Cardiovascular Risk Assessment in Male and Female Patients With and Without Depression: an Electronic Health Record Evaluation in Wales.

Running title: CV risk assessment & depression

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ABSTRACT

Aim: To investigate rates of cardiovascular risk factor assessment (blood pressure, lipid and QRISK score) in routine clinical practice for primary prevention of cardiovascular disease (CVD) in patients with and without depression.

Methods: A retrospective observational cohort study using electronic health record data sources was carried out. Rates of blood pressure measurement, lipid checks and QRISK documentation in primary care were calculated for non-depressed, and patients prior and subsequent to depression diagnosis. Poisson regression adjusting for age and sex was used to explore associations between depression status and rate of assessment. Differences in rates of assessment by deprivation and location of residence (urban/rural) were also explored.

Results: Of 2,290,075 patients, 176,062 had depression diagnosed. Patients with depression had blood pressure and lipid levels checked and QRISK score documented more frequently, after adjustment for sex and age group. Sex differences were noted, with younger females more likely to have blood pressure assessment and males more likely to have lipid levels checked, irrespective of depression status. There were significant three-way interactions between depression*sex*age group for all outcomes, with sex difference in blood pressure assessment highly dependent on age, and sex/depression status difference in lipid assessment most notable in the 60-74 age group.

Conclusion: Patients with depression are more likely to have their blood pressure, lipid levels and QRISK documented than patients without depression. Sex differences in assessment of blood pressure and lipid assessments may also impact on future cardiovascular risk management, providing opportunities for potential improvements in assessment of risk factors.

Lay summary

We explored if patients with depression were more or less likely to have key risk factors for heart disease checked or a risk score recorded than those without depression.

- Patients with depression had higher rates of blood pressure and lipid level assessment, and record of risk score calculation.
- Younger females were more likely to have their blood pressure assessed, particularly those with depression, than males.
- Depressed males were more likely to have their lipid levels checked than non-depressed males and all females.

Key words: Depression, risk factors, blood pressure, lipids, cardiovascular disease

Abbreviations

CVD cardiovascular disease

NHS National Health Service

TRE trusted research environment

UK United Kingdom (not defined technically in methods)

IGRP Information Governance Review Panel

SAIL Secure Anonymised Information Linkage

CKD Chronic kidney disease

WDSD Welsh Demographic Service Dataset

LSOA Lower-layer Super Output Area

WIMD Welsh Index of Multiple Deprivation

WLGP Welsh Longitudinal General Practice Data

SD standard deviation

HTN hypertension

DM diabetes

INTRODUCTION

Primary prevention is key to reducing the development of cardiovascular disease (CVD) and subsequent events in the population. Patients with severe mental illness die prematurely, most frequently from CVD, highlighting the potential benefit of timely and effective (primary) prevention in patients with mental health conditions[1]. Depression is also associated with an increase in risk of CVD, but the mechanisms as to why are not fully understood[2]. Garriga et al. have shown that patients on long term antidepressants were more likely to attend a National Health Service (NHS) health check in England than those not on antidepressants[3]. However, antidepressants are often prescribed for conditions other than depression and NHS health checks are limited to those aged 40-74 and may also reflect a non-representative sub-population.

Therefore, it was uncertain what assessments occur in those with a diagnosis of depression, in those under 40 and over 74, or in areas where health check programmes for CVD risk are not formally supported, such as Wales.

Sex differences also need to be considered, given women are more likely to be diagnosed with depression and men more likely to have CVD events at a younger age. However, females often have worse outcomes post CVD event and are commonly less likely to have effective and intensive management of risk factors than males[4-6]. Additionally, other factors such as socio-economic status and location of residence (being urban or rural) can also impact on likelihood of having and/ or being diagnosed with depression, increased CVD risk and able to access effective treatment[7-11].

The aim of this study was to investigate cardiovascular risk factor assessment (blood pressure, lipid and QRISK score) for the primary prevention of CVD within the general practice setting, in patients with and without a depression diagnosis. The impact of sex, socioeconomic status (deprivation) and location patients lived (urban or rural) on the relationship between depression status and risk factor assessment was also explored.

METHODS

A retrospective observational cohort study using individual level linked anonymised routinely-collected electronic health record (EHR) data sources for patients who were initially free from atherosclerotic CVD, depression or severe mental illness, aged 18 years or over and had at least 1 year of data within SAIL prior to entry into the cohort was carried out. Patients entered the cohort on the 1st January 2010, or on date of meeting the inclusion criteria. Patients remained in

the cohort until 31st December 2019, death or upon leaving a SAIL providing general practice. Access to data was within the privacy-protecting SAIL Databank TRE[12,13].

Presence of hypertension, dyslipidaemia, ischaemic heart disease, chronic kidney disease (CKD) stage 4+, chronic liver disease, dementia, cancer, depression, anxiety, severe mental illness, prescriptions for lipid lowering medication, antihypertensive therapy, antipsychotics, anxiolytics and antidepressant therapy were identified from primary care data. Secondary care data sources were also used to describe prior history of or contemporary myocardial infarction, peripheral vascular disease, heart failure, diabetes mellitus and ischaemic stroke. The Welsh Demographic Service Dataset (WDSD) was used to link other variables such as the Lower-layer Super Output Area (LSOA) version 2001 of residence and from this linkage to the area-based deprivation measure Welsh Index of Multiple Deprivation (WIMD) 2011, an indicator or socio-economic status and to provide location (rural and urban). The code used to generate the cohort is also available at (https://github.com/r-sum-1/SAIL0800-CVD-Depression.git).

Depression characterisation

The Welsh Longitudinal General Practice Data (WLGP) were used to identify patients who had a record of any of the following: a diagnosis of depression or mixed anxiety and depression, anxiety, severe mental illness (including, bipolar, schizophrenia, and other psychotic disorders), depressive symptoms, anxiety symptoms, prescriptions for antidepressants or anxiolytics. A list of diagnostic (Read) codes was created based on previous work from our group[14]. Patients were categorised as having depression during the study period if they met the following criteria (to be identified as depression forthwith), a diagnosis of depression or mixed anxiety and depression in their medical history, or a record of depressive symptoms together with a prescription of antidepressants within 6 months of record of the depressive symptoms. Depressive symptoms

were included in the depression categorisation to reflect changes within coding behaviour as specified in John et al and used in other studies looking at common mental disorders, with only those patients with both symptoms and a prescription for antidepressants being included in the depressed group [14-16]. This approach has been validated through linkage to survey data by John et al.[14]. Antidepressants can be prescribed for other conditions than depression. To ensure that prescriptions were associated with the identification of depressive symptoms in primary care, we only included patients prescribed antidepressants who had a code for depressive symptoms with a tight timeline of 6 months within the first prescription. This approach has been validated against depression diagnoses using linked data[14]. Therefore, patients prescribed antidepressants, but without a record of depression diagnosis or symptoms were not categorised as depressed. Patients who developed depression during the study period were identified as pre-depressed for the period of time from entry into the cohort up until the date of diagnosis and identified as depressed following the date of diagnosis.

