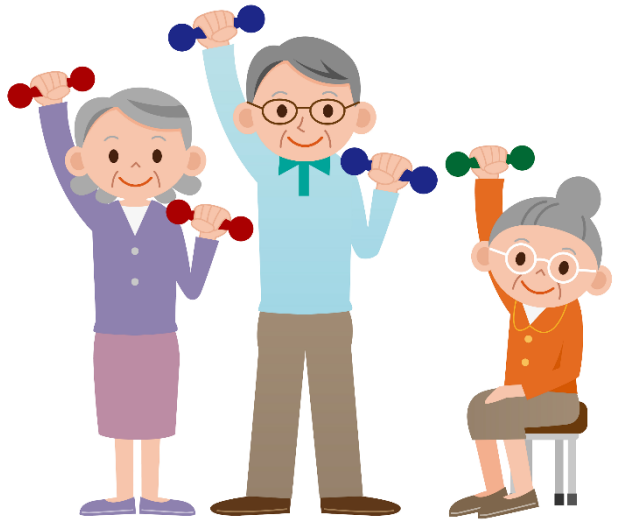
Screening tool – SARC – F

High specificity but low sensitivity

Table 2: SARC-F screen for sarcopenia

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None= 0 Some =1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None= 0 Some =1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None= 0 Some =1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None= 0 Some =1 A lot or unable = 2
Falls	How many times have you fallen in the last year?	None= 0 1-3 falls= 1 4 or more falls= 2
≥4: sarcopenia		

Resistance exercise



- Resistance exercise improves
  - Muscle strength
  - Muscle mass
  - Balance

Sayer AA et al 2013
Alfonso J C-J et al 2019

Nutrition - Protein and caloric supplementation

- Better to couple with resistance exercise (Tieland et al)
- Protein
  - ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and osteoarthritis) recommends intake of 1 to 1.2g/kg BW per day
  - Before or after exercise – no difference
  - Supplementation with leucine and HMB

DM and Sarcopenia

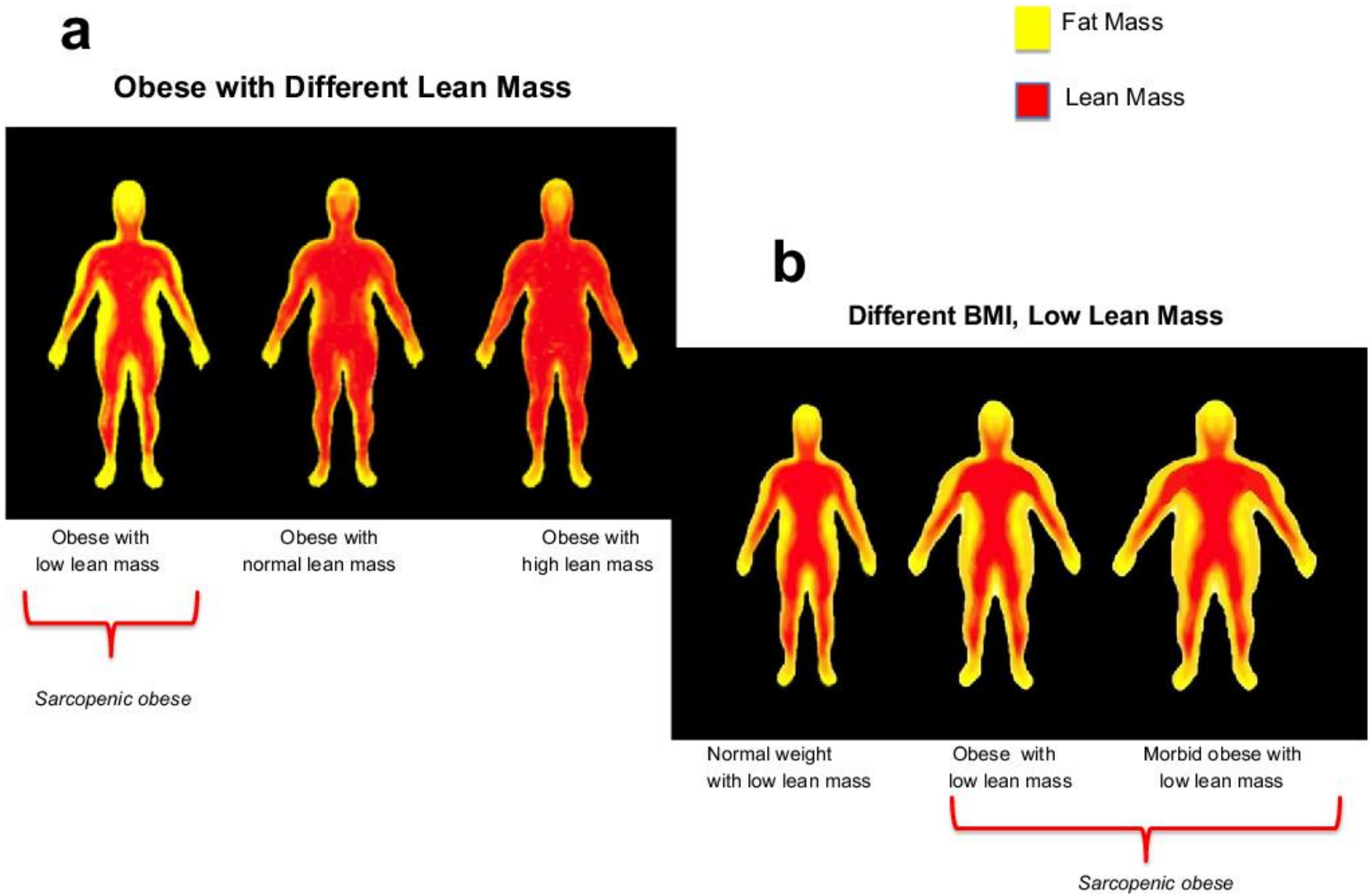
- DM accelerates the decline of muscle mass and function
- Loss of muscle increase chance of DM

