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# Gender-specific association of biochemical variables with depression: a population-based case-control study from North India

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## Abstract

**Background:** Depression is a highly prevalent mental disorder with complex aetiology. An emerging body of evidence shows that depression tends to co-occur with abnormal blood glucose levels and dyslipidaemia. This study aimed to understand the overall and gender-specific associations of abnormal glucose levels and dyslipidaemia with depression in a single Mendelian population from rural Haryana, India. To achieve the aim, a population-based case-control study, which constituted of 251 depressed (cases) and 251 non-depressed (controls) individuals, was set up. The study was conducted among the Jat community of Palwal District, Haryana (North India). Data collection was done using a pre-tested interview schedule through the household survey method. Depression status was ascertained using Beck Depression Inventory-II. Fasting blood glucose analysis and lipid profiling were done using commercial kits (Randox, USA) through spectrophotometry. Statistical analysis was done using MS-Excel 2010 and SPSS version 16.0.

**Results:** In the present study, overall fasting blood sugar level was not found to be associated with depression. However, high blood sugar posed a 3.6-folds elevated risk for depression among females with borderline significance ($p = 0.058$). Further, higher levels of TC and LDL were found to be inversely associated with depression. In the sex-wise analysis inverse association of TC and LDL with depression remained significant among males but not among females. Instead, high TG and high VLDL showed an increased risk for depression in females.

**Conclusions:** This study suggests gender-specific associations of some of the studied biochemical variables with depression. Longitudinal studies are warranted to explicate cause-effect relationships between the studied biochemical variables and depression.

**Keywords:** Dyslipidaemia, Blood glucose, Depression, Mental health, Rural population

## Background

Depression is an affective disorder characterized by low mood, sadness, loss of appetite, disturbed sleep, loss of interest or pleasure, poor concentration, and low energy [1]. As per the World Health Organization, depression is prevalent among 264 million people globally, making it one of the most common mental disorders in the world [1]. Recent studies have revealed that depression tends to co-occur with two highly prevalent metabolic disorders, which are abnormal blood glucose levels and dyslipidaemia [2, 3].

The trend of co-occurrence of hypoglycaemia and depression among diabetics has been reported in various studies [4, 5]. Similarly, evidence suggests that depression may have a close association with hyperglycaemia and diabetes [2, 6]. Further, an individual's mood and emotional behaviour have been reported to be substantially influenced by the lipid composition of the brain [7]. Depressed individuals are reported to have low total cholesterol (TC) levels [8, 9]. A positive correlation of high

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triglyceride (TG) and low serum high-density lipoproteins (HDL) levels with major depression has also been reported [10].

The high prevalence of diabetes, dyslipidaemia and depression in Indian populations [11, 12] and the fact that these disorders can co-occur and cause severe morbidity [2, 3] create an urgent need to take up studies trying to understand the relationship between depression and abnormal blood glucose levels/dyslipidaemia in Indian populations. Though hospital-based studies exploring this relationship are available [6, 13]; however, participants of hospital-based studies are mostly under treatment symptomatic cases. Their awareness about their medical condition as well as the treatment that they are receiving are likely to influence their depression status as well as glucose and lipid levels. Hence, population-based studies, where the participants are usually unaware of their disorders, can yield unbiased results. Also, there is a dearth of studies associating abnormal glucose levels and dyslipidaemia with depression in rural communities of India. Thus, in the present study, an attempt is made to explore the overall and gender-specific associations of abnormal glucose levels and dyslipidaemia with depression in a single Mendelian population from rural Haryana, India.

## Methods

### Study design and recruitment of participants

Data for the present study is derived partly from a major project sponsored by the Department of Biotechnology, Government of India (DBT) and partly from another minor project sponsored by Delhi University-Research and Development Grant (DU-R&D). Both these studies were cross-sectional and were carried out across 15 villages of Palwal District of Haryana, India. Ethical clearance for the study was obtained from the departmental ethics committee (approval number: Ref. No. Anth/2010/455/1). Informed written consent, transcribed in the local language, was obtained from each participant before recruitment.