Cardiovascular risk factor assessment

Patients were identified as having a cardiovascular risk assessment if they had a record of any of the following in their GP records, systolic or diastolic blood pressure, low density lipoprotein, high density lipoprotein, triglycerides, non-high-density lipoprotein or total cholesterol, a risk score calculation QRISK1 or QRISK2 score[17,18].

The number of blood pressure, lipid assessments or QRISK documentations were counted for each patient for the duration of time they were in the cohort. All lipid measures recorded on the same date within the GP record were counted as 1 assessment as were systolic and diastolic blood pressure measurements. For patients with depression, assessments were counted separately pre- and post-depression diagnosis. Observed rates were calculated per person year (number of

blood pressures assessed during study divided by time in study [or time pre/post-depression diagnosis]). These were explored in the whole cohort and in the those with a history of hypertension or a history of diabetes.

Statistical analysis

Variables are presented as mean (standard deviation [SD]) for continuous and frequency (percentage) for categorical variables. Comparisons between depressed and non-depressed groups were carried out using a two-sample t-test or chi square as appropriate. Crude rates of blood pressure and lipid assessment and QRISK documentation were calculated as per person year, based on depression status. Rates of assessment were explored in those with and without depression by sex, age group (18-39, 40-59, 60-74 & 75+), deprivation and geographic location (urban/rural). Due to overdispersion, a quasi-Poisson regression model was used to estimate the association between depression and rates of assessment for each risk factor, adjusting for sex and age group. A further analysis was performed including adjustment for available co-morbidities: WIMD (deprivation), location of residence, history of diabetes and history of hypertension. For incident depression, a time-dependent covariate approach was used, whereby person-years and assessment counts were assigned initially to the pre-depression category, and following diagnosis, to the depression category. We did not have information in the SAIL data to take into account possible delays in diagnosis as this information is not routinely entered in the record even if known to the clinicians. Interactions between depression and sex, depression and age group and a three-way interaction between depression, sex and age group were explored for each outcome. Analyses were carried out using SPSS version 26 and R studio version 2024.24.0.

RESULTS

The cohort consisted of 2,290,075 patients, with a total of 16,838,089 patient years of data, depression was recorded in 176,062 (7.7%) during the study period (Figure 1). Table 1 shows the baseline characteristics at time of entry to the cohort and at time of depression diagnosis. On entry to the cohort, pre-depression patients were younger than non-depressed (32.0 [15.5] vs 40.7 [19.3] yrs, p<0.001), more likely to be female (56.4% vs 46.2%, p<0.001) and be in the most deprived quintile (26.8% vs 16.8%, p<0.001), and had fewer comorbidities such as dyslipidaemia, diabetes or chronic liver disease than non-depressed. However, at the point of depression diagnosis a greater proportion of depression patients had developed these comorbidities (Table 1).

At least one assessment of a cardiovascular risk factor was made in 1,400,490 (61.2%) of the cohort. Blood pressure was the most frequently assessed risk factor with 1,362,771(59.5%) of the population having at least one measurement. Lipids were assessed in 789,709 (34.5%) individuals, with QRISK documented in only 355,598 (15.5%) patients.

Assessment of blood pressure

Rate of blood pressure assessment (unadjusted per person year) was more frequent in the depressed group, both pre- and post-depression diagnosis, than in the non-depressed (Pre depression 0.761 95%CI [0.759-0.763], depression 0.813 95%CI [0.811 - 0.815] & non-depressed 0.621 [0.620-0.621] Table 2). Females had a higher unadjusted rate of testing than males in both the depressed and non-depressed groups, with the greatest rate in depressed females prior to depression diagnosis (Female non-depressed 0.774 95%CI [0.774 - 0.775], pre depression 1.011 95%CI [1.008 - 1.014] & depression 0.988 95%CI [0.985 - 0.991], male non-

depressed 0.490 95%CI [0.489 - 0.490], pre depression 0.477 95%CI [0.474 - 0.479], depression 0.568 95%CI [0.566 - 0.571]).

Due to the age difference between the depressed and non-depressed groups, rates of testing were stratified by age group. The rate of blood pressure assessment increased with rising age in both the depressed and non-depressed groups, with higher rates of blood pressure assessment observed in the depressed vs non-depressed patients in all age groups (Table 2).

In the Poisson regression, there were significant effects of depression, sex and age on the rate of testing (Supplementary Table 1A). However, the estimated effects were not simply additive. There was a significant three-way interaction between depression status, sex and age group (p=<0.001). This is illustrated in Figure 2. By far the largest differences between males and females was found for the higher assessment rates for females at the youngest age group, and with a greater difference for the depressed groups. At older age categories, the male/female differences were all very small. The impact of depression (higher assessment rates) tended to increase with age (Figure 2 & Supplemental Table 1A). Models adjusted for comorbidities returned very similar effect sizes and significant interactions (Supplemental Table 1B).

There was no clear trend towards a difference in rates of blood pressure assessment according to deprivation status (Table 2). With regards to location of residence, no consistent geographical trends were noted. Of the patients with depression, those living in urban areas were least likely to be tested (urban 0.800 95%CI [0.797 - 0.802] & rural 0.853 95%CI [0.849 - 0.857]), whereas of the non-depressed patients, those living in rural areas were least likely to be tested (urban 0.629 95%CI [0.629 - 0.630] & rural 0.610 95%CI [0.610 - 0.611], Table 2).

Assessment of Lipids

Rates of lipid assessment were several-fold lower than for blood pressure. Lipid assessment was greater in the non-depressed than depressed (Table 2). Rates were similar in the non-depressed comparing males and females (males 0.183 95%CI [0.183 - 0.184] vs females 0.182 95%CI [0.182 - 0.182]), but males with depression were more likely to have lipids assessed during both pre-depressed and depressed periods (depressed males post diagnosis 0.191 95%CI [0.190 - 0.192] vs depressed post diagnosis females 0.168 95%CI [0.167 - 0.169]).

