Are normoglycaemic individuals at risk of depression? The depression-dysglycaemic phenotype from a European population-based cross-sectional study

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Abstract

Background Depression is an ever more common chronic non communicable disease and its control constitutes a growing public health concern given its links with a number of co-morbidities, including diabetes mellitus. The study aimed to estimate the prevalence of depression at a population level across groups of different glycaemic status, whilst establishing its socioeconomic phenotypic characteristics.

Methods A nationally representative cross-sectional study was conducted in Malta between 2014 and 2016. Participants were categorized into different sub-populations according to their glycaemic status. Depression prevalence rates and socio-economic characteristics for each sub-population were established. Multiple regression analysis was performed to identify links with depression.

Results Depression was prevalent in 17.15% (CI 95%: 16.01 – 18.36) with a female predominance. The normoglycaemic sub-population had the highest depression rates. However, persons with known diabetes had a higher probability of having a history of depression (OR:2.36 CI 95%:1.12 – 4.96), as well as with being of the female gender, having lower educational status, having a history of smoking tobacco and having established cardiovascular disease.

Conclusions Depression was highly prevalent among the normoglycaemic population especially as age progress. Physicians in primary care should implement a depression screening tool as part of their routine health check-ups, with special attention to those with cardiovascular co-morbidities and any signs of psycho-socio-economic burden.

Background

Depressive illness is a chronic non-communicable disease which is ever more prevalent and constitutes a public health concern leading to considerable worldwide disability and global burden [1, 2]. Across Europe the prevalence of depression has been found to vary considerably. This can be attributed to contextual factors such as demographic, environmental, cultural and economic factors [3]. Different comorbidities such as coronary heart disease, stroke and diabetes have been found to be associated with depression [4–7]. In fact, it was reported that individuals with diabetes are two-times more likely to develop depressive symptoms when compared to none diabetics [8, 9]. However, there have been contradictory findings with regards to this depression-diabetes link [10].

This study was set up to explore the varying phenotypes and the relationships between depression and dysglycaemia at a population level. The southern European country of Malta, which is constitutes two small islands in the Mediterranean Sea, has an established risk for dysglycaemia [11, 12]. Considering the small size of the country (316 Km^2), a representative population-based study could easily be conducted in order to examine the associations between depression and dysglycaemia as well as to explore the model for neighboring Mediterranean countries.

The aim of this study was to establish the prevalence of depression and depressive symptoms at population level. Its objectives included determining the biological, psychological, socio-economic characteristics of depression in accordance with the varying glycaemic status of the population. Additionally, to establish the links between groups with differing glycaemic status, depression and depressive symptoms while considering potential confounding factors. To our knowledge, such a study has never performed within the Mediterranean region and this was the first study to be conducted within the Maltese Islands at a population level.

Method

The University of Malta conducted a nationally representative cross-sectional study between 2014 and 2016. The detailed methodology of the health examination study is found elsewhere [13]. Briefly, a single stage randomized stratified (by age, gender and locality) sample was obtained from a national register. The sample population (18 to 70 years) represented approximately 1% of each Maltese town. An informed written consent was obtained from each participant. Trained interviewers distributed a validated demographic, social and medical co-morbidity (including self-reported depression) questionnaire. This questionnaire also included the PHQ–9 (patient health questionnaire) for depression symptoms [14]. During the health examination blood pressure, height, weight, waist circumference and hip circumference measurements were recorded for each participant. Fasting bloodletting for fasting plasma glucose (FPG) and lipid profile was undertaken. Ethical and data protection approvals were granted from the University of Malta Research Ethical Committee (UREC) and the Information and Data protection national commissioner respectively

This study followed the PHQ–9 score definition used by Katon *et al. [*15], where the total score and depression severity were divided and defined as follows: 1—4 score as “No depression”; 5—14 score as “Minor depression” and 15 to 27 score as “Major depression”. Those individuals not previously aware of depression or not on anti-depression medication and scoring >14 were considered as having *newly diagnosed depression* [16]. The segment of the study population reporting an established history of depression, were considered as being *aware of depression.* The combination of the population ‘aware of depression’ with those ‘on medication’ and ‘newly diagnosed depression’score >14) sub-populations were labeled as the *global depression population.*