In the DBT sponsored project, a total of 1634 individuals of both sexes aged 30 years and above belonging to a single Mendelian population (Jat community) were randomly recruited. From these participants, fasting blood samples were collected and biochemical parameters were analyzed. Of these 1634 individuals, a total of 808 individuals were randomly selected to assess their depression status using the Beck Depression Inventory-II (BDI-II) tool (as a part of the DU-R&D sponsored project). All the recruited participants were apparently healthy (had no self-reported physical or mental illness). Individuals suffering from any major chronic physical or mental disorder were excluded.

For the present study, a case-control study design was formulated from the 808 individuals assessed for depression. Of these 808 participants, altogether 251 depressed individuals (cases) were identified. Subsequently, their age and sex-matched non-depressed individuals (controls) were also identified. Thus, the present study consisted of a total of 502 participants.

From each participant data about demographic variables like age, gender, family structure, education, occupation, socio-economic status, and marital status were collected using a pre-tested interview schedule through household survey method (for detailed information on sample size calculation and data collection refer to Kaur et al. [12]).

### Depression status

Beck Depression Inventory-II (BDI-II) was used to ascertain the depression status. For the present study, individuals with minimal depression (score 0–13) were considered as controls and those with mild, moderate or severe depression (score 14 and above) were considered as cases.

### Blood collection and biochemical analysis

Two milliliters of overnight fasting blood was collected in a vacutainer without EDTA by a trained technician, from which serum was separated for biochemical analysis. Fasting blood glucose (FBG) analysis and lipid profiling (TC, TG and HDL) were done using commercial kits (Randox, USA) through spectrophotometry. The values of low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) were calculated using Friedwald's and Fredrikson formula [14]. FBG level < 80 mg/dl was considered as low blood glucose [15], whereas > 110 mg/dl as high blood glucose [16]. Normal values of various TC, TG, HDL (male and female), LDL and VLDL were taken as 100–200 mg/dl, 50–150 mg/dl, male > 40 mg/dl; female > 50 mg/dl, up to 130 mg/dl, 10–30 mg/dl, respectively [17].

### Statistical analysis

Statistical analysis was done using MS-Excel 2010 and SPSS version 16.0 (Statistical Package for Social Sciences).

## Results

### Socio-demographic characteristics of the study participants

Numbers of individuals in depressed and non-depressed groups were not found to be significantly different for any of the studied socio-demographic variables (as the cases and controls were matched for age, sex, community and geography) except for marital status where the number

of widowed individuals was significantly higher in the depressed category (Table 1).

### Distribution of glucose and lipid variables among cases and controls

The difference in the distribution of individuals between non-depressed and depressed categories was not found to be statistically significant for differential blood glucose levels (normal, low and high) (Table 2). The numbers of individuals having high TC and high LDL were significantly higher in the control group than in the case group (Table 2). Sex-wise distribution analysis showed that females having high blood sugar levels tended to be in the depressed category (though this result was not