Lipids were tested most frequently in the 60–74-year age group in both non-depressed and depressed patients, with higher lipid testing rates observed in the depressed patients across all age groups (Table 2). In the Poisson regression, there were significant effects of depression, sex and age on the rate of testing (Supplementary Table 2A). Again, there was a significant three-way interaction between depression status, sex and age group (p=<0.001). Figure 3 shows the rate of documentation increased significantly with age until age 60, after which it declined slightly. The sex differences were generally higher male assessment rates, especially at the 60-74 group. The impact of depression was a generally higher assessment rate, again, most notable at the 60-74 age group. Small differences due to sex or depression status were noted at the youngest age group (Figure 3). Models adjusted for comorbidities returned very similar effect sizes and significant interactions (Supplementary Table 2B).

With regard to deprivation status, rates of assessment were slightly greater overall in non-depressed patients than depressed, but there was no directional trend across the socioeconomic gradient, with testing rates slightly highest in those in the middle quintile compared with the highest and lowest quintiles in both non-depressed and depressed patients (Table 2). Within the Poisson regression the most deprived were more likely to be tested. Regarding location of

residence, depressed patients living in a rural area were most likely to be tested and for non-depressed patients those living in an urban setting, were least likely (Table 2).

Cardiovascular risk score (QRISK) documentation

Only a very small proportion of the cohort had a QRISK score entered in their record. Of these patients, the QRISK score was documented more frequently in those with depression than the non-depressed (depressed 0.049 [0.049 - 0.050], non-depressed 0.047 [0.047 - 0.047]). Depressed males were the most likely to have a QRISK score documented, but no sex difference was observed in the non-depressed group (Table 2). Rates of QRISK documentation increased with age in both the depressed and non-depressed up until 60-74 years, followed by a decrease for the 75+ age group.

In the Poisson regression, there were significant effects of depression, sex and age on the rate of testing (Supplementary Table 3A). Again, there was a significant three-way interaction between depression status, sex and age group (p=<0.001). Figure 4 shows depressed patients had QRISK documented more frequently, although there were only small differences at the youngest age group (in which documentation was rare). Males tended to have the greater rate of documentation up until aged 60, after which females had higher rates (Figure 4). Models adjusted for comorbidities returned very similar effect sizes and significant interactions (Supplementary Table 3B).

Rates of QRISK documentation were slightly higher in depressed vs non-depressed patients at most levels of deprivation, with the most deprived least likely to have had a record of QRISK (Table 2). Regarding location of residence, both depressed and non-depressed patients living in a rural area were most likely to have a QRISK documented (Table 2).

Risk factor testing in patients with a history of hypertension or diabetes

To explore whether there were differences in risk factor assessment in patients with and without depression with prior documentation of a cardiovascular risk factor diagnosis, patients with a prior diagnosis of hypertension (HTN) or diabetes (DM) were identified.

History of hypertension

There were 22,5933 (10.7%) ND and 16,824 (9.6%) depressed patients with a history of HTN. Rates of testing for blood pressure, lipids and QRISK documentation were all greater in patients with a history of HTN (Supplemental table 4) than those without.

In those with a documented diagnosis of HTN, depressed patients had higher rates of blood pressure assessment than ND (Supplemental Table 1). Depressed females with HTN had the greatest rate of blood pressure testing and non-depressed males the lowest rate (Supplemental Figure 1).

Depressed patients with HTN also had a slightly higher rate of lipid testing than non-depressed with HTN, with lower rates noted in females than males (Supplemental Figure 1). Lipid testing in these patients increased with age across all groups up to 74 years, with a fall in testing rates in those aged 75+ (Supplemental Figure 1).

QRISK documentation in patients with a history of HTN, was more frequent in those with depression than in the non-depressed (0.144 95%CI [0.141-0.148] vs 0.122 [0.121 - 0.122] respectively, Supplemental Table 4). Rates of documentation were similar between depressed males and females with a history of HTN, whereas in the non-depressed, females had a lower

rate of documentation (males 0.125 95%CI [0.125 - 0.126] vs females 0.118 95%CI [0.117 - 0.119]) Supplemental Figure 1).

Documentation of QRISK in those with a history of HTN increased with age until 40-59 years and then fell.

History of diabetes mellitus

There were 72,266 (3.4%) non-depressed and 6843 (3.9%) depressed patients with a prior diagnosis of diabetes (DM). Rates of testing for blood pressure, lipids and QRISK were greater in patients with DM than those without (Supplemental Table 4).

In patients with a DM those with depression were more likely to have blood pressure assessment than non-depressed. Females with DM were more likely to have blood pressure assessment than males with DM regardless of depression status (Supplemental Figure 1). Rates of blood pressure testing in those with DM increased with age but plateaued in the non-depressed patients in the upper age groups (Supplemental Figure 2).

Conversely, the rate of lipid testing was marginally greater in non-depressed than depressed patients with DM (0.986 [0.983 - 0.989] vs 0.971 [0.957 - 0.984] respectively). This difference appeared to be accounted for by marginally higher rates of lipid testing in non-depressed males with DM (Supplemental Table 4 & Supplemental Figure 2).

Rate of QRISK documentation remained low in patients despite their history of DM, compared with blood pressure and lipid assessment (Supplemental figure 2). Patients with DM and depression were more likely to have a QRISK score documented than non-depressed (Supplemental Table 4). Rates of QRISK documentation increased with age until 60-74 in both

depressed and non-depressed and then decreased (Supplemental Table 4 & Supplemental Figure 2).

DISCUSSION

In this population-level study evaluating assessment and documentation of cardiovascular risk factors for the primary prevention of cardiovascular disease in patients with and without depression, we found that those with depression were more likely to have blood pressure and lipid assessment as well as documentation of QRISK than those without, notably even after adjusting for the effect of sex and age.

In general women were more likely to have blood pressure assessed than men, particularly in the younger age groups, whereas men were more likely to have their lipids tested. Importantly, both male and female patients with depression were more likely to have blood pressure or lipids tested than non-depressed patients of the same sex. The frequency of global risk documentation with QRISK score was very low, albeit more frequently documented in patients with depression than without - regardless of age or sex, although QRISK was also documented more frequently in younger males than younger females and more frequently in older females than older males.