Biochemical Mechanisms Underlying Impaired Glucose Regulation and Muscle Dysfunction

Insulin resistance in skeletal muscle are associated with

- mitochondrial dysfunction
- fat accumulation
- intramyocellular lipid deposition
- muscle inflammation
- oxidative stress

Sarcopenic obesity

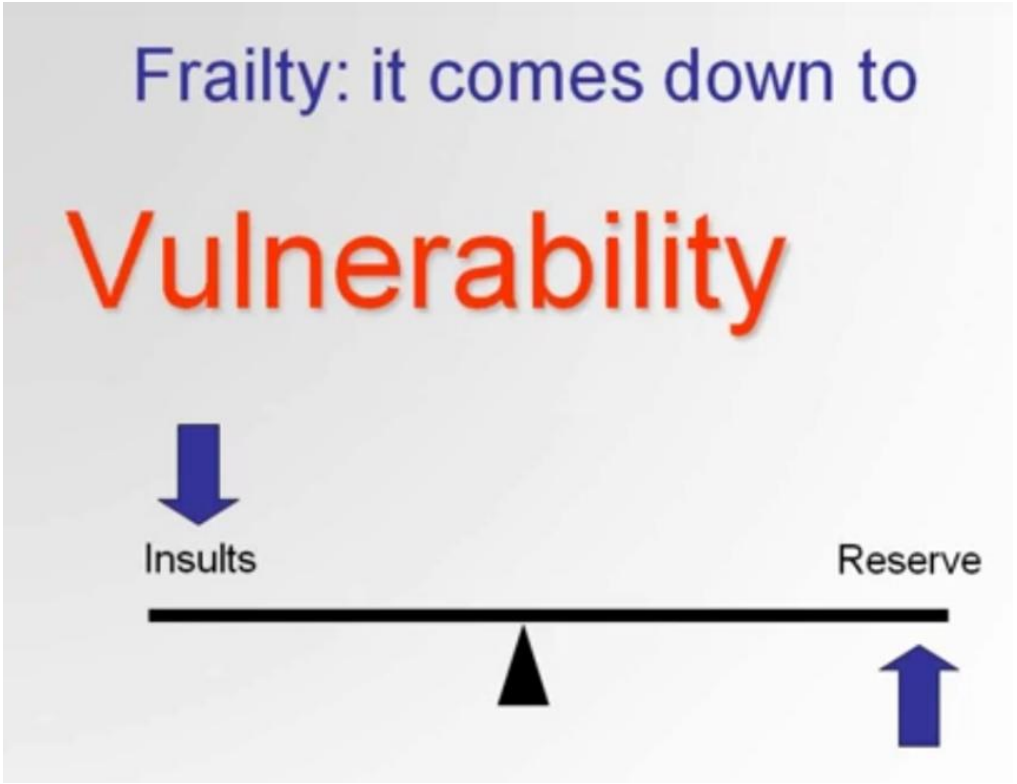


Frailty

Luk JKH, Chan DKY. Frailty and sarcopenia—from theory to practice HKMJ 2022

- A biological syndrome of decreased reserve and resistant to stressors, resulting from cumulative decline across multiple physiologic systems, and causing vulnerability to adverse outcomes

- (Fried et al 2001; Buchner DM et al 1992; Hamerman D 1999)