The study population was subdivided into four glucose regulatory subgroups and represented a continuum of glycaemic transition from normal to disordered glucose metabolism. The four sub-groups were: (1) normoglycaemia (NGR), (2) impaired fasting glucose (IFG), (3) newly diagnosed diabetes mellitus (NDM) and (4) known diabetes mellitus (KDM) subgroups. The subdivision was based on the fasting plasma glucose results obtained during the health examination survey while incorporating any self-reported history of diabetes mellitus and oral hypoglycaemic agents. Those participants obtaining a fasting plasma glucose (FPG) level between 5.60 - 6.99 mmol/L were labeled as *Impaired Fasting Glucose* (IFG) while those with a FPG > = 7mmol/L were labeled as *Newly diagnosed diabetes mellitus* (NDM), provided they were not previously diagnosed as diabetics or were on oral hypoglycaemic agents

[17]. Identifying newly diagnosed diabetics following a single fasting blood glucose reading is of common practice in population-based health examination surveys [18]. The participants with a previous history of diabetes mellitus or on oral hypoglycemic agents, irrespective of their measured fasting plasma glucose, were labeled as cases of *Known diabetes mellitus* (KDM). Those individuals who did not fall within these glucose dysglycaemic categories were considered to be *Normoglycaemic (*NGR). The depression prevalence rate for each sub-population was calculated.

The most common literature based biological, social, socioeconomic and medical co-morbidities factors associated with depression were considered during the analyses. Multivariate logistic regression analyses were performed while considering self-reported depression, major depression symptoms and global depression as the outcomes (respectively). The normoglycaemic sub-population was considered as the reference category.

Results

The global depression prevalence for the entire population was of 17.15% (CI 95%: 16.01 – 18.36) with a female preponderance (58.35% CI 95%: 54.59 – 62.00). The global depression population (n=677) constituted of 60.86% (CI 95%: 57.13 – 64.46) having self-reported depression while the remainder exhibited depressive symptoms (PHQ-9 score >14) or was on medication but was not aware they suffered from depression.

The study population was further subcategorized according to the glycaemic and depression status as seen in Table 1. The normoglycaemic status (NGR) exhibited the highest depression prevalence rate (11.00% CI 95%: 10.06 – 12.01) at population level, followed by impaired fasting glucose (IFG) status (3.78% CI 95%: 3.22 – 4.42) and diabetes status (2.38% CI 95%: 1.95 – 2.91). The known diabetes (KDM) had a depression prevalence of 1.65% (CI 95%: 1.29 – 2.10) while the newly diagnosed diabetes (NDM) had a depression prevalence of 0.73% (0.51 – 1.06). Of note, this study did not identify any new depressive symptoms within the diabetic status (both KDM and NDM) sub-groups although a number of these individuals were on medication but reported not to be aware of their underlying depression.

The phenotypic characteristics of the global depression population are shown in Table 2. As the glycaemic status shifted from normoglycaemic to diabetes, the median age, fasting plasma glucose (FPG) and body mass index (BMI) increased. Of note, the lipid profile

followed the same incremental trend up till newly diagnosed diabetes. The known diabetes exhibited a better lipid profile which corresponds to the fact that all diagnosed diabetics are started on lipid lowering agents.

Multivariate logistic regression analyses were performed with (i) self-reported depression, (ii) depressive symptoms cutoff score >14 (iii) and global depression as the outcome, while adjusting for bio-socio-economic factors and medical comorbidities. Only the KDM subgroup exhibited a significant association with self-reported depression, as seen in Table 3. However, KDM subgroup had a borderline significant association with global depression as well. A similar association trends could be observed for both the self-reported depression and the global depression with various factors including the female gender, low levels of education, smoking and a history of cardiovascular comorbidities. No dysglycaemic associations were evident with major depressive symptoms, which could have resulted from the small population sample size (Table 3).