The finding that patients with depression were more likely to have lipid and blood pressure assessments even after taking into account age and sex, does agree with previous work[3]. Patients in England on long term antidepressants were shown to be more likely to attend a National Health Service "Health Check" and consequently have blood pressure and lipid assessment[3]. However, in a previous study from our group looking at secondary prevention in patients who had undergone percutaneous coronary intervention, we found that patients with a prior diagnosis

of depression were less likely to have their lipids tested within a year of the intervention[19]. This discrepancy may reflect different clinical considerations and priorities between primary and secondary prevention practice, as the cohort in the current study were free from clinical atherosclerotic cardiovascular disease. Interactions between patients with depression and primary healthcare providers may be more focused on issues regarding their mental health than CVD risk management, which may detract from prioritisation and the time available for addressing CVD prevention issues in the secondary prevention setting. However, in the primary prevention setting the more frequent interactions depressed patients have with primary care may provide a greater opportunistic potential for CVD risk factor assessment and documentation, as seen in a previous study[20]. It is worth noting that in our study the rates of assessment were higher in depressed patients both before and post-depression diagnosis.

Non-depressed patients may have less need to visit their GP, particularly in the primary prevention setting and therefore have less opportunity for opportunistic testing or as part of a formal health check. However, even in those patients with a history of hypertension, patients with depression were more likely to have their risk factors assessed, although the scale of the difference in frequency of risk factor testing between those with and without depression was less in patients with DM. Whether the greater testing in patients with depression results in improved cardiovascular outcomes for these patients is unclear and was beyond the scope of this current study.

Differences in risk factor assessment and risk score documentation were seen between the sexes, with blood pressure testing more frequent in females and lipid testing more frequent in males; with depressed patients more likely to have the assessments than non-depressed in each sex category.

QRISK also tended to be more likely to be documented in males in the younger age groups but was more likely to be documented in females in the older two age groups. This may be indicative of males being more likely to have CV events at an earlier age than females and an earlier prioritisation of their CVD risk assessment, albeit infrequently documented in general. Other studies have seen mixed results in this area. In a study of Dutch primary care patients aged 40-70 without prior CVD, women were more likely to have lipids and blood pressure assessed[21]. Whereas an Australian primary care study, which did include both primary and secondary prevention patients at high CV risk, found that women were less likely to have blood pressure and lipids assessed and, in the primary prevention setting, also less likely to have sufficient risk factors recorded for a risk score calculation[22]. In a previous study of very high-risk patients, we have shown that women, particularly those with depression, were less likely to have their lipid levels tested[19].

Notably, in our study blood pressure testing was much more frequent in females than males irrespective of depression status. Importantly, this largely appeared to be driven by age, with the youngest females having a relatively greater rate of assessment than the males of equivalent age, with the difference in testing rates between the sexes diminishing with age, as the frequency of testing rose with increasing age. Females are more likely to interact with health services than males, particularly as a younger adult[23]. This early difference may in part be due to healthy females having to have more interaction with health services than healthy males in early adulthood to middle age, for example for contraception and pregnancy which often require assessment and monitoring of blood pressure, increasing the opportunity for identification of hypertension in particular. Females also have higher rates of depression so would also be more likely to attend primary care and have additional health monitoring for this. Whereas males

(particularly young) have no such requirement to visit their General Practitioner, consequently reducing the likelihood for an opportunistic risk factor assessment as well as being less likely to seek medical attention than women in general[23].

Overall, it is important to note, that the frequency of lipid level assessment was low in this study irrespective of depression status. However, males were still more likely to undergo lipid testing than females across all age groups, especially in those with depression, in contrast to blood pressure assessment which was far more frequently undertaken than lipid testing in all patient groups and most frequently in females with depression. The reasons for these discrepancies are unclear. More frequent blood pressure testing in females may reflect indication for testing beyond atherosclerotic CVD risk management relevant to female reproductive health and contraception as well as frequency of attendance as discussed above. Whereas more frequent lipid testing in males may reflect an outdated misconception of atherosclerotic CVD as a primarily male disease, and less relevant for younger females.

Importantly, we observed that patients with depression were more likely to be in the lowest quintiles of deprivation than those without depression, as expected[7]. However, rates of blood pressure assessment were greater in depressed than non-depressed patients at all deprivation levels, whereas rates for lipid testing were greater in non-depressed than depressed patients at most levels of deprivation and QRISK documentation was similar for depressed and non-depressed patients at each level of deprivation. Whilst there was no clear trend in direction of rates of blood pressure testing, the most deprived group were tested more than the least deprived as were lipid rates following multivariate adjustment. Whereas, for QRISK documentation there was a trend towards less testing in the most deprived groups. This would indicate that there are still improvements to be made in the overall cardiovascular risk assessment of more deprived

patients who are at greater risk of developing CVD[8]. This may require action at a Government level with clearer actions and targets within policy documents such as Health Plans or including specific targets for CVD prevention in the more deprived within the contracts for General Practitioners.

The majority of both non-depressed and depressed patients lived in urban areas, but overall, there did not appear to be a consistent influence of the geographical location of residence on the relationships between depressed status and risk factor documentation.

Only one indicator of socio-economic status (deprivation) was used within this study, the addition of further measures such as education level may have added further nuance to the findings within the study. Information on pregnancy was also not included within the analysis and may have influenced the findings on blood pressure assessment in younger females and would be an interesting point to investigate in future studies. Equally additional measures often assessed in General Practice were not included in the study as comparators between those with and without depression such as blood cell counts and renal function.

A strength of this study is that the cohort covers the majority of the population of Wales and the data is representative of routine clinical care. The healthcare system within the UK is free to access so the findings of the study may not be generalisable to those countries with different systems for accessing care and different policies towards risk factor assessment. Whilst the data within this study are likely to be representative of Western populations, further studies would need to be carried out to replicate findings in other populations of interest. Another limitation is that it is not possible to evaluate patients who did not engage with their General Practitioner, which may lead to an underestimation of patients with depression as well as fewer diagnoses of hypertension, diabetes and clinical CVD. Additionally, this data as with other studies using

routinely collected data was not collected for research purposes and therefore may contain errors within the data entered or not entered. Patients who had a prescription for antidepressants were also required to have an associated depression diagnosis or symptom within six months to be categorised as depressed. Despite this tight time window, it remains possible that some of these antidepressant prescriptions were issued for mental health diagnoses other than depression or indeed musculo-skeletal or neurological problems in patients who also had depressive symptoms documented recently in their record. Therefore, some patients may be miscategorised if an appropriate clinical diagnostic code was not entered into their records.