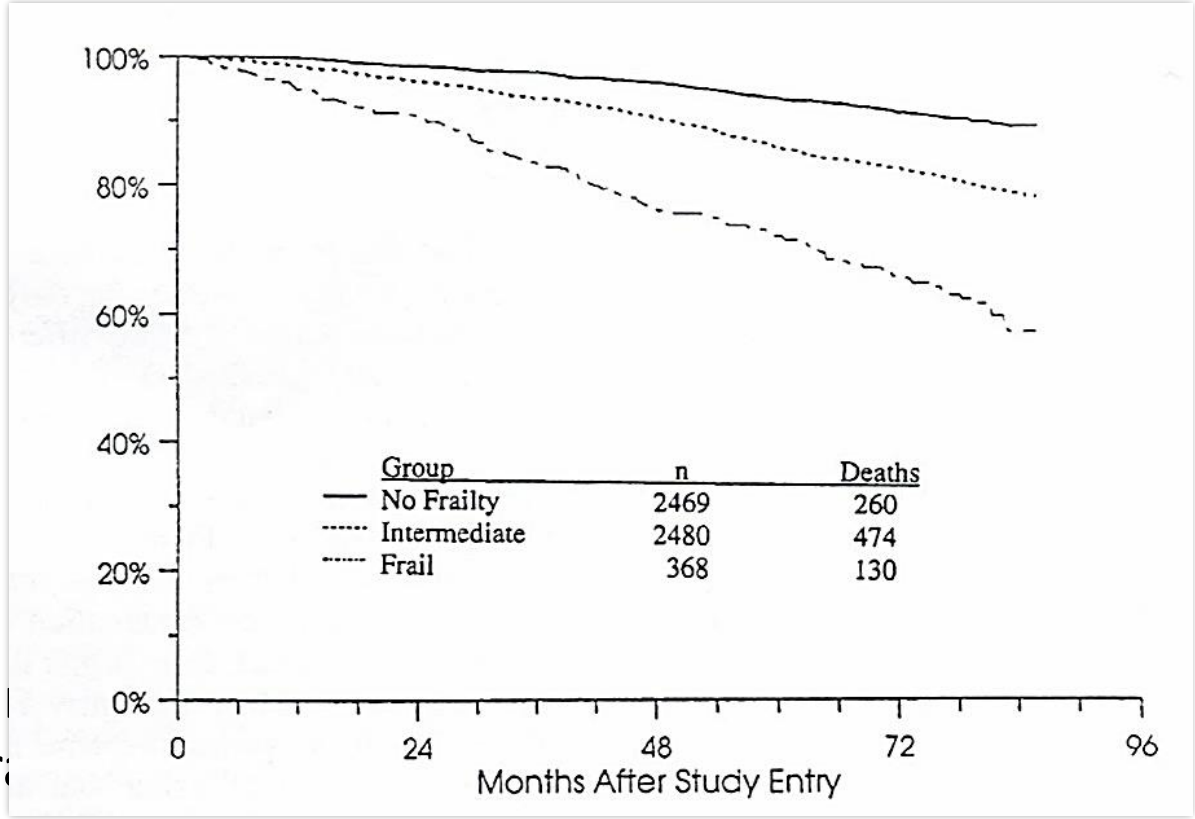
Epidemiology

- Prevalence varies depend on definition
- US *(Collard RM et al. JAGS 2012;60:1487-92)*
  - 9.9% for frailty (Fried scale)
- Asia-Pacific Region
  - 3.5-27%
- HK *(Lee JS et al JAMDA 2014;15:281-286)*
  - 7.9% for frailty

Frailty more common in older woman

Consequences of frailty

- Associated with adverse outcomes:
  - Falls
  - Disability
  - Hospitalization / readmission
  - Institutionalization
  - Death
- Health care expenses around US 4000 ove
  older adults with frailty (5X cost for non-fr



Biological underpinnings of frailty are multifactorial

- A proinflammatory state (Walston J, 2002)
- Sarcopenia (Ferrucci L, 2002)
- Anemia (Chaves PH, 2005)
- Relative deficiencies in androgens (DHEAS) (Leng SX et al 2004)
- Decreased growth hormone and IGF-1 (Chu LW et al 2001; Nass R et al 2002)
- Excess exposure to catabolic hormones (cortisol) (Varadhan R et al 2008)
- Insulin resistance (Barzilay JI, 2007)
- Compromised altered immune function (Yao X, 2011)
- Micronutrient deficiencies and oxidative stress (Semba RD, 2007)
- Decreased 25(OH) vitamin D levels (Pabst G et al 2015)
- Chronic CMV infection (Wang GC et al 2010)
- Dysregulation of autonomic nervous system (Varadhan R et al 2009)

CLINICAL FRAILTY SCALE BY ROCKWOOD (5 MIN)

Using in geriatric inpatient, GDH, SOPD, ICDS, GaFD, CGAT EOL services in HKWC

CLINICAL FRAILTY SCALE



1 VERY FIT — People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.



2 FIT — People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g., seasonally.



3 MANAGING WELL — People whose **medical problems are well controlled**, even if occasionally symptomatic, but often are **not regularly active** beyond routine walking.



4 LIVING WITH VERY MILD FRAILTY — Previously "vulnerable," this category marks early transition from complete independence. While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up" and/or being tired during the day.



5 LIVING WITH MILD FRAILTY — People who often have **more evident slowing**, and need help with **high order instrumental activities of daily living** (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.



