Effects of Multimorbidity and Frailty on Diabetes

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Multimorbidity and frailty are highly prevalent in older people with diabetes. This high prevalence is likely due to a combination of ageing and diabetes-related complications and other diabetes-associated comorbidities. Both multimorbidity and frailty are associated with a wide range of adverse outcomes in older people with diabetes, which are proportionally related to the number of morbidities and to the severity of frailty.

older people diabetes multimorbidity frailty outcomes

1. Effects of Multimorbidity

Twelve studies investigated the association of multimorbidity and diabetes outcomes (**Table 1**). Heikkala et al., reported that multimorbidity was associated with achievement of glycaemic and LDL treatment targets. However, this was a cross-sectional study which did not reflect a cause-and effect relationship and the findings were just an indication that clinicians focused on patients with multimorbidity to achieve targets more than on patients with diabetes as a single disease [1]. Umeh et al., have shown that multimorbidity is associated with poor self-rated health in a proportionate manner and this association was unconnected to glycaemic control [2]. Certain multimorbidity combinations especially those that include depression, hypertension and arthritis increased the risk of disability in older people with diabetes as demonstrated by McClellan et al., while Coles B et al., in their large retrospective analysis found that, in addition to the level of multimorbidity, cardiovascular multimorbidity increased the risk of subsequent cardiovascular events, mortality and cardiovascular mortality [3][4]. However, the effect of multimorbidity on mortality may be affected by the ethnicity of the population studied. For example, data from the UK Biobank (a population predominantly of European origin), showed that a combination of coronary heart disease and heart failure, while the Taiwan National Diabetes Care Management Program (a population predominantly of Chinese ethnicity), showed that a combination of painful conditions and alcohol problems to be associated with the largest effect size on mortality, respectively. Although the UK cohort tended to have higher body weight than that of the Taiwanese cohort, which may increase their cardiovascular risk, {median (IQR) body mass index 30.8 (27.7, 34.8) kg/m^2 vs. 25.6 (23.5, 28.7) kg/m^2, there is still a need for further exploration of the effects of different patterns of multimorbidity on outcomes across different ethnic groups as suggested by Chiang et al. [5]. Increased risk of emergency department visits and hypoglycaemia-related hospitalisation are another multimorbidity-related outcomes which increases in proportion with the number of morbidities as demonstrated by McCoy et al. [6]. Another retrospective report by McCoy et al., demonstrated that HbA1c levels declined as the number of comorbidities increased reflecting clinical practice of tighter glycaemic control in multimorbid patients, rather than a

direct relationship between multimorbidity and glycaemic control [7]. Similarly, Chiang et al., have demonstrated no association between multimorbidity and glycaemic control in their large cross-sectional general practice study [8]. Wong et al., found that health-related quality of life was impaired with increasing number of morbidities [9]. Mental health conditions such as depression, schizophrenia, substance use disorder and anxiety, which was present in 1 in 5 of older people with diabetes, was also associated with increased risk of mortality and hospital services use as reported by Guerrero Fernández de Alba et al. in their retrospective analysis [10]. Chiang el al, found no association between multimorbidity-related adverse outcomes and glycaemia markers such as HbA1c, glycaemic variability or time blood glucose in normal range suggesting that other factors, rather than dysglycaemia, contribute to the adverse outcomes associated with multimorbidity in older people with diabetes [11]. Among comorbidities, Quiñones et al., found that the presence of depressive symptoms or stroke, in particular, pose a substantial functional burden and contributed more to disabilities in ADL and IADL in older people with diabetes than other conditions [12].

Table 1. Recent studies exploring effects of multimorbidity on outcomes in older people with diabetes.

