

# Familial clustering and presence of maternal influence on the transmission of type 2 diabetes in South Indians

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## Abstract

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder, characterized by hyper glycaemia caused by impaired glucose homeostasis and represents a serious public health problem. T2D is a multi-factorial disorder depending on complex interactions between environmental factors and genetic variants. **Objective:** To evaluate the degree of familial aggregation and maternal influence on the transmission of type 2 diabetes in the South Indian population. **Methodology:** A total of 1063 subjects with type2 diabetes with knowledge of history of presence or absence of diabetes in relatives were randomly recruited. 652 were male and 411 were female. **Results:** This study showed familial clustering and maternal transmission in our study population. 78.3% of the subjects had at least one relative with diabetes. Familial aggregation was significant with presence of diabetes in 1<sup>st</sup> degree relative like parents and in siblings. 2<sup>nd</sup> degree relatives too had significantly associated with diabetes to a similar extent like 1<sup>st</sup> degree relatives. Patient's age range between 50-59 showed highest incidence of diabetes at 44% followed by 37% in age group 40-49. Our study showed an advancement of incidence of diabetes by one decade compared to similar studies in different regions. **Conclusion:** Maternal factors do play an important role in the incidence of diabetes, prevalence of diabetes. Several factors may be involved in this in terms of polycystic ovaries, gestational diabetes, malnourishment during pregnancy, and other socioeconomic factors. We need studies and further research in ascertaining the exact mechanisms. Familial aggregation is common and may help us to screen for diabetes in high risk populations. Preventive strategies for type 2 diabetes should be directed at these high risk groups.

**Key words:** Familial clustering, maternal, Type 2 diabetes mellitus, South Indians

## Introduction

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder, characterized by hyperglycemia caused by impaired glucose homeostasis, and represents a serious public health problem. Prevalence of diabetes is increasing at the global level with large variation from one population to another depending on the ethnic origin. [1,2]. In India, similar to in other developing countries, there is a growing alarm for the important socioeconomic impact of the disease-high medical costs and disturbed quality of life [3,4].

T2D is a multifactorial disorder depending on complex interactions between environmental factors and genetic variants. Incidence of T2D is triggered by a genetic susceptibility, as reported by monozygous twin studies

and familial aggregation in several populations [5-8]. Although, with recent advances in defining the molecular basis of T2D, the mode of inheritance of this disease is still debated. Several studies reported that the risk of diagnosed T2DM increases when one or both parents are affected and some studies suggest that persons whose mothers had diabetes are more likely to develop diabetes themselves, compared with persons whose fathers had diabetes [9-12]. Numerous studies have concluded that individuals with maternal history of diabetes are at a higher risk of developing the disease than individuals with a paternal diabetes history. To evaluate the degree of familial aggregation and maternal influence on the transmission of type 2 diabetes in the South Indian population. To ascertain the peak onset of diabetes in the studied population. To assess if maternal factors have a major influence on the development of diabetes in the progeny.

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## Materials and Methods

Subjects with type 2 DM attending the outpatient department at Karnataka Institute of Endocrinology and research, Bengaluru were recruited for the study. Detailed family history of the subjects recruited were elicited and recorded. Those who were doubtful of the family history were excluded. A total of 1063 subjects with type 2 diabetes were randomly recruited. The study recorded confirmed diabetes in relatives as mentioned below

- 1<sup>st</sup> degree relative included parents, brothers and sisters.
- 2<sup>nd</sup> degree relative included maternal and paternal uncles, aunts, and cousins.
- 3<sup>rd</sup> degree relatives included grandparents and second cousins.

### Inclusion criteria

1. Adult subjects above the age of 18 years are included.
2. Subjects with a diagnosis of type 2 diabetes in the above age criteria.
3. Subjects with available information on status of diabetes in close relatives are recruited.