6 LIVING WITH MODERATE FRAILTY — People who need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.



7 LIVING WITH SEVERE FRAILTY — **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).



8 LIVING WITH VERY SEVERE FRAILTY — Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.



9 TERMINALLY ILL — Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise living with severe frailty.** (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILTY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

In **very severe dementia** they are often bedfast. Many are virtually mute.

DALHOUSIE UNIVERSITY

www.geriatricmedicineresearch.ca

Clinical Frailty Scale ©2005–2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: www.geriatricmedicineresearch.ca

Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

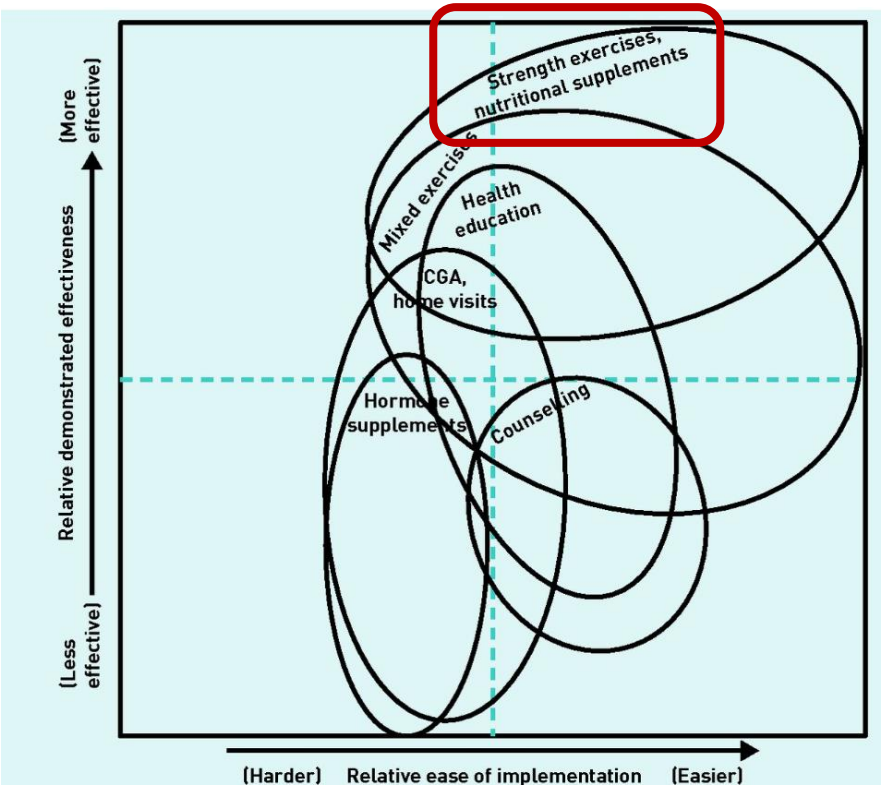
Research

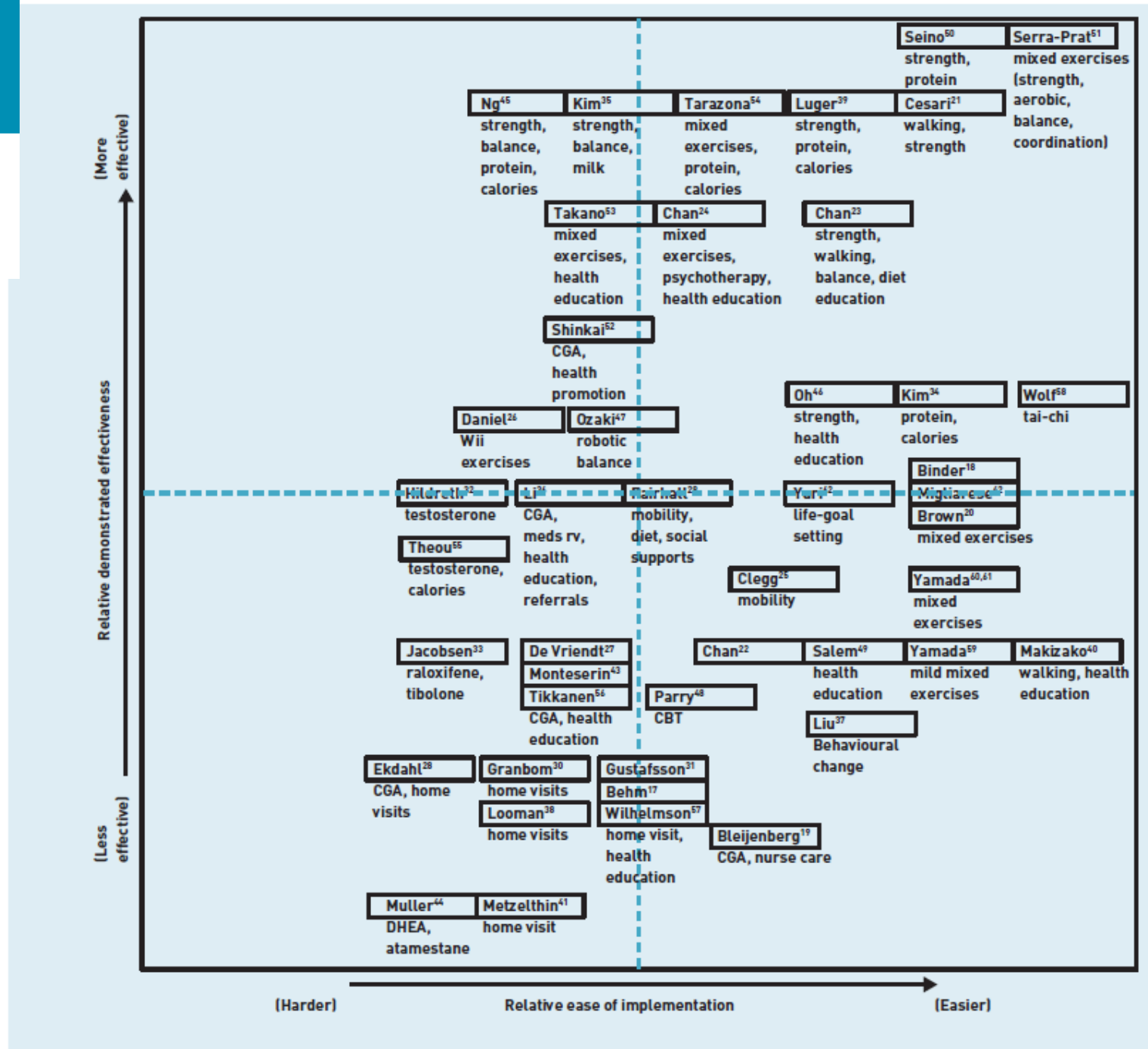
John Travers, Roman Romero-Ortuno, Jade Bailey and Marie-Therese Cooney