Analyses were not adjusted for number of visits to health care providers which may influence likelihood of risk factor assessment for patients attending their General Practitioner more frequently. However, the primary clinical interest of this paper was whether CVD risk factors were being assessed or documented "at all" as well as the frequency of the risk factor checking. Clearly a variety of factors may influence whether or not an assessment is undertaken or the frequency of checking, the actual testing and determination of whether people are at risk in the first place is the most important outcome, with the underlying reasons of secondary interest and importance. Whilst location of residence (urban/rural) has been included in the analyses which can impact on access to health services, with those in rural areas likely to have to travel further, distance to services was could not be accurately taken into account.

Additionally, adherence to preventive medication for blood pressure or lipid levels was not taken into account as dispensing data is not accessible within the SAIL Databank. Patients prescribed preventive therapy but who do not take it may be more likely to require risk factor assessment. Non-adherence to medications is thought to be more likely in those with depression and therefore

may contribute to higher rates of assessment, however, this cannot be evaluated in a study of this nature [24].

A strength of this study is the usage of a broad definition of depression including symptoms alongside medication and diagnoses. However, this covers a differing degree of severity, duration and recurrence within those patients with depression. Routinely collected EHR does not provide clear evidence of these factors without the use of crude proxy measures such as admission. Therefore, there may be subgroups of patients with depression who are at greater risk of CVD and would be an important focus for future research. It is also worth noting that the majority of the medical care of patients with depression occurs in the primary care setting. Only the patients' documented sex is available in the electronic records, therefore whilst differences in assessment due to sex have been investigated it was not possible to explore the influence of gender characteristics on the relationship between risk factor assessment and depression within this analysis.

Conclusion

To conclude, patients with depression are more likely to have their risk factors assessed and a cardiovascular risk score documented than patients without depression in the context of primary prevention of cardiovascular disease. There were differences in rates of blood pressure and lipid assessment between the sexes and across age groups and these relationships were also associated with depression status. These data would suggest that a lower frequency of CVD risk factor testing in the primary prevention setting does not account for the increased risk of developing cardiovascular disease in patients with depression. Further analyses will evaluate treatment and control of blood pressure and lipids, which were beyond the purpose, size and scope of this paper.

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CONFLICT OF INTEREST

JPH, AA and MBG are investigators on an unrestricted research grant from Amgen Inc., related to cardiovascular risk management in clinical practice which is investigating related issues but does not overlap in scope with the current work.

AUTHORS CONTRIBUTIONS

JPH and EAE contributed to the conception of the work. EAE, RS, AJ, DO, KL, MBG and JPH contributed to the study design and analysis plan. EAE, RS, MBG and JPH undertook the analysis and interpretation of data for the work which was reviewed by AJ, DO and KL. EAE drafted the manuscript. RS, AA, AJ, DO, KL, MBG and JPH critically revised the manuscript for

important intellectual content. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

DATA AVAILABILITY STATMENT

The data used in this study are available within the national trusted research environment (TRE) for Wales, the Secure Anonymised Information Linkage (SAIL) Databank at Swansea University, Swansea, United Kingdom. Due to the sensitive nature of these data, all proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). SAIL has an established application process for all projects and users who want to access data https://www.saildatabank.com/application-process. This project was approved by the IGRP at Swansea University (SAIL project number 0800).

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FIGURE LEGENDS

Figure 1. Flow chart showing cohort selection. aCVD, atherosclerotic cardiovascular disease; GP, General Practice data; MH, mental health conditions

Figure 2. Estimated rates of blood pressure assessment per person year obtained from Poisson regression model including depression, age, sex and all 2- and 3-way interactions. D; depression, ND; no depression, PD: pre depression, F; female, M; Male.

Figure 3. Estimated rates of lipid assessment per person year obtained from Poisson regression model including depression, age, sex, and all 2- and 3-way interactions. D; depression, ND; no depression, PD: pre depression, F; female, M; Male.

Figure 4. Estimated rates of QRISK documentation per person year obtained from Poisson regression model including depression, age, sex and all 2- and 3-way interactions. D; depression, ND; no depression, PD: pre depression, F; female, M; Male.

TABLES

1 *Table 1: Baseline characteristics for non-, pre- and at time of depression diagnosis*

	Non-depressed	Depressed		
	(n= 2114013)	Pre diagnosis (n= 176062)	At diagnosis (n= 176062)	ND vs at diagnosis p
% population	92.3	7.7		
Characteristic n (%)				
Female	977352 (46.2)	99262 (56.4)	99262 (56.4)	<0.001
Ethnic group				<0.001
Asian	36166 (1.7)	1257 (0.7)		
Black	9211 (0.4)	553 (0.3)		
Mixed	6590 (0.3)	534 (0.3)		
Other	14359 (0.7)	790 (0.4)		
White	770774 (36.5)	92220 (52.4)		
Unknown	1276913 (60.4)	80708 (45.8)		
Deprivation index (WIMD) quintile (n=2204033)				<0.001
1 (most deprived)	340421 (16.8)	4686 (26.8)		
2	385767 (19.0)	38232 (22.0)		
3	413840 (20.4)	33121 (19.1)		
4	446437 (22.0)	27662 (15.9)		
5 (least deprived)	443978 (21.9)	28089 (16.2)		
Location of residence n=2237778				<0.001
Rural	659058 (32.0)	44700 (25.5)		
Urban	1403182 (68.0)	130838 (74.5)		
Age y (SD)	40.7 (19.3)	32.0 (15.5)	36.4 (16.1)	<0.001
BMI (SD) (n=467997)	26.37 (6.1)	27.0 (6.9)	27.8 (7.2)	<0.001
Current smoker	108760 (5.1)	22574 (12.8)	22535 (12.8)	<0.001
No of days in study	2748 (1277)	3179 (860)	1709 (1058)	<0.001
Past medical history n (%)				
Hypertension	225933 (10.7)	12233 (6.9)	16824 (9.6)	<0.001
Dyslipidaemia	72266 (3.4)	4489 (2.5)	6843 (3.9)	<0.001
Diabetes Mellitus	64938 (3.1)	4753 (2.7)	6928 (3.9)	<0.001
Chronic kidney disease CKD4+	3313 (0.2)	133 (0.1)	334 (0.2)	<0.001
Chronic liver disease	9242 (0.4)	775 (0.4)	1691 (1.0)	<0.001
Dementia	3348 (0.2)	144 (0.1)	661 (0.4)	<0.001
Cancer	76220 (3.6)	3603 (2.0)	6135 (3.5)	0.009
Medications on entry to cohort n (%)				
Statins	109075 (5.2)	6383 (3.6)	8871 (5.0)	0.027
Angiotensin II or ACE inhibitors	116063 (5.5)	7010 (4.0)	10010 (5.7)	<0.001
Diuretic	73899 (3.5)	4054 (2.3)	4923 (2.8)	<0.001
SSRI's	9992 (0.5)	3755 (2.1)	9794 (5.6)	<0.001
Tricyclics	13103 (0.6)	2099 (1.2)	3561 (2.0)	<0.001