## Results

**Study subjects with presence of family history:** Among the study subjects, 652 were male and 411 were female. (table1). It was observed that the first-degree relatives had a strong correlation 1<sup>st</sup> Degree relative with diabetes were seen in 64.25% of individuals with either a mother, father or a sibling as diabetic. 2<sup>nd</sup> degree relatives being diabetic were seen in 38.1% and 3<sup>rd</sup> degree relatives being diabetic were seen in 22.4%. (Fig 1)

Subject's father with diabetes were seen in 28.9 % (n=307) and without diabetes in 71.1 % (n=756). (Table 2)

Subject's mother with diabetes were seen in 35.3% (n=375) and no-diabetes in 64.7% (n=688). (Table-3)

Subject's sisters being diabetic seen in 32.2% and brothers being diabetic in 35.7%.

Both parents with diabetes was seen in 23.7% of male subjects compared to 13.1% in female subjects.

Presence of diabetes in siblings is significant and has a comparable risk to that of diabetes in parents.

There is no significant difference between the presence of diabetes in brothers or sisters.

Patients aged with 50-59 were 44% followed by 37% aged 40-49. Our study showed an earlier shift by 1 decade peaking between 50-59, this trend may continue in future with a shift of prevalence in younger age groups leading to higher economic burden on the health.

78.3% of the subjects had at least one relative with diabetes. Familial aggregation is significant with presence of diabetes in 1<sup>st</sup> and 2<sup>nd</sup> degree relative. Diabetes in siblings is significant with risk comparable to diabetes in parents. The age of onset in age group 40-49 is comparable to 50-59 years which signifies earlier onset and has implications on the prevalence of diabetes with its burden on the healthcare system. Excess maternal transmission is significant with frequency in mother being high at 63.2% compared to 24.6% in fathers. The calculated p value 0.001 is significant.

**Table-1: Frequency Table Indicating Subject's Gender Data.**

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	652	61.3	61.3	61.3
	Female	411	38.7	38.7	100.0
	<b>Total</b>	<b>1063</b>	<b>100.0</b>	<b>100.0</b>	

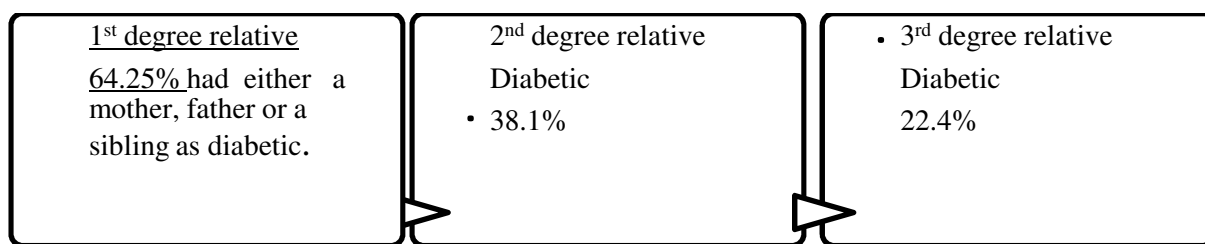


Figure 1

Table-2: Frequency Table indicating Subject’s Father’s Diabetic History Data.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Diabetic	307	28.9	28.9	28.9
	Non Diabetic	756	71.1	71.1	100.0
	<b>Total</b>	<b>1063</b>	<b>100.0</b>	<b>100.0</b>	

Table-3: Frequency Table indicating Patient’s Mother’s Diabetic History Data.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Diabetic	375	35.3	35.3	35.3
	Non Diabetic	688	64.7	64.7	100.0

Table-4: Either parent with diabetes

	Father	%	Mother	%
Male subject	97	22.2%	126	58.6%
Female subject	72	28.7%	111	69.4%
<b>Total</b>	<b>169</b>	<b>24.6%</b>	<b>237</b>	<b>63.2%</b>