Table 1. The population with depression by glycaemic status and gender

	NGR *n*=2,615	IFG *n*=925	NDM *n*=158	KDM *n*=249
Depression Category	Male *n*=1,164; Female *n*=1,451	Male *n*=563; Female *n*=362	Male *n*=103; Female *n*=55	Male *n*=168; Female *n*=81
Self-reported				
Total *n* (% CI 95%)	262 (10.02; 8.92 - 11.23)	91 (9.84; 8.07 - 11.93)		42 (16.87; 12.70 - 22.04)
Males *n* (CI 95%)	78 (6.70; 5.40 - 8.29)	47 (8.35; 6.32 - 10.94)	11 (10.68; 5.91 - 18.28)	22 (13.10; 8.74 - 19.10)
Female *n* (% CI 95%)	184 (12.68; 11.06 - 14.50)	44 (12.15; 9.16 - 15.95)	6 (10.91; 4.74 - 22.18)	20 (24.69; 16.52 - 35.15)
Unaware but on Rx				
Total *n* (% CI 95%)	159 (6.08; 5.22 - 7.06)	53 (5.73; 4.40 - 7.43)	12 (7.59; 4.28 - 12.92)	23 (9.24; 6.18 - 13.53)
Males *n* (CI 95%)	71 (6.10; 4.86 - 7.63)	25 (4.44; 3.00 - 6.50)	8 (7.77; 3.78 - 14.79)	18 (10.71; 6.81 - 16.38)
Female *n* (% CI 95%)	88 (6.06; 4.94 - 7.42)	28 (7.73; 5.37 - 10.99)	4 (7.27; 2.38 - 17.75)	5 (6.17; 2.33 - 13.98)
Unaware with PHQ-9 score >14				
Total *n* (% CI 95%)	13 (0.50; 0.28 - 0.86)	5 (0.54; 0.19 - 1.30)	0	0
Males *n* (CI 95%)	2 (0.17; 0.01 - 0.67)	0	0	0
Female *n* (% CI 95%)	11 (0.76; 0.41 - 1.37)	5 (0.34; 0.12 - 0.83)	0	0
Global depression				
Total *n* (% CI 95%)	434 (16.60; 15.22 - 18.07)	149 (16.11; 13.88 - 18.62)	29 (18.25; 13.05 - 25.16)	65 (26.10; 21.03 - 31.91)

Males *n* (CI 95%)	151 (12.97; 11.16 - 15.03)	72 (12.79; 10.27 - 15.81)	19 (18.45; 12.06 - 27.11)	40 (23.81; 17.97 - 30.82)
Female *n* (% CI 95%)	283 (19.50; 17.55 - 21.62)	77 (21.27; 17.36 - 25.79)	10 (18.18; 9.99 - 30.53)	25 (30.86; 21.83 - 41.63)

NGR = Normoglycaemia

IFG = Impaired fasting glucose

NDM = Newly diagnosed diabetes

KDM = Known diabetes

CI = Confidence Interval

Rx = Medication

Table 2. Phenotypic characteristics for the global depression population

	Global Depression				
	NGR	**IFG**	**NDM**	**KDM**	***p*-value***
N	434	149	29	65	
Age (years)	41 (27)	54 (18)	63 (8)	64 (11)	**<0.01**
BMI (Kg/m^2)	26.40 (5.80)	28.90 (7.96)	28.72 (5.04)	30.86 (6.08)	**<0.01**
FBG (mmol/L)	5.07 (0.48)	5.85 (0.43)	8.05 (1.91)	8.50 (3.61)	**<0.01**
LDL-C (mmol/L)	3.21 (1.09)	3.32 (1.14)	3.08 (1.45)	2.41 (1.23)	**<0.01**
HDL-C (mmol/L)	1.49 (0.73)	1.39 (0.54)	1.15 (0.51)	1.26 (0.37)	**<0.01**
Triglycerides (mmol/L)	0.92 (0.54)	1.06 (0.99)	1.68 (0.96)	1.03 (0.57)	**<0.01**
Total cholesterol (mmol/L)	5.23 (1.37)	5.50 (1.24)	5.28 (1.19)	4.38 (1.50)	**<0.01**
Education in years					**<0.01**
<=10 years	59 (13.59)	43 (28.86)	15 (51.72)	35 (53.85)	
11 - 13 years	270 (62.21)	78 (52.35)	10 (34.48)	26 (40)	
>=14 years	105 (24.19)	28 (18.79)	4 (13.79)	4 (2.46)	
Current smoking	187 (43.09)	38 (25.50)	14 (48.28)	21 (32.31)	0.06
Occupation					**<0.01**
Employed	291 (67.05)	73 (48.99)	11 (37.93)	15 (23.08)	
Unemployed	9 (2.07)	5 (3.36)	0	0	
Student	18 (4.15)	11 (7.38)	0	0	
Retired	32 (7.37)	36 (24.16)	13 (44.83)	32 (49.23)	
Domestic work	84 (19.35)	24 (16.11)	5 (17.24)	18 (27.69)	
Medical history					
Coronary heart disease	25 (5.76)	6 (4.03)	8 (27.59)	14 (21.54)	**0.01**
Myocardial infarction	18 (4.15)	6 (4.03)	0	6 (9.23)	0.41
Stroke	17 (3.92)	6 (4.03)	8 (27.59)	0	0.12
Hypertension	76 (17.51)	52 (34.90)	21 (72.41)	43 (66.15)	**<0.01**

Data: median (IQR), *n* (%)

*p-value: Kruskal-Wallis test and Chi test respectively

Table 3. Multivariate logistic regression analyses with self-reported depression, major depression symptoms and global depression as an outcome