**Table 1** Distribution of demographic variables among cases and controls

| | | Non-depressed | | Depressed | | $\chi 2$ *p*-value |
|---|---|---|---|---|---|---|
| | | *N* | % | *N* | % | |
| Age cohort | 30–40 | 30 | 12.0% | 33 | 13.1% | 0.85 |
| | 41–50 | 65 | 25.9% | 70 | 27.9% | |
| | 51–60 | 83 | 33.1% | 83 | 33.1% | |
| | 61 and above | 73 | 29.1% | 65 | 25.9% | |
| Sex | Male | 82 | 32.7% | 82 | 32.7% | 1.00 |
| | Female | 169 | 67.3% | 169 | 67.3% | |
| Educational status | Literate | 104 | 41.4% | 101 | 40.2% | 0.78 |
| | Illiterate | 147 | 58.6% | 150 | 59.8% | |
| Employment status | Employed | 22 | 8.8% | 20 | 8.0% | 0.74 |
| | Agriculturist | 229 | 91.2% | 231 | 92.0% | |
| Family structure | Joint | 172 | 68.5% | 177 | 70.5% | 0.62 |
| | Nuclear | 79 | 31.5% | 74 | 29.5% | |
| Marital status | Married | 238 | 94.8% | 227 | 90.4% | **0.0059*** |
| | Unmarried | 5 | 2.0% | 0 | 0.0% | |
| | Widow | 8 | 3.2% | 24 | 9.6% | |
| Socioeconomic status (based on per capita annual income) | > 50,000 | 26 | 10.4% | 19 | 7.6% | 0.27 |
| | < 50,000 | 225 | 89.6% | 232 | 92.4% | |

*Statistical significance at *p*-value < 0.05

**Table 2** Distribution of glucose and lipid variables among cases and controls

| | | Overall | | | | $\chi 2$ *p*-value | Males | | | | $\chi 2$ *p*-value | Females | | | | $\chi 2$ *p*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Non-depressed | | Depressed | | | Non-depressed | | Depressed | | | Non-depressed | | Depressed | | |
| | | *N* | % | *N* | % | | *N* | % | *N* | % | | *N* | % | *N* | % | |
| FBG | Normal | 92 | 37.9% | 88 | 35.2% | 0.42 | 30 | 37.50% | 26 | 31.70% | 0.537 | 62 | 38.00% | 62 | 36.90% | 0.067 |
| | Low | 140 | 57.6% | 144 | 57.6% | | 42 | 52.50% | 50 | 61.00% | | 98 | 60.10% | 94 | 56.00% | |
| | High | 11 | 4.5% | 18 | 7.2% | | 8 | 10.00% | 6 | 7.30% | | 3 | 1.80% | 12 | 7.10% | |
| TC | Normal | 166 | 68.3% | 192 | 76.8% | **0.035*** | 46 | 57.50% | 67 | 81.70% | **0.001*** | 120 | 73.60% | 125 | 74.40% | 0.871 |
| | High | 77 | 31.7% | 58 | 23.2% | | 34 | 42.50% | 15 | 18.30% | | 43 | 26.40% | 43 | 25.60% | |
| TG | Normal | 199 | 82.2% | 190 | 76.0% | 0.089 | 59 | 73.80% | 60 | 73.20% | 0.933 | 140 | 86.40% | 130 | 77.40% | **0.033*** |
| | High | 43 | 17.8% | 60 | 24.0% | | 21 | 26.20% | 22 | 26.80% | | 22 | 13.60% | 38 | 22.60% | |
| HDL | Normal | 135 | 55.8% | 136 | 54.6% | 0.795 | 49 | 62.00% | 56 | 69.10% | 0.344 | 86 | 52.80% | 80 | 47.60% | 0.35 |
| | Low | 107 | 44.2% | 113 | 45.4% | | 30 | 38.00% | 25 | 30.90% | | 77 | 47.20% | 88 | 52.40% | |
| LDL | Normal | 167 | 69.9% | 193 | 78.8% | **0.025*** | 46 | 59.00% | 66 | 82.50% | **0.001*** | 121 | 75.20% | 127 | 77.00% | 0.701 |
| | High | 72 | 30.1% | 52 | 21.2% | | 32 | 41.00% | 14 | 17.50% | | 40 | 24.80% | 38 | 23.00% | |
| VLDL | Normal | 200 | 82.6% | 190 | 76.0% | 0.069 | 60 | 75.00% | 60 | 73.20% | 0.791 | 140 | 86.40% | 130 | 77.40% | **0.033*** |
| | High | 42 | 17.4% | 60 | 24.0% | | 20 | 25.00% | 22 | 26.80% | | 22 | 13.60% | 38 | 22.60% | |

*Statistical significance at *p*-value < 0.05

statistically significant). The number of males having high TC and high LDL were significantly higher in the non-depressed category, whereas the number of females having high TG and high VLDL were significantly higher in the depressed category.