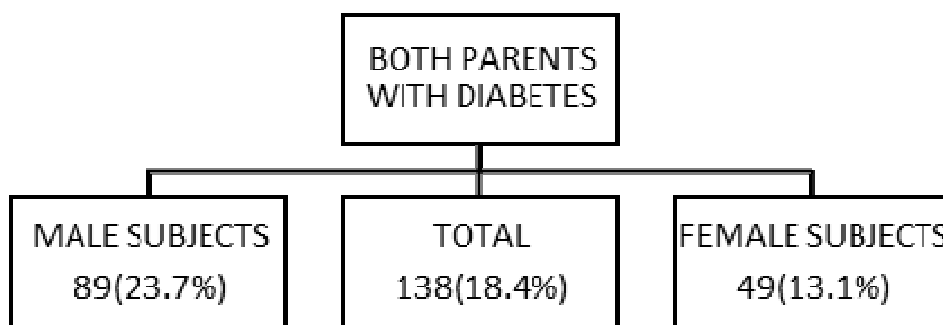


Figure 2

**Table-5: Correlations between various variables under consideration.**

		Subjects Gender	Subject's father	Subject's mother	Subject's brother	Subject's Sister	Subject's 2° relative	Subject's 3° relative	Subject's Family History
Subject's Gender	Pearson Correlation	1	-.010	-.061*	-.114**	-.139**	-.014	-.069*	-.105**
	Sig. (2-tailed)		.749	.048	.000	.000	.659	.024	.001
	N	1063	1063	1063	1062	1062	1063	1063	1063
Subject's father	Pearson Correlation	-.010	1	.129**	.177**	.112**	.201**	.096**	.306**
	Sig. (2-tailed)	.749		.000	.000	.000	.000	.002	.000
	N	1063	1063	1063	1062	1062	1063	1063	1063
Subject's mother	Pearson Correlation	-.061*	.129**	1	.182**	.161**	.207**	.114**	.370**
	Sig. (2-tailed)	.048	.000		.000	.000	.000	.000	.000
	N	1063	1063	1063	1062	1062	1063	1063	1063
Subject's brother	Pearson Correlation	-.114**	.177**	.182**	1	.380**	.132**	.105**	.389**
	Sig. (2-tailed)	.000	.000	.000		.000	.000	.001	.000
	N	1062	1062	1062	1062	1061	1062	1062	1062
Subject's sister	Pearson Correlation	-.139**	.112**	.161**	.380**	1	.054	.094**	.349**
	Sig. (2-tailed)	.000	.000	.000	.000		.081	.002	.000
	N	1062	1062	1062	1061	1062	1062	1062	1062
Subject's 2° relative	Pearson Correlation	-.014	.201**	.207**	.132**	.054	1	.355**	.399**
	Sig. (2-tailed)	.659	.000	.000	.000	.081		.000	.000
	N	1063	1063	1063	1062	1062	1063	1063	1063
Subject's 3° relative	Pearson Correlation	-.069*	.096**	.114**	.105**	.094**	.355**	1	.278**
	Sig. (2-tailed)	.024	.002	.000	.001	.002	.000		.000
	N	1063	1063	1063	1062	1062	1063	1063	1063
Subject's F/H	Pearson Correlation	-.105**	.306**	.370**	.389**	.349**	.399**	.278**	1
	Sig. (2-tailed)	.001	.000	.000	.000	.000	.000	.000	
	N	1063	1063	1063	1062	1062	1063	1063	1063
*. Correlation is significant at the 0.05 level (2-tailed).									
**. Correlation is significant at the 0.01 level (2-tailed).									

## Discussion

Type 2 diabetes is a chronic metabolic disorders with multiple aetiopathological factors including genetic inheritance. The existence of excess maternal transmission of type 2 diabetes is currently debated (17-19). Both environmental and genetic hypotheses have been proposed as mechanisms for maternal transmission (17, 19-22). Proposed environmental mechanisms include maternal effects on intrauterine environment. Behavioural risk factors preferentially passed on by mothers like dietary or physical activity behaviours that increase the risk of obesity and diabetes.