2

Table 2. Observed rates of blood pressure assessment, lipid assessments, and QRISK documentation according to depression status, and stratified by sex, age, deprivation index, and urban/rural location (n per person year & 95% CI)

	Blood pressure			Lipids			QRISK		
	Non-depressed	**Pre depression**	**Depression**	**Non-depressed**	**Pre depression**	**Depression**	**Non-depressed**	**Pre depression**	**Depression**
	0.621 [0.620 - 0.621]	0.761 [0.759 - 0.763]	0.813 [0.811 - 0.815]	0.183 [0.182 - 0.183]	0.150 [0.150 - 0.151]	0.178 [0.177 - 0.178]	0.047 [0.047 - 0.047]	0.033 [0.032 - 0.033]	0.049 [0.049 - 0.050]
Sex									
Male	0.490 [0.489 - 0.490]	0.477 [0.474 - 0.479]	0.568 [0.566 - 0.571]	0.183 [0.183 - 0.184]	0.153 [0.151 - 0.154]	0.191 [0.190 - 0.192]	0.047 [0.047 - 0.047]	0.033 [0.032 - 0.034]	0.053 [0.052 - 0.054]
Female	0.774 [0.774 - 0.775]	1.011 [1.008 - 1.014]	0.988 [0.985 - 0.991]	0.182 [0.182 - 0.182]	0.149 [0.147 - 0.150]	0.168 [0.167 - 0.169]	0.047 [0.047 - 0.047]	0.033 [0.032 - 0.033]	0.046 [0.046 - 0.047]
Age									
18-39	0.366 [0.365 - 0.366]	0.602 [0.600 - 0.604]	0.651 [0.649 - 0.653]	0.045 [0.045 - 0.045]	0.056 [0.056 - 0.057]	0.073 [0.072 - 0.073]	0.012 [0.012 - 0.012]	0.010 [0.009 - 0.010]	0.015 [0.015 - 0.016]
40-59	0.619 [0.618 - 0.620]	0.927 [0.922 - 0.931]	0.939 [0.935 - 0.944]	0.229 [0.229 - 0.230]	0.308 [0.306 - 0.311]	0.319 [0.317 - 0.322]	0.075 [0.075 - 0.076]	0.087 [0.085 - 0.088]	0.110 [0.108 - 0.111]
60-74	1.147 [1.146 - 1.148]	1.704 [1.69 - 1.717]	1.610 [1.599 - 1.622]	0.432 [0.431 - 0.433]	0.591 [0.583 - 0.599]	0.579 [0.572 - 0.585]	0.097 [0.096 - 0.097]	0.113 [0.110 - 0.117]	0.145 [0.142 - 0.149]
75+	1.393 [1.390 - 1.396]	2.031 [2.007 - 2.055]	2.064 [2.042 - 2.087]	0.377 [0.375 - 0.378]	0.534 [0.521 - 0.546]	0.474 [0.463 - 0.485]	0.020 [0.020 - 0.021]	0.031 [0.028 - 0.034]	0.046 [0.043 - 0.050]
Deprivation (WIMD)									
1 (most deprived)	0.656 [0.655 - 0.657]	0.730 [0.726 - 0.734]	0.812 [0.808 - 0.816]	0.188 [0.187 - 0.188]	0.139 [0.137 - 0.141]	0.176 [0.174 - 0.177]	0.041 [0.041 - 0.041]	0.021 [0.020 - 0.021]	0.045 [0.044 - 0.046]

2	0.641 [0.640 - 0.642]	0.766 [0.762 - 0.770]	0.825 [0.821 - 0.829]	0.187 [0.187 - 0.188]	0.150 [0.148 - 0.152]	0.180 [0.178 - 0.182]	0.044 [0.044 - 0.045]	0.032 [0.031 - 0.033]	0.050 [0.049 - 0.051]
3	0.657 [0.656 - 0.658]	0.775 [0.771 - 0.780]	0.831 [0.826 - 0.836]	0.197 [0.196 - 0.197]	0.157 [0.155 - 0.159]	0.185 [0.183 - 0.188]	0.052 [0.051 - 0.052]	0.037 [0.035 - 0.038]	0.051 [0.050 - 0.052]
4	0.577 [0.576 - 0.578]	0.780 [0.775 - 0.785]	0.818 [0.813 - 0.823]	0.169 [0.169 - 0.170]	0.154 [0.152 - 0.156]	0.174 [0.172 - 0.177]	0.049 [0.049 - 0.049]	0.044 [0.042 - 0.045]	0.052 [0.051 - 0.053]
5 (least deprived)	0.602 [0.601 - 0.603]	0.769 [0.764 - 0.775]	0.778 [0.773 - 0.783]	0.180 [0.180 - 0.181]	0.160 [0.157 - 0.162]	0.173 [0.170 - 0.175]	0.048 [0.048 - 0.048]	0.039 [0.038 - 0.040]	0.050 [0.049 - 0.051]
Location									
Rural	0.610 [0.610 - 0.611]	0.809 [0.805 - 0.813]	0.853 [0.849 - 0.857]	0.187 [0.186 - 0.187]	0.172 [0.170 - 0.174]	0.192 [0.190 - 0.194]	0.057 [0.056 - 0.057]	0.046 [0.046 - 0.047]	0.055 [0.054 - 0.056]
Urban	0.629 [0.629 - 0.630]	0.743 [0.741 - 0.746]	0.800 [0.797 - 0.802]	0.181 [0.181 - 0.182]	0.143 [0.142 - 0.144]	0.172 [0.171 - 0.173]	0.042 [0.042 - 0.042]	0.028 [0.027 - 0.028]	0.047 [0.047 - 0.048]