Delaying and reversing frailty:

a systematic review of primary care interventions

British Journal of General Practice
Jan 2019





DM and Frailty

- **DM is implicated in the development of frailty.**
  - Hyperglycemia is linked with incident frailty
  - HBA1c are associated with frailty severity
  - Recent meta-analysis : prevalence of frailty in older adults with DM 20%*
  - Vascular complications from type 2 DM are also associated with physical and cognitive decline
- **It is less clear if frailty leads to DM**
- Frailty in DM associated with worse outcomes – death, hospitalization, A&E visits**

* *Kong LN et al: Int J Nuts Stud 2021*

** *Li CL et al. Clin Interv Aging 2018*

Frailty in DM associated with increased mortality (Study in HKWC)

Whitney Ip et al

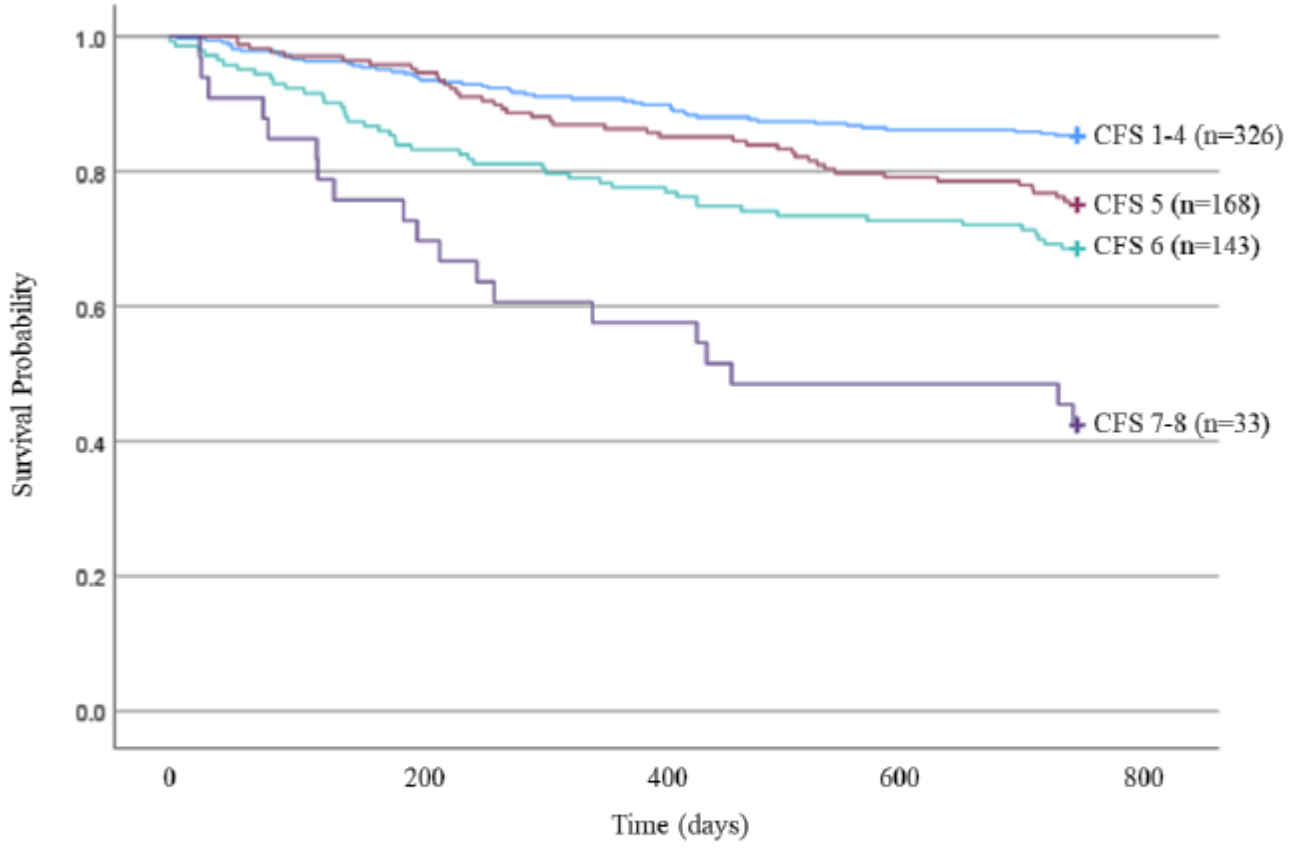


Figure 3. Kaplan-Meier survival curves for two-year mortality in elderly diabetic patients stratified by frailty categories (log-rank test, $p<0.001$)

2 important points for DM management in frail elderly

Detecting frailty in older people with DM is important to target interventions that reduce functional decline and risk of disability

Personalized management for HBA1c target in frail elderly with emphasis on avoiding hypoglycemia

Personalized management for HBA1C target in frail elderly

- In general, a strict glycemic goal of ≤7%, or 7-7.5%7 is appropriate for elderly people who are independent and without major comorbidities to minimize vascular complications. (largely based on expert opinion)

Table 41.4 Recommended HbA1c targets for elderly diabetic patients in various international guidelines7-9

Patient characteristics	HbA1c		
	International Diabetes Federation (2013)[7]	European Diabetes Working Party (2011)[8]	American Geriatrics Society (2012)[9]
Independent relatively healthy elderly patient	7.0-7.5%	7-7.5% (fasting glucose 6.5-7.5 mmol/L)	≤7.5%
Functionally dependent (frail, dementia) or with life expectancy of <5 years	7.0-8.5%	7.6-8.5% (fasting glucose 7.6-9.0 mmol/L)	8-8.5%

Abbreviation: HbA1c = glycated haemoglobin

U shape curve in older people

