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Maternal vs paternal diabetes: The parental history is different in younger onset versus older onset type 2 diabetes

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ABSTRACT

Background: A number of previous studies exploring family history of type 2 diabetes have reported a predominance of maternal diabetes. These studies have not explicitly compared parental history of diabetes across the spectrum of disease onset from youth to later adulthood.
Methods: Family history data from 11,467 patients with type 2 diabetes were extracted from the RPA Diabetes Centre database. Parental histories of diabetes were compared across a range of age of diagnosis strata (15-<30, 30-<40, 40-<50, 50-<60 and 60-<70 years). For the young-onset group (diagnosed between 15 and 30 years of age), associations between parental history of diabetes and the presence of cardio-metabolic risk factors and diabetic complications were also explored.
Results: For the total cohort and within each age of diagnosis strata, more individuals reported maternal history than paternal history of diabetes. The young-onset group demonstrated the highest prevalence of any parental history of diabetes (60.7%), the highest combined maternal and paternal history (15.8%) and the smallest differential between maternal (25.1%) and paternal (19.7%) history of diabetes. Within the young-onset group, no significant association between parental history and cardio-metabolic risk factors or diabetic complications were identified after a median of 15.0 years of diabetes exposure.
Conclusion: Overall, our results demonstrate a consistent maternal excess of diabetes which could be consistent with an underlying epigenetic effect. However, the differential between maternal and paternal history is significantly lower in the young-onset group. Earlier emergence of type 2 diabetes may therefore reflect a different interaction and impact of genetic and environmental factors.

1. Introduction

At present, the burden of type 2 diabetes lies predominantly with the subgroup of the population over 45 years of age.[1] However, while type 2 diabetes affects smaller numbers of youth and young adults, it is concerning to see that the incidence and prevalence in this demographic group continues to increase.[2,3] Moreover, evidence of the aggressive nature of young-onset type 2 diabetes has been accumulating over recent years. We and others have reported a higher risk of complications and premature mortality in people with young-onset type 2 diabetes compared to those with type 1 diabetes of equivalent age and duration of diabetes exposure.[4–6] A greater understanding of the factors driving the increase in prevalence of type 2 diabetes in young adults will help guide both prevention and treatment strategies moving forward.

Type 2 diabetes is a complex, multifactorial disease, but genetic susceptibility clearly plays an important role in its pathogenesis. Over the past decade, genome wide association studies have identified in excess of 100 genetic susceptibility loci for type 2 diabetes.[7] In addition to genetic susceptibility, there is emerging evidence of the importance of epigenetic factors in the development of type 2 diabetes. In particular, in utero exposure to hyperglycaemia has been associated with epigenetic changes in the children of mothers who developed gestational diabetes.[8] Interestingly, a number of studies have found an excess of maternal diabetes in patients with type 2 diabetes.[9–16] It has been hypothesized that epigenetic factors may be one of the driving forces behind this observation.[17,18] However, the finding of an excess of maternal history of diabetes has not been universal. A number of studies have reported no difference in the reported rates of maternal and paternal history of diabetes.[19–21] The potential role of paternal factors in the

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development of type 2 diabetes remains unclear. In the recent American Diabetes Association position statement regarding the evaluation and management of youth-onset type 2 diabetes, no specific comment on paternal factors was documented.[22] Clearly, uncertainty persists in this area of our knowledge of diabetes.

We utilized prospectively collected data on parental history of diabetes to explore differences between maternal and paternal histories of diabetes. In particular, our data allowed for comprehensive analysis across a broad range of age of diagnosis strata. With an understanding that the prevalence of type 2 diabetes in the young adult population is increasing, we also set out to explore associations between parental history of diabetes and cardio-metabolic risk factors and diabetic complications in the setting of young-onset type 2 diabetes.

2. Materials and methods

2.1. Participants and data collection

The Royal Prince Alfred Hospital (RPAH) Diabetes Centre maintains a computerized clinical database that contains data relating to >30,000 patients who have attended this secondary and tertiary care referral service since 1986. In year 2000, the method of documenting family history of diabetes was standardised and improved. During their first clinical visit to the Centre, all patients were routinely asked by a diabetes educator if their father or mother also has diabetes and the answers were entered into the database. Patients who are uncertain of their family history at the first visit are asked to clarify