Further, median levels of TC and LDL were found to be higher in controls as compared to cases ($P = 0.066$; $P = 0.004$*) (Table 3). However, in sex-wise analysis, the difference in median levels of TC and LDL remained significant only among males but no such trend was observed among females.

### Correlation and odds ratio analysis

Spearman rank correlation analysis (details not included), suggested no significant correlation between abnormal blood glucose levels (both low and high) and depression. Among lipid variables, while TC and LDL showed negative correlation with depression ($r = -0.95$, $p = 0.035$*; $r = -0.102$, $p = 0.025$* respectively), other lipid variables did not show any significant correlation. Furthermore, in sex-wise correlation analysis, TC and LDL showed statistically significant negative correlation with depression among males ($r = -0.263$, $p = 0.001$*; $r = -0.259$, $p = 0.001$* respectively) but not among females. On the other hand, TG and VLDL showed a statistically significant positive correlation with depression among females ($r = 0.117$, $p = 0.033$*; $r = 0.117$, $p = 0.033$* respectively) but not among males.

In odds ratio analysis (Fig. 1), high TC and high LDL showed statistically significant inverse association with depression (OR = 0.652, $p = 0.038$*; OR = 0.637, $p = 0.034$* respectively). In sex-wise odds ratio analysis, high TC and high LDL showed a reduced risk for depression in males (OR = 0.303, $p = 0.001$*; OR = 0.305, $p = 0.001$* respectively) but not in females. On the other hand, high levels of glucose, TG and VLDL showed 3.618, 1.793, and 1.796 folds ($p = 0.058$, $p = 0.050$, and $p = 0.050$) respectively increased risk for depression in females.

**Table 3** Median distribution of glucose and lipid variables in cases and controls

| | | | FBG (mg/dl) | TC (mg/dl) | TG (mg/dl) | HDL (mg/dl) | LDL (mg/dl) | VLDL (mg/dl) |
|---|---|---|---|---|---|---|---|---|
| Overall | Non-depressed | *N* | 243 | 243 | 242 | 242 | 239 | 242 |
| | | Median | 77.41 | 175.50 | 99.16 | 50.35 | 106.15 | 19.80 |
| | Depressed | *N* | 250 | 250 | 250 | 249 | 245 | 250 |
| | | Median | 77.04 | 169.16 | 106.02 | 51.87 | 93.22 | 21.20 |
| | *p*-value | | 0.375 | 0.066 | 0.163 | 0.647 | **0.004*** | 0.125 |
| Males | Non-depressed | *N* | 80 | 80 | 80 | 79 | 78 | 80 |
| | | Median | 79.52 | 187.94 | 110.745 | 48.00 | 119.73 | 21.52 |
| | Depressed | *N* | 82 | 82 | 82 | 81 | 80 | 82 |
| | | Median | 75.35 | 168.31 | 110.155 | 46.40 | 90.71 | 22.031 |
| | *p*-value | | 0.288 | **0.001*** | 0.912 | 0.563 | **< 0.001*** | 0.899 |
| Females | Non-depressed | *N* | 163 | 163 | 162 | 163 | 161 | 162 |
| | | Median | 75.38 | 171.04 | 93.997 | 51.22 | 98.618 | 18.799 |
| | Depressed | *N* | 168 | 168 | 168 | 168 | 165 | 168 |
| | | Median | 77.55 | 169.30 | 103.315 | 49.60 | 95.442 | 20.663 |
| | *p*-value | | 0.064 | 0.999 | 0.074 | 0.835 | 0.370 | 0.074 |