	Self-reported depression		**PHQ-9 major depression (score >14)**		**Global depression**	
	Odd's ratio (95% CI)	*p*-value	Odd's ratio (95% CI)	*p*-value	Odd's ratio (95% CI)	*p*-value
Glucose status						
NGR	Reference		Reference		Reference	
IFG	1.05 (0.71 - 1.55)	0.81	1.633 (0.28 - 9.40)	0.58	0.82 (0.54 - 1.25)	0.35
NDM	0.52 (0.21 - 1.33)	0.18	0.87 (0.60 - 4.97)	1.00	0.59 (0.23 - 1.51)	0.27
KDM	2.36 (1.12 - 4.96)	**0.02**	0.95 (0.50 - 2.39)	1.00	2.16 (0.97 - 4.80)	0.06
Female*	1.85 (1.26 - 2.71)	**<0.01**	1.59 (0.45 - 5.56)	0.47	1.61 (1.07 - 2.43)	**0.02**
Age (years)	0.99 (0.98 - 1.01)	0.48	0.90 (0.85 - 0.95)	**<0.01**	1.00 (0.98 - 1.01)	0.64
BMI (Kg/m^2)	1.00 (0.97 - 1.03)	0.81	1.06 (0.98 - 1.14)	0.13	1.00 (0.97 - 1.03)	0.99
FBG (mmol/L)	1.03 (0.92 - 1.15)	0.62	1.31 (0.26 - 6.44)	0.74	1.03 (0.92 - 1.15)	0.59
LDL-C (mmol/L)	0.64 (0.18 - 2.24)	0.49	0.36 (0.01 - 18.43)	0.77	0.72 (0.23 - 2.29)	0.58
HDL-C (mmol/L)	0.36 (0.10 - 1.26)	0.11	0.27 (0.01 - 48.54)	0.71	0.40 (0.12 - 1.31)	0.13
Triglycerides (mmol/L)	0.70 (0.41 - 1.19)	0.19	0.49 (0.02 - 10.77)	0.65	0.73 (0.44 - 1.20)	0.21
Total cholesterol (mmol/L)	2.15 (0.63 - 7.34)	0.22	3.12 (0.01 - 44.34)	0.75	2.04 (0.66 - 6.33)	0.22

Education in years								
<=10 years	1.90 (1.05 - 3.45)	**0.04**		0.37 (0.22 - 1.00 13.98)			1.74 (0.93 - 3.29)	0.09
11 - 13 years	1.73 (1.08 - 2.77)	**0.02**		0.61 (0.44 - 1.00 25.88)			1.62 (0.98 - 2.66)	0.06
>=14 years	Reference			Reference			Reference	
Current smoking	1.99 (1.42 - 2.79)	**<0.01**		1.97 (0.70 - 0.20 5.53)			1.99 (1.38 - 2.85)	**<0.01**
Occupation								
Employed	0.71 (0.45 - 1.11)	0.13		0.20 (0.06 - 0.71)		**0.01**	0.75 (0.46 - 1.23)	0.26
Unemployed	1.90 (0.65 - 5.52)	0.24		3.72 (0.56 - 24.81)			1.14 (0.31 - 4.21)	0.84
Student	0.24 (0.05 - 1.11)	0.07		1.45 (0.23 - 7.89)			0.33 (0.07 - 1.58)	0.17
Retired	1.18 (0.70 - 1.97)	0.54		1.08 (0.18 - 6.64)			1.20 (0.69 - 2.10)	0.53
Domestic work	Reference			Reference			Reference	
Medical history								
Coronary heart disease**	2.90 (1.35 - 6.21)	**<0.01**		1.20 (0.45 - 13.67)		1.00	3.43 (1.56 - 7.53)	**<0.01**
Myocardial infarction***	0.75 (0.29 - 1.93)	0.55		1.78 (0.98 - 16.98)		1.00	0.80 (0.31 - 2.09)	0.65
Stroke****	3.03 (1.13 - 8.09)	**0.03**		1.29 (0.67 - 18.32)		1.00	3.42 (1.19 - 9.84)	**0.02**
Hypertension*****	1.44 (1.00 - 2.06)	**0.05**		1.06 (0.33 - 3.36)		0.92	1.31 (0.89 - 1.93)	0.17
Anti-depression treatment******	1.12 (0.74 - 1.70)	0.59		0.47 (0.15 - 1.42)		0.18	1.38 (0.60 - 15.89)	1.00

*Male as reference

** No history coronary heart disease as the reference category

*** No history myocardial infarction as the reference category

**** No history stroke history as the reference category

***** No history of hypertension as the reference category

****** No history of anti-depression treatment as the reference category

Discussion

This Malta population-based study showed that that the highest depression prevalence rate was within the normoglycaemic population. Such findings are in contrast to those of previously reported studies, where the diabetic population was reported to have a more highly prevalent depression rate [8, 9, 19–21]. In fact, the previously diagnosed diabetics had lower depression prevalence when compared to both the normoglycaemic and the impaired glucose sub-populations at a population level.