Study	Patients	Aim to	Main Findings
Heikkala E et al., cross-sectional, Finland, 2021 [1].	4545 subjects with type 2 DM, mean (SD) age 70.9 (12.3) Y.	Investigate associations of multimorbidity and treatment goals, HbA1c, LDL cholesterol and SBP.	A. 93% of subjects had general, 21% concordant, 8 % discordant and 64% both multimorbidities, respectively. B. General multimorbidity, concordant multimorbidity and discordant multimorbidity significantly associated with achievement of HbA1c target (OR 1.32, 95% CI 1.01 to 1.70, 1.47, 1.10 to 1.95 and 1.32, 1.01 to 1.72, respectively). C. Similar findings with attainment of LDL target (1.34, 1.03 to 1.74, 1.33, 1.00 to 1.78 and 1.36, 1.05 to 1.78, respectively).
Umeh K, cross sectional, UK, 2021 [2].	280 subjects with type 2 DM, median age 65–74 Y.	Examine self-rated health related to multimorbidity, glycaemia and BMI.	Odds of 'fair/bad/very bad' increased 10-fold in patients with 3 conditions (OR 10.11, 95% CI 3.36 to 30.40) and 4 conditions (10.58, 2.9 to 38.25) irrespective of glycaemic control ($p < 0.001$).
McClellan SP et al., prospective cohort, Mexico, 2021 [3].	Total 2558 subjects with DM, 1997 with and 561 without morbidities.	Investigate relationship of combinations of morbidities and disability.	A. Top 3 combinations were diabetes-hypertension (31.9%), diabetes-hypertension-depression (19.4%) and diabetes-depression (10.6%). B. DM-hypertension-depression (IRR 2.44, CI 1.65 to 3.60), DM-depression (2.37, 1.34 to 4.21) and DM-hypertension-arthritis-

Study	Patients	Aim to	Main Findings
			depression (3.74, 2.08 to 6.73) associated with higher ADL-IADL scores.
Coles B et al., retrospective, UK, 2021. [4]	Total 120,409 subjects with type 2 DM, mean (SD) age 63.5 (13.4) Y.	Quantify risk of CVD events, all-cause mortality and CV mortality in DM and multimorbidity.	A. Compared with DM only, ≥4 morbidities increased risk of CV events (HR 2.57, 95% CI 2.45 to 2.69), all-cause mortality (1.73, 1.68 to 1.78) and CV mortality (2.68, 2.52 to 2.85). B. Compared with no CVD morbidity, ≥2 morbidities increased risk of CV events (2.42, 2.35 to 2.49), all-cause mortality (1.44, 1.42 to 1.47) and CV mortality (2.44, 2.35 to 2.54).
Chiang JI et al., longitudinal cohort, UK-China, 2020 [5].	UK Biobank, 20,569 subjects, mean (SD) age 60.2 (6.8) Y, Taiwan NDCMP 59,657 subjects, mean (SD) age 60.8 (11.3) Y.	Explore associations of multimorbidity with baseline HbA1c and all-cause mortality in type 2 DM.	Increasing total and discordant multimorbidity were associated with lower HbA1c and increased mortality in both datasets. A. In UK Biobank, HRs (95% CI) for all-cause mortality in people with 1, 2, 3 and 4 morbidities compared with no morbidities were 1.20 (0.91 to 1.56), 1.75 (1.35 to 2.27), 2.17 (1.67 to 2.81) and 3.14 (2.43 to 4.03), all $p < 0.001$. B. HRs for mortality in Taiwan NDCMP were similar. C. Largest effect size on mortality was CHD and HF in UK Biobank (HR 4.37, 95% CI 3.59 to 5.32) $p < 0.001$, and painful conditions and alcohol in Taiwan NDCMP (4.02, 3.08 to 5.23) $p < 0.001$.
McCoy RG et al., cohort, US, 2020 [6].	201,705 subjects with DM, mean (SD) age, 65.8 (12.1) Y.	Examine associations of multimorbidity and other factors with hypoglycaemia-related ED visits and hospitalisations.	Risk of hypoglycaemia-related ED visits and hospitalisations increased by number of comorbidities (IRR of 1.66, 95% CI 1.42 to 1.95) in the presence of 2 comorbidities to IRR of 4.12, 3.07 to 5.51 with ≥8 comorbidities compared with ≤1 morbidity.
McCoy RG et al., retrospective, US, 2020 [7].	194,157 patients with type 2 DM, mean (SD) age 66.2 (11.7) Y.	Examine impact of DM-concordant, discordant and advanced morbidities on HbA1c.	A. 45.2% patients had DM-concordant, 2.7% discordant, 30.6% both morbidities and 13.0% had ≥1 advanced morbidities. B. Mean (SD) HbA1c was highest