*Statistical significance at *p*-value < 0.05

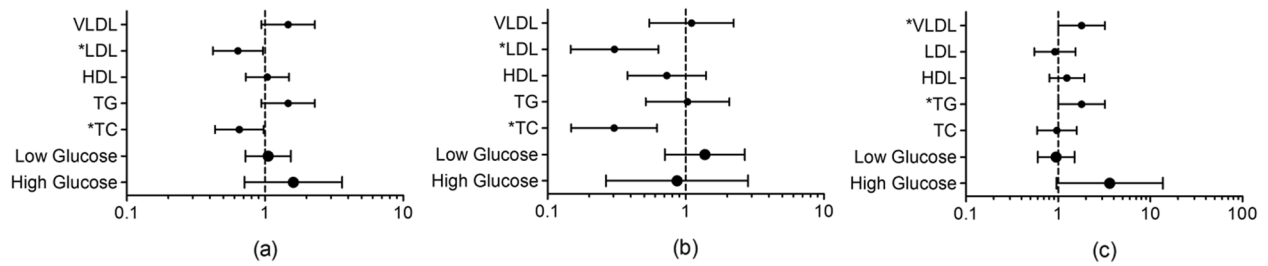


**Fig. 1** Forest plot showing odds ratio for depression in **a** overall participants, **b** males, and **c** females

## Discussion

Hypoglycemia is reported to be strongly associated with depression in diabetic patients [4, 5]; however, the contrary observation in the present study can be because the present study deals with low blood glucose levels in people without diabetes. This calls for the need to take up population-based studies to understand the association of depression with low blood glucose in the non-diabetics/general populations.

Overall high blood glucose level was also found to be not associated with depression in the present study. This observation is contrary to reports suggesting a higher prevalence of depression among individuals with diabetes [2, 6]. Possible explanations of this contrary observation are the low prevalence of high blood glucose levels and diabetes in the studied population (Table 2), and unawareness of participants about their high blood glucose level (being a population-based study, most of the participants were naive about their blood glucose level). Most of the studies reporting a strong association of depression with hyperglycaemia were conducted among individuals who were aware of their diabetic condition which is likely to influence their depression status [6]. According to Fisher et al., depression in diabetic individuals can be due to the worries, concerns and fears collectively called "diabetes-related emotional distress" among individuals struggling with progressive chronic disease [18]. In fact, a meta-analysis revealed that the risk for depression in individuals with undiagnosed diabetes was similar to those with normal glucose metabolism and higher for those who were aware of their diabetic status [19]. Moreover, in a recent population-based study conducted among Venezuelan adults, depression was not found to be associated with diabetes [20].

Interestingly, high blood glucose level was observed to pose a 3.618-folds increased risk for depression in females ($p = 0.058$) in the present study, however, no such relationship was found among males. Several studies have highlighted that diabetic females are at a greater risk of depression than their male counterparts [6]. However, this apparent association between high blood sugar levels and depression in those females who were unaware of their impaired glucose metabolism/ diabetes needs more investigation.

Further, in the present study, TC and LDL were found to be inversely associated with depression. These observations are in concordance with earlier reports [8, 9, 13]. However, several studies have reported contrary findings as well [10, 21]. Other lipid variables did not show any significant association with depression. Of all the lipid variables, the inverse correlation between high TC and depression has been the most consistent and strongest [9].

Various explanations are put forward to explain the association of low serum cholesterol with depression. Lipid plays an important role in neuronal function [7]. Cholesterol is an essential component in the functioning of neurotransmitters, particularly serotonin, disruption in which may lead to depression [7, 22]. According to a hypothesis, cholesterol is loosely bound with the phospholipid layers of biological membranes and is freely exchanged with serum cholesterol [22]. Any reduction in serum cholesterol can decrease the membrane-bound cholesterol of neurons leading to a lower lipid microviscosity and altered functioning of serotonin transporters and receptors [22]. These processes can effectively reduce serotonin in the brain and cause depression. However, the relationship between cholesterol and depression appears to be bidirectional. Poor appetite, a very common symptom of depression, may lead to lower fat and cholesterol intake [23]. Cholesterol synthesis can also be impaired due to depression associated cytokines activation [9].