The normoglycaemic sub-population exhibited higher medical comorbidities than the rest of the dysglycaemic sub-populations, which may explain the current findings. This coincides with the established link between medical comorbidities and depression [22]. In fact, in this study, the medical comorbidities of coronary heart disease, stroke and hypertension were found to be associated with self-reported depression, while coronary heart disease and stroke were also associated with global depression. Such findings coincide with the previously reported literature associating psychological distress and comorbidities to the development of depression [4, 6, 23].

It was reported that individuals with depressive symptoms in combination with metabolic dysregulation are at higher risk of diabetes [24]. Known diabetes was only associated with self-reported depression and not with depressive symptoms, which coincides with a Finnish Study conducted in 2007 [10]. A probable explanation to this association follows the fact that diagnosed diabetic individuals are engaged in a healthy lifestyle management plan including weight management as well as prescription of both anti-diabetic and anti-dyslipidaemic medication [17, 25]. These management plans may create stress and anxiety for the individual, resulting in depression [26]. Furthermore, it was reported that those with multi-factorial treatment plans show higher distress levels than do those with less intensive treatments [27]. Due to the diabetic management intervention plans, these diabetic individuals are expected to have controlled blood glucose, lipid profile levels and body mass index. In fact, the previously diagnosed diabetics in this study exhibit a controlled lipid profile but poor glucose and body mass control. It has been reported that depression is associated with poor glycaemic control in diabetic individuals and therefore susceptible to comorbidities [20, 28]. This poor glycaemic control could be related to the effect

of depression on the individual's diabetes self-care including maintaining a healthy diet, physical activity and adherence to medication [29, 30].

Interestingly this study identified that being on anti-depression treatment was not linked with depression or depression symptoms, which contradicts the literature [10].

This study suggests that depression rates may be a multifactorial condition and country specific. Biological factors (such as inflammation and activation of nervous system), in combination with psychological stress that may be originating from clinical identification of a medical condition (such as cardiovascular disease and diabetes) may have an effect on depression development. These factors, along with socioeconomic status may possibly be the contributing factors for the development of depression. Therefore, the presence of any depression symptoms should be sought out as part of routine check-ups at primary health level, irrespective of the glycaemic status of an individual. Clinical tools are available that can be easily implemented by physicians as part of their routine work-up [14, 31, 32]. Individuals with cardiovascular comorbidities, especially coronary heart disease, hypertension and stroke, should be screened for presence of depression symptoms. Health education on depression and its related symptoms should be implemented on a population level since a substantial amount of the population reported to be unaware of their condition or related symptoms.

Conclusion

The study concludes that compared with normal glucose regulation, none of the dysglycaemic groups were associated with higher global depression or depressive symptoms. Normoglycaemic individuals exhibited the highest depression prevalence. Physicians should implement depression screening clinical tools as part of their routine health check-ups, irrespective of the glycaemic status of their patients, with special attention to those with cardiovascular co-morbidities and any signs of psycho-socio-economic burden.

Strengths and limitations

Such a study has never been conducted before at a population level within the Maltese population, a country considered as at high-risk of dysglycaemia. Therefore, the data from this study could act as evidence for other high-risk dysglycaemic populations.

The study limitations for this study were that data was self-reported, so that human recall error and bias may have been present. Depression symptoms were determined using the PHQ-9 tool, which is a self-reported tool that may miss less severe cases of depression [33]. In fact, only major depression symptoms were considered for this study, which may have had an effect on the findings. Also, the study was based on cross-sectional data and was unable to draw any conclusions about causality.

List Of Abbreviations

BMI -	Body mass index
CI -	Confidence interval
FPG -	Fasting plasma glucose
IFG -	Impaired fasting glucose
IQR -	Interquartile range
KDM -	Known diabetes mellitus
NDM -	Newly diagnosed diabetes mellitus
NGR -	Normoglycaemia
OR -	Odds ratio
PHQ-9 -	Patient health questionnaire

Declarations

Ethics approval and consent to participants

Ethics approval was granted by the University of Malta Research Ethics Committee (UREC). All participants gave their written informed consent

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing interest

The authors declare that they have no competing interests

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manuscript.

Authors' contributions

SC analyzed and interpreted the patient data. JM reviewed and proved the final manuscript.

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