1

1 **FIGURES**

2 Graphical abstract

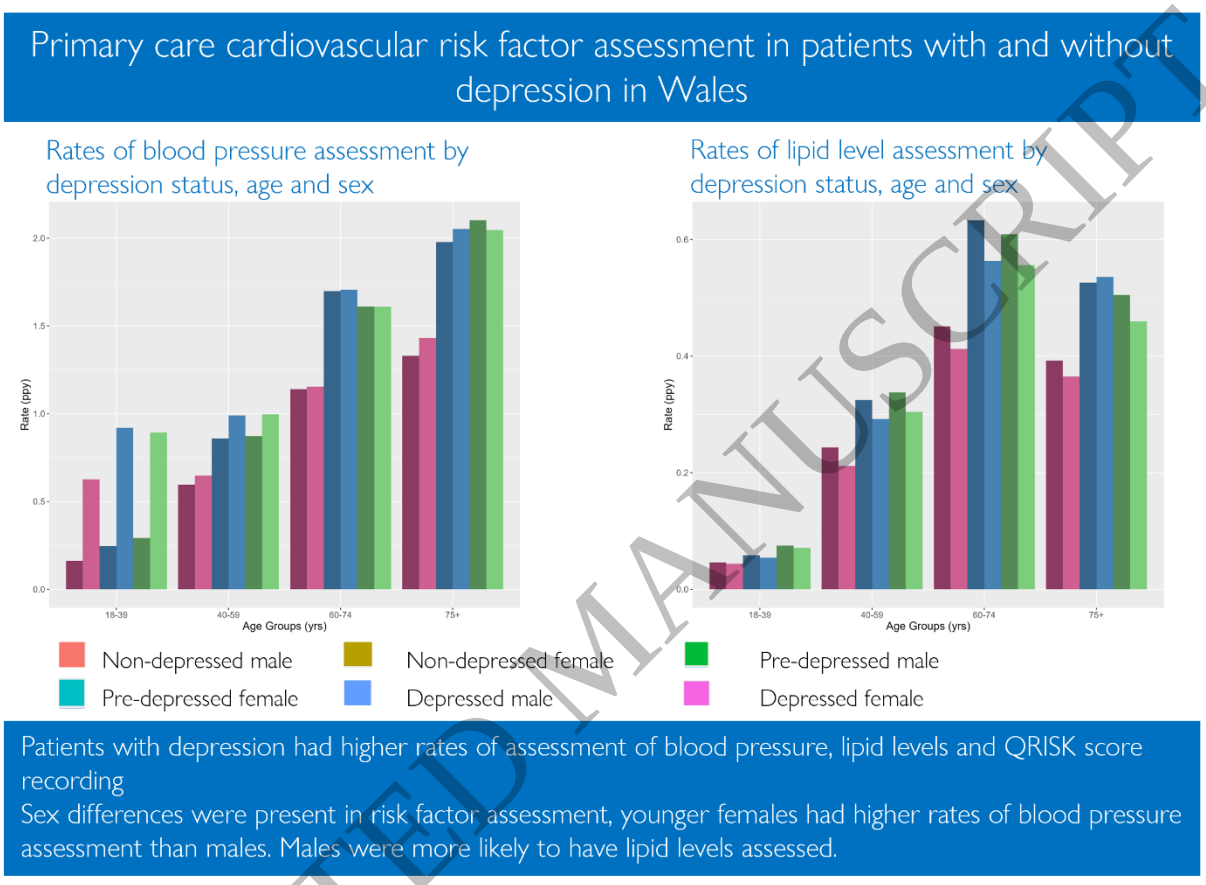

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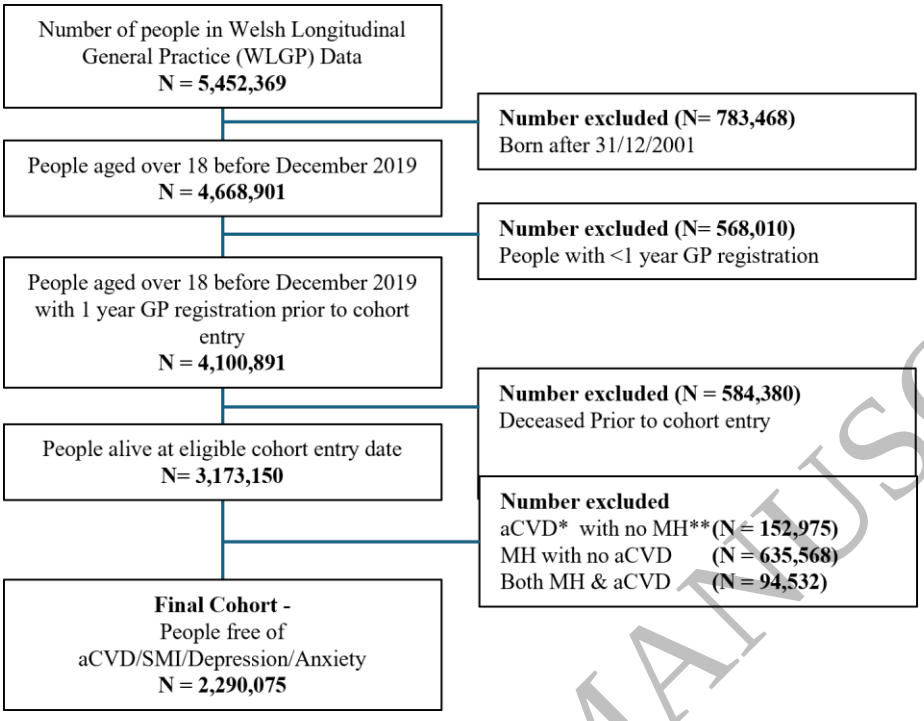
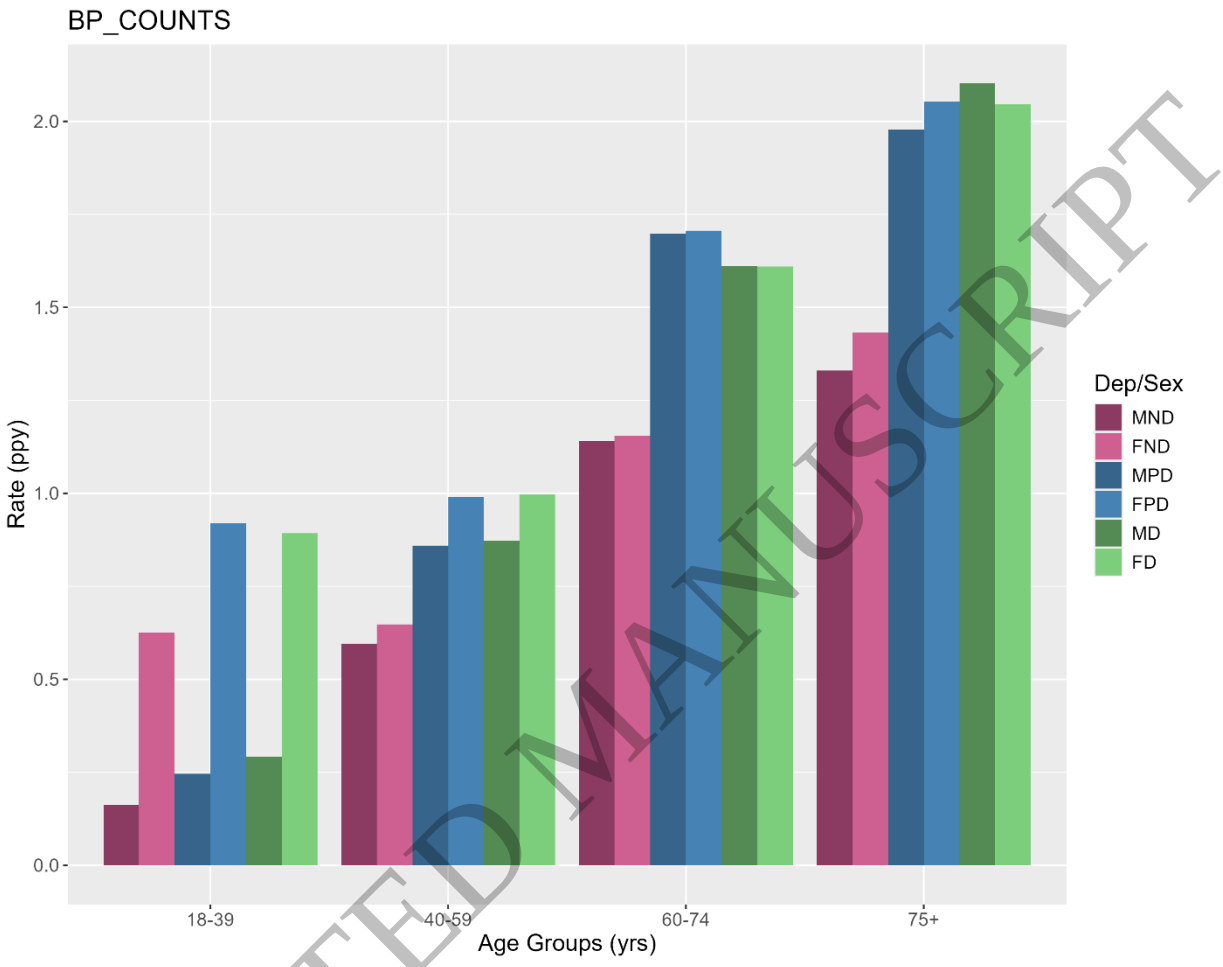
Figure 1.