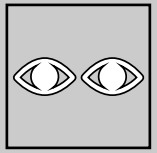
- A U-shaped association between HbA1c and mortality where HbA1c of about 7.5% had the lowest hazard ratio, supporting a slightly higher targeted goal in the elderly population.

- HbA1c goal to >9% is not recommended as the risk of developing acute hyperglycemic complications will increase.

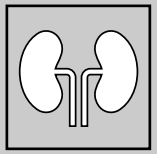
Intensive therapy not be suitable for frail elderly



Intensive therapy was associated with 2x to 3x hypoglycemic episodes



It takes >5 years for intensive glycaemic control to achieve microvascular benefit and >10 to 20 years for macrovascular benefit.



For patients with limited life expectancy and multiple co-morbidities, the adverse effects > benefits.

(*Nguyen TN et al. Diabetes Care 2021; Niznik JD et al. Diabetes care 2022*

Diabetes in older people: position statement of The Hong Kong Geriatrics Society and the Hong Kong Society of Endocrinology, Metabolism and Reproduction

CW Wong *, Jenny SW Lee, KF Tam, HF Hung, WY So, CK Shum, CY Lam, JN Cheng, SP Man, TW Auyeung

TABLE 2. Comparison of adverse outcomes of older diabetic patients (≥65 years) who presented to five accident and emergency departments with hypoglycaemia according to different glycated haemoglobin values between 1 January 2014 and 31 January 2014*

Variable	All	HbA1c (%)†								
		≤6	>6	P value	≤7	>7	P value	≤8	>8	P value
Age ≥65 years	105	18 (17‡)	87 (79‡)	-	54 (49‡)	51 (47‡)	-	81 (74‡)	24 (22‡)	-
LOS (days)	4.3 ± 5.7	6.8 ± 5.9	3.8 ± 5.5	0.001	4.6 ± 5.5	4.1 ± 5.8	0.65	4.3 ± 5.8	4.3 ± 5.3	0.61
28-Day readmission§	31	5 (27.8%)	26 (29.9%)	1.00	14 (25.9%)	17 (33.3%)	0.41	22 (27.2%)	9 (37.5%)	0.33
12-Month mortality	21	8 (44.4%)	13 (14.9%)	0.01	15 (27.8%)	6 (11.8%)	0.04	16 (19.8%)	5 (20.8%)	1.00
Age <65 years	28	3 (1‡)	25 (19‡)	-	7 (5‡)	21 (15‡)	-	15 (11‡)	13 (9‡)	-
LOS (days)	4.4 ± 4.1	-	4.3 ± 4.2	-	4.6 ± 2.4	4.3 ± 4.6	0.31	3.9 ± 2.5	4.9 ± 5.6	0.66
28-Day readmission§	7	1 (33.3%)	6 (24.0%)	1.00	2 (28.6%)	5 (23.8%)	1.00	5 (33.3%)	2 (15.4%)	0.40
12-Month mortality	5	0	2 (8.0%)	1.00	2 (28.6%)	3 (14.3%)	0.57	3 (20%)	2 (15.4%)	1.00

Abbreviations: HbA1c = glycated haemoglobin; LOS = length of stay

* The five hospitals were Alice Ho Miu Ling Nethersole Hospital, Caritas Medical Centre, Pok Oi Hospital, Queen Elizabeth Hospital, and Tuen Mun Hospital; comparison of adverse outcomes was performed by Student's *t* test

† Data are shown as No. of patients, No. (%) of patients, or mean ± standard deviation

‡ No. of patients who were admitted to a ward

§ Emergency readmission to hospital within 28 days of discharge

DM and Falls

Luk JKH, TY Chan, Chan DKY. Falls prevention in the elderly: translating evidence into practice HKMJ 2015

Mnemonic (A E I O U, A B B C C C) of risk or precipitating factors for falls (A is shared between vowels and ABC)

Frail older people with DM

A	Anti-depressants, antipsychotics, anticholinergics, antiepileptics, anti-hypertensives
E	Environmental hazards e.g. home, outdoors
I	Infectious diseases e.g. urinary tract infection, chest infection and others
O	Osteoarthritis and musculoskeletal problems
U	Unwell patients are more prone to falls
B	Blindness and visual impairment e.g. refractive, cataract, macular degeneration, glaucoma, visual field defect, hemi-spatial neglect after cortical stroke
B	Biochemical abnormalities e.g. hyponatraemia, hypokalaemia, hypoglycaemia
C	Cardiovascular problems e.g. postural hypotension, heart block, arrhythmias, carotid sinus hypersensitivity
C	Central nervous system or peripheral nervous system disorders, Parkinsonism
C	Cognitive impairment e.g. dementia, delirium

Adopted from Chan's Practical Geriatrics, 2nd Edition

Medication review and minimization

- The risk of falls increases with the no of medications prescribed
- Especially:
  - Psychoactive drugs e.g. Benzodiazipine, phenothiazines, tricyclic antidepressants
  - Codeine
  - Diuretics
  - Antihistamines
  - Anti-hypertensive
  - DM medications



DM increases Fall risks

- Sarcopenia
- Frailty
- Cognitive impairment
- Hypoglycemia
- Peripheral neuropathy
- DM amyotrophy
- DM myopathy
- Unstable bladder with urge incontinence
- Poor vision (DMR, Cataract)
- Polypharmacy
- Specific drug side effect e.g. diuretics, psych med, gabapentin for neurogenic pain etc

Osteoporosis and DM

- DM associates with osteoporosis and low-impact fractures.
- DM aggravates osteopenia and osteoporosis

DM drugs and osteoporosis

OHA that may benefits bone

- Metformin-treated rats showed positive effects of metformin on osteoblast differentiation and function
- Glimepiride has been shown to stimulate proliferation and differentiation of primary rat osteoblasts *in vitro*

OHA that may harm bone

- Thiazolidinediones antidiabetic drugs, such as rosiglitazone, may contribute to bone loss and fracture

Pioglitazone



Treatment of patients with prediabetes or T2DM with for up to 3 years was associated with decreased BMD at the level of the lumbar spine.

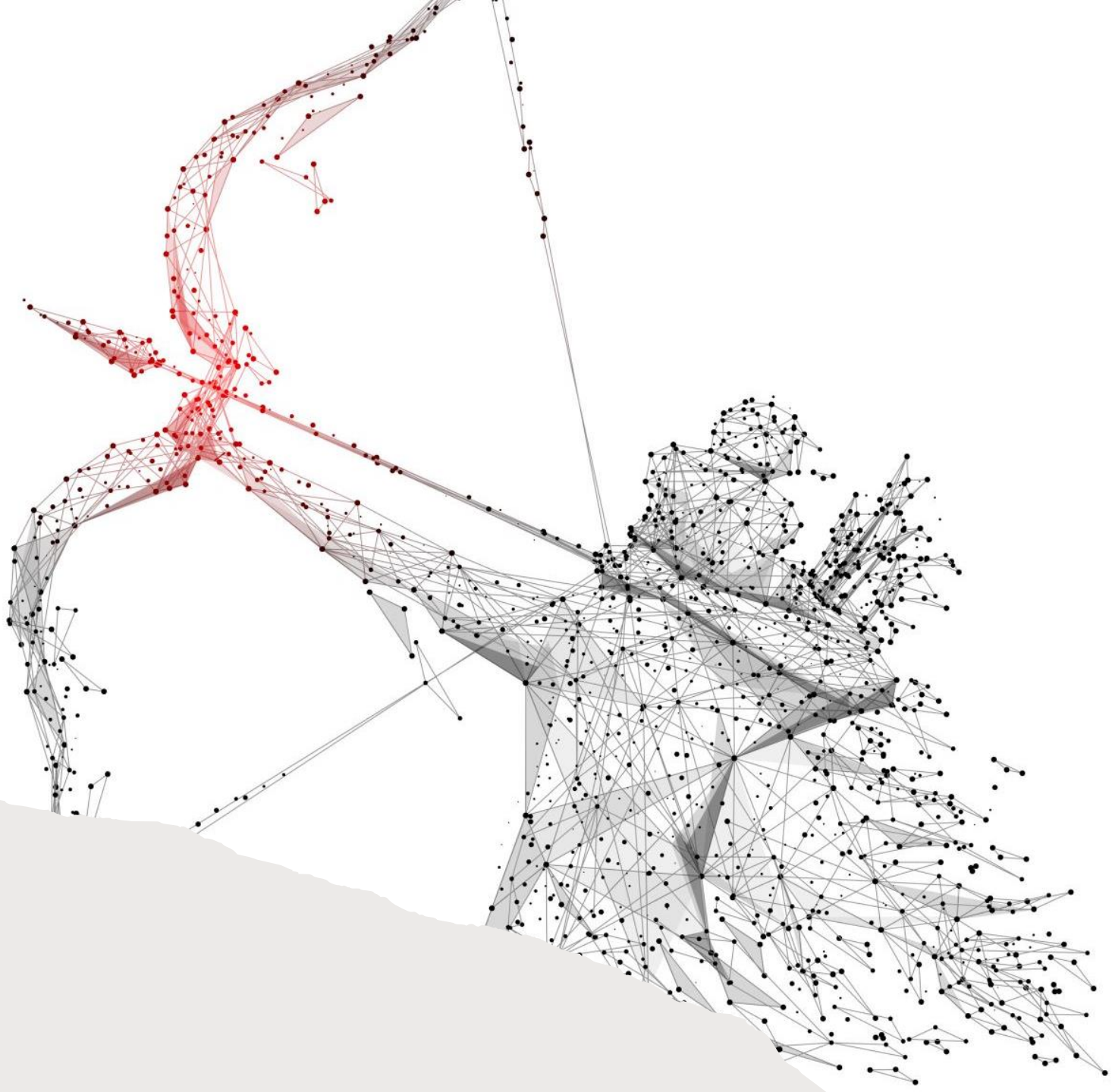


The loss of bone is more severe in women than in men

Ann V. Schwartz et al. J Clin Endocrinol Metab. 2006 September ; 91(9): 3349–3354.



No conclusion if adding vitamin D to piogliotazone can help bone health in Vit D replete people.



DM and polypharmacy

Polypharmacy

- The regular use of 5 or more medications
- Polypharmacy linked to poor outcomes e.g. falls, hospitalizations, frailty etc
- A recent meta-analysis found 64% older patients with DM have polypharmacy *(Quinones et al. J Gen Intern Med 2019)*
  - Associated with poor DM control
  - Hypoglycemia
  - Falls
  - Hospitalization
  - Death

BMJ Open

Potential workload in applying clinical practice guidelines for patients with chronic conditions and multimorbidity: a systematic analysis

BMJ Open 2016;6:e010119. doi:10.1136/bmjopen-2015-010119

Céline Buffel du Vaure,[1,2,3] Philippe Ravaud,[2,3,4,5,6] Gabriel Baron,[2,3,4,5]
Caroline Barnes,[2,3] Serge Gilberg,[1,2] Isabelle Boutron[2,3,4,5]

In order to comply with all disease specific guidelines patients with 3 chronic conditions (any combination of COPD, IHD, T2D, OA, HT, depression) -> take 6-13 drugs per day;
In patients with all 6 conditions -> 18 drugs per day

T2D is a polypharmacy condition

- Glycemic control*
- Cholesterol control*
- BP control*
- Neuropathy drugs
- Aspirin
- Non-DM drugs

*Use different drugs with different mechanisms of action to achieve treatment goals



CLINICAL TOOLS TO COMBAT POLYPHARMACY AND REDUCE INAPPROPRIATE PRESCRIPTIONS

- American Geriatrics Society (AGS) Beer's Criteria

- STOPP & START criteria (UK and Ireland)
  - Screening Tool to Alert Doctors to Right Treatment (START)
  - Screening Tool of Older Person Prescriptions (STOPP)

Take home message – Comprehensive Geriatric Assessment (CGA)

Complex interactions between DM and geriatric syndromes

Screening for dementia, depression, frailty, sarcopenia and polypharmacy

Early intervention of geriatric syndromes can mitigate adverse outcomes downstream, fostering better glycemic control

Personalized approach in setting HbA1c target, especially those who are very old and frail


Thank You