Further, after gender stratification, the inverse relationship of high TC and high LDL with depression remained significant in males but not in females. Previous studies have also highlighted the gender difference in the association of depression with lipid variables [9, 24]. In a study conducted on suicide attempters, a significantly lower value of serum cholesterol levels was found in males but not in females [24]. Another study reported an association of depression with lower LDL levels in men but not in women (this report is partially in concordance with the observation of the present study) [25]. In the present study, high TG and high VLDL appeared to increase the risk for depression in females but not in males. This observation has not been widely reported and requires further investigation.

Gender plays an important role in lipid and lipoprotein metabolism [26]. Gender-specific association of lipid variables with depression can be due to gender-specific genetic architecture. Studies have indicated that both depression [27] and dyslipidaemia [28] may have sex-specific genetic architecture. Other quantitative traits like serum cortisol and whole blood serotonin as well have been reported to show sex differences [28]. In fact, sex can influence both penetrance and expressivity of a variety of traits including lipid traits [28]. Steroid-related genes and hormones have also been implicated in gender-specific effects on lipid metabolism and depression [26, 29, 30]. Hence, the differential association of lipid variables with depression in men and women can be due to complex genetic, hormonal, and environmental interactions. Nevertheless, since the present study is cross-sectional, the association of lipid variables with depression should not be inferred as causality.

The present study has several limitations that should be mentioned. Firstly, the depression status of the participants was ascertained using BDI-II. Although BDI-II is a widely used, cross-culturally validated and cost-effective tool, it is not the gold standard for determining depression status. Clinical interview, which is considered the gold standard method, should ideally be employed for confirmation of depression. However, time and cost considerations did not permit us to conduct clinical interviews in the present study. Also, since clinical interviews were not conducted, participants could not be given diagnosis or therapeutic advice. Further, the cross-sectional nature of the present study can, at best, examine the association of independent variables with depression, which should not be inferred as causality. Longitudinal studies should be conducted to explicate cause-effect relationships between the studied biochemical variables and depression. Lastly, the number of female participants was (nearly twice) more than the number of male participants. As the data collection was done using the household survey method (in the north Indian rural setting, where male members are more likely to be not present at their homes during the day hours), field investigators encountered (and hence recruited) eligible female individuals at a much higher frequency than male individuals (which is also reflected in the sample composition). Since the sample was not gender-balanced, (apart from the overall analysis) all the relevant analyses have been performed separately for both males and females.

## Conclusions

It can be concluded from this study that abnormal levels of blood glucose and lipid variables may not act the same way in both the sexes as far as their association with and risk posed for depression are concerned. In the present study, while high TC and high LDL appeared to be inversely associated with depression in males, high TG and high VLDL (and to some extent high blood glucose) showed a positive association with depression in females. These gender-specific associations of studied biochemical variables with depression warrant further investigation. Longitudinal studies should be taken up to explore cause-effect relationships (if any) between the studied biochemical variables and depression, and further elucidate specific biochemical pathways behind the observed associations. Also, the high prevalence of depression in India should be scrutinized in light of the fact that Indians tend to have lower TC levels than the normal cut-off.

#### Abbreviations

FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; VLDL: Very low-density lipoproteins; BDI-II: Beck Depression Inventory-II.

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#### Authors' contributions

KNS acquired funds and participated in the conception and design of the study. VC and GK carried out data collection during fieldwork. IL performed the laboratory/biochemical analysis. VC analysed the data and drafted the manuscript. All authors read and approved the final manuscript.

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#### Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

## Declarations

#### Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional ethical committee, Department of Anthropology, University of Delhi, Delhi 110007, India, approval number: Ref. No. Anth/2010/455/1. Prior to data collection, permission was sought from all the local authorities and informed written consent, transcribed in the local language, was obtained from each participant before recruitment.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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