1 Figure 2.



2

3

1 Figure 3.

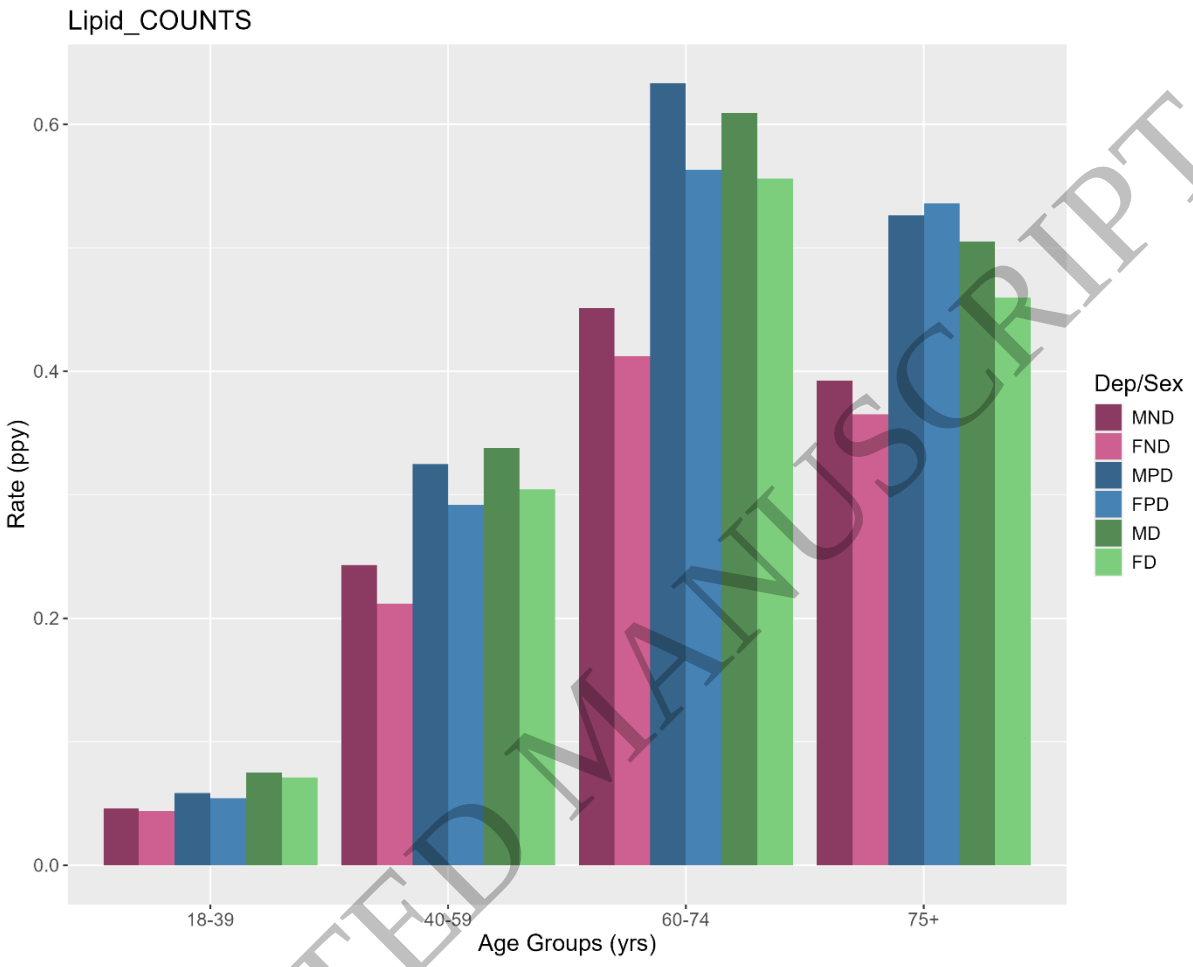


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Figure 4.