Transmission of mitochondrial genes (passed only from mother to children) is the most common genetic hypothesis. Excess maternal transmission of type 2 diabetes has not been consistently observed across races. Although this inheritance pattern has been observed in populations with lower prevalence of disease, North American, English, French, and Chinese populations, negative findings have been reported in at least two ethnic groups with high prevalence of diabetes (i.e., Hispanics and South Asian Indians, South Indians and Koreans) [15,22].

However, excess maternal transmission has also been observed in Pima Indians. Different methods of quantifying excess maternal transmission make studies from different populations difficult to compare. Potential bias in the reporting of family history data and equivocal findings, especially between the various racial groups, have contributed to the controversy over the existence of excess maternal transmission of diabetes [17,18].

Although understanding the completeness and accuracy of diabetes family history data would seem to be necessary to the study of patterns of inheritance, there have been very few evaluations of its quality and associated biases [17]. Studies of excess maternal transmission would be particularly sensitive to bias if the subject's ability to provide complete and accurate histories differed for the maternal versus paternal arms of the pedigree [18].

Preventive strategies for type 2 diabetes should be directed at these high risk groups. Factors that may be causing a shift towards an earlier age group need to be addressed and studied. Excess maternal transmission is significant with frequency in mother being high, 63.2% in mothers compared to 24.6% in fathers. A number of studies have shown an excess maternal transmission in

different populations. Our study results showed similar results to De Silva et al in Srilankan population that an excess maternal transmission with familial aggregation [13]. This study group showed 78.3% of the subjects had at least one relative with diabetes. Investigation in previous study showed the parental transmission patterns of T2DM showing an excess of maternal transmission of T2D as mothers were implicated two times more frequently than fathers. This inheritance pattern has been reported for several populations including English, French, South African, Chinese, North American, Caucasians and West Indian patients have shown similar results [23].

Viswanathan M et al in a South Indian population showed that there is no maternal influence on the transmission of type 2 DM. Kim J et al also showed a lack of excess maternal transmission in Korean population [15].

In the CURES study the peak prevalence of diabetes was in 60-69 age group with 33% but in this study we have seen an advance of one decade peaking between 50-59. This trend may continue in future with a shift of prevalence in younger age groups leading to higher economic burden on the health. Peak age of onset of diabetes in the study population is in between 50-59. The age group between 40-49 is comparable to that of 50-59 suggesting an earlier onset of diabetes. Mohan et al have shown in the CURES study a similar phenomenon of shift in onset of diabetes to earlier age group [16].

## Conclusion

Maternal factors play an important role in the increasing prevalence of diabetes. The reasons for this need to be evaluated. Maternal nutrition during pregnancy, presence of GDM, diabetes during pregnancy, genetic and maternal side consanguinity and other factors may play a role. Familial aggregation is common and may help us to screen for diabetes in high risk populations. Preventive strategies for type 2 diabetes should be directed at these high risk groups. Factors that may be causing a shift towards an earlier age group need to be addressed and studied. In our study we found an excess of maternal transmission and familial aggregation against to a similar study in South Indian population. This may need further evaluation as to whether consanguineous marriages, maternal nutrition, intrauterine foetal growth, gestational diabetes, polycystic ovarian disease or other factors influence this

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trend. Our study also addresses the need to educate and counsel these set of population to apply preferential screening and preventive strategies. In this study we have overcome the study bias by excluding subjects without a proper and confirmed knowledge of diabetes status in the first degree relatives.

Hence we can now address and look into factors that may contribute to this phenomenon in our population in future studies. IRB approval obtained and KIER ethics committee approval obtained.

**Contribution by authors**

Authors Dr Anil Kumar R and Dr Surekha Shetty have helped in study design and in the analysis of data. They have contributed to the discussion and preparation of manuscript.

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