Study	Patients	Aim to	Main Findings
			in patients with no comorbidities, 7.4% (1.7), slightly lower in those with concordant, 7.3% (1.5), much lower in those with discordant, 7.1% (1.5), both, 7.1% (1.4) and advanced comorbidities, 7.0 (1.3). C. In patients with discordant comorbidities, HbA1c declined as number of comorbidities increased, 7.1% (1.6) with 1 to 6.6% (1.2) with ≥3 morbidities.
Chiang JI et al., cross sectional, Australia, 2020 [8].	69,718 subjects with type 2 DM, mean (SD) age 66.42 (12.70) Y.	Explore prevalence of multimorbidity and its association with HbA1c.	A. >90% of participants had multimorbidity, 83.4% discordant and 69.9% concordant conditions. B. Top 3 discordant were painful diseases (55.4%), dyspepsia (31.6%), depression (22.8%) and concordant were hypertension (61.4%), CHD (17.1%) and CKD (8.5%). C. No association of multimorbidity and HbA1c.
Wong FLY et al., cross sectional, China, 2020 [9].	2326 patients with DM, 60% aged ≥65 Y.	Estimate health scores by sociodemographics.	Patients with ≥3 morbidities are more likely to show a lower health-related quality of life scores than those with DM alone.
Guerrero Fernández de Alba I et al., retrospective, Spain, 2020 [10]	63,365 subjects with type 2 DM, mean (SD) age 69.9 (12.1) Y.	Study mental health comorbidity prevalence and its association with outcomes.	Mental health multimorbidity prevalent in 19% of subjects and increased mortality risk (OR 1.24, 95% CI 1.16 to 1.31), all-cause hospitalisation (1.16, 1.10 to 1.23), DM-related hospitalisation (1.51, 1.18 to 1.93) and emergency room visits (1.26, 1.21 to 1.32).
Chiang JI et al., cross-sectional, Australia, 2020 [11].	279 subjects with type 2 DM, mean (SD) age 60.4 (9.9) Y.	Explore associations of multimorbidity and HbA1c, GV and TIR.	A. 89.2% of subjects had multimorbidity. B. Most prevalent was hypertension (57.4%), painful conditions (29.8%), CHD (22.6%) and depression (19.0%). C. Multimorbidity was not associated with HbA1c, GV or TIR.
Quiñones, AR et al., prospective cohort, US, 2019 [12].	3841 subjects with DM, mean (SD) age 68.1 (9.5) Y.	Identify multimorbidity combinations and their association with poor functional status.	Depressive symptoms or stroke, added to DM-multimorbidity combinations associated with higher ADL-IADL limitations:

2. Effects of Frailty

Twelve studies investigated the association of frailty and diabetes outcomes (**Table 2**). Hanlon et al., analysed a large UK Biobank data (20,566 participants) using two frailty and two multimorbidity measures and found that each

Study	Patients	Aim to	Main Findings
[13]	[14]		A. DM-arthritis-hypertension-depressive symptoms vs. DM-arthritis-hypertension: IRR 1.95, 95% CI 1.13 to 3.38). B. DM-arthritis-hypertension-stroke vs. DM-arthritis-hypertension: (2.09, 1.15 to 3.82).

and fall or railty and s reported ovascular t al., who ol [15]. In a retrospective analysis by Sable-Morita et al., frailty was a predictor of hospitalisations, institutional admissions, emergency outpatient visits, fractures, and mortality in older people with diabetes [16]. Ferrucci et al., prospectively demonstrated association of frailty with all-cause hospitalisation and mortality independent of comorbidity [17]. Usui et al., investigated the impact of frailty on the outcome of a very old (≥80 years) cohort with diabetes and acute coronary syndrome. The association between patients and outcomes (incidence of death or readmission after 6 months) was not significant in robust patients, but was significant in frail patients [18]. Among patients with diabetic kidney disease, frailty increased the risk of progression to end stage renal disease on a dose–response relationship and mortality, compared to those without frailty as reported by Chao et al. [19]. The prospective study by Kitamura et al., showed that all-cause mortality and disability in older people with mild diabetes were strongly affected by the presence of frailty [20]. Frailty was associated with low health related quality of life, depression, lean body mass and higher numbers of health-care visits in people with diabetes and chronic kidney disease as demonstrated in a cross-sectional analysis by Adame Perez et al. [21]. Chao et al., showed that both pre-frailty and frailty were associated with increased mortality, cardiovascular events, hospitalisation and health care utilisation [22]. In the community prospective study by Thein et al., frailty was associated with disability, which was potentiated by the presence of cognitive impairment. In addition, frailty, cognitive impairment or both were strong predictors of mortality [23]. In another community study by Li et al., frailty was associated with increased hospitalisation while both pre-frailty and frailty were associated with increased emergency department visits [24].

DM = Diabetes mellitus, SD = Standard deviation, Y = Years, SBP = Systolic blood pressure, OR = Odds ratio, CI = Confidence interval, BMI = Body mass index, ADL = Activities of daily living, IADL = Instrumental ADL, CVD = Cardiovascular disease, HR = Hazard ratio, NDCMP = National Diabetes Care Management Program, CHD = Coronary heart disease, HF = Heart failure, ED = Emergency department, IRR = Incidence rate ratio, CKD = Chronic kidney disease, GV = Glycaemic variability, TIR = Time in range.

Table 2. Recent studies exploring effects of frailty on outcomes in older people with diabetes.

Study	Patients	Aim to	Main Findings
Hanlon P et al., longitudinal cohort, UK, 2021 [13].	UK Biobank, 20,566 with type 2 DM aged 40–72 Y.	Assess implications of frailty/multimorbidity in middle/older-aged people with type 2 DM using 2 morbidity and 2 frailty measures.	A. 42% of participants were frail or multimorbid by at least one measure, 2.2% by all four measures. B. Each measure was associated with mortality, MACE, hypoglycaemia, fall or fracture. C. Mortality risk was higher in older vs. younger participants with a given level of frailty (1.9%, and 9.9% in men aged 45 and 65, respectively or multimorbidity (1.3% and 7.8% in men with 4 morbidities aged 45 and 65, respectively).

Study	Patients	Aim to	Main Findings
Espeland MA et al., prospective, US, 2021 [14].	3842 subjects with type 2 DM aged 45–76 Y at baseline, F/U 8 Y.	Examine effect of multimorbidity and frailty on cognition, physical function and mortality.	Increases in both multimorbidity and frailty index were associated with poor composite cognitive function and 400 m walk speed and increased risk for death (all $p < 0.001$).
Nguyen Tu N et al., retrospective, multicentre, 2021 [15].	11,140 subjects with type 2 DM, mean (SD) age, 65.78 (6.39) Y.	Explore effect of frailty on intensive glycaemic and blood pressure control.	A. Frailty increased risk of combined macro- and microvascular events (HR 1.03, 95% CI 0.90 to 1.19, $p = 0.02$) and all-cause mortality (1.11, 0.92 to 1.34). B. Severe hypoglycaemia was higher in frail, 8.39 (6.15 to 10.63) vs. 4.80 (3.84 to 5.76) in non-frail ($p < 0.001$). C. No significant difference in discontinuation of BP treatment due to hypotension/dizziness between frail and non-frail.
Sable-Morita S et al., retrospective, Japan, 2021 [16].	477 subjects with DM, mean (SD) age 74.2 (6.2) Y.	Assess whether frailty and DM-related factors could predict occurrence of adverse events.	Microvascular complications and frailty were significant predictors of adverse event incidence, respective OR (95% CI) 1.403 (1.11 to 1.78) per additional complication, 2.419 (1.33 to 4.40) for frailty; both $p < 0.05$).
Ferri-Guerra J et al., retrospective, US, 2020 [17].	763 subjects with DM, mean (SD) age 72.9 (6.8) Y.	Determine association of frailty with all-cause hospitalisations and mortality.	Frailty was associated with higher all-cause hospitalisations, HR 1.71 (95% CI 1.31 to 2.24), $p < 0.0001$ and greater mortality, 2.05, 1.16 to 3.64), $p = 0.014$.
Gual M et al., prospective, Spain, 2019 [18].	Total 532 subjects with ACS, 212 with DM, mean (SD) age 83.7 (5.0) Y.	Evaluate impact of DM on mortality or 6-month readmission according to frailty status.	Association of DM and incidence of clinical outcomes was significant only in patients with established frailty (HR 1.72, 1.05 to 2.81) compared to non-frail patients.
Chao CT et al., retrospective, Taiwan, 2019 [19].	165,461subjects with DKD, aged >20 Y.	Examine effect of frailty on DKD progression to ESRD, mortality, and adverse episodes.	A. Subjects with 1, 2, and ≥3 on FRAIL scale had increased risks of ESRD and mortality HRs 1.13, 1.18, and 1.2 and 1.25, 1.41, and 1.34, respectively. B. frailty increased risk of CV events and ICU admission in a dose response-manner.
Kitamura A et al., prospective, Japan, 2019 [20].	1271 subjects, 174 with DM, mean (SD) age 71.0 (5.6) Y, F/U 8.1 Y.	Clarify risks of death and disability in diabetes, frailty, both or neither.	A. Compared with non-frail subjects without diabetes, those with diabetes and frailty had higher risks of mortality, HR 5.0, 95% CI 2.4 to 10.3)

Study	Patients	Aim to	Main Findings
			and incident disability (3.9, 2.1 to 7.3). B. Non-frail with diabetes did not have a significant increased risk of mortality, but a tendency for disability compared with non-frail without diabetes.
Adame Perez SI et al., cross-sectional, Canada, 2019 [21].	41 subjects with DM and CKD, median (range) age 70 (65–74) Y.	Compare differences in body composition, HRQoL, mental health, cognition and vitD status with health-care utilization by frail and non-frail.	Frail, compared with non-frail, subjects had lower lean body mass, lower HRQoL scores, more depression (p = <0.05) and higher numbers of health visits (p < 0.05). No differences in health-care visit types or vitD status were noted between frail and non-frail participants.
Chao CT et al., longitudinal cohort, Taiwan, 2018 [22].	560,795 subjects with type 2 DM, mean (SD) age 56.4 (13.8) Y, 3.14 Y F/U.	Examine frailty impact on long-term mortality, CV risk, all-cause hospitalisation, and ICU admission.	Pre-frailty (1, 2 FRAIL scale) and frailty (≥3) increased risk of: A. Mortality, HR 1.05, 1.13, and 1.25 (95% CI 1.02 to 1.07, 1.08 to 1.17 and 1.15 to 1.36, respectively). B. CV events, 1.05, 1.15, and 1.13 (1.02 to 1.07, 1.1 to 1.2 and 1.01 to 1.25, respectively). C. Hospitalisation, 1.06, 1.16, and 1.25 (1.05 to 1.07, 1.14 to 1.19, and 1.18 to 1.33, respectively). D. ICU admission, 1.05, 1.13, and 1.17 (1.03 to 1.07, 1.08 to 1.14, and 1.06 to 1.28, respectively) compared to non-frail.
Thein FS et al., prospective, Singapore, 2018 [23].	2696 subjects, 486 with DM, mean (SD) age 67.3 (7.5) Y.	Investigate effect of frailty and cognitive impairment on functional and mortality outcomes.	A. Frailty associated with higher prevalence of IADL disability, OR 6.72, 95% CI 1.84 to 24.5. B. Frailty and cognitive impairment associated with highest prevalence of IADL (17.8, 3.66 to 8.68) and ADL disabilities (93.8, 23.6 to 372.4). C. Cognitive impairment (HR 2.72, 95% CI 1.48 to 5.01), frailty (4.30, 1.88 to 9.82) and cognitive impairment with frailty (8.41, 3.95 to 17.9) associated with mortality.
Li CL et al., cross-sectional, Taiwan, 2018 [24].	3203 subjects, 719 with DM, aged ≥ 65 Y.	Investigate prevalence of frailty and its relationship with health care.	A. Frailty, but not pre-frailty, significantly associated with hospitalisation, OR 5.31, 95% CI 1.87 to 15.10).

evement of treatment goals among patients with type 2 diabetes: A primary care, real-world study. BMC Health Serv. Res. 2021, 21, 964.

Study	Patients	Aim to	Main Findings
			B. Pre-frail and frail significantly associated with emergency department visits (2.64, 1.35 to 5.17 and 4.05, 1.31 to 12.49, respectively).

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DM = Diabetes mellitus, Y = Year, MACE = Major adverse cardiovascular events, F/U = Follow up, SD = Standard deviation, HR = Hazard ratio, CI = Confidence interval, BP = Blood pressure, OR = Odds ratio, DKD = Diabetic kidney disease, ESRD = End stage renal disease, CV = Cardiovascular, ICU = Intensive care unit, HRQoL = Health-related quality of life, vitD = vitamin D, IADL = Instrumental activities of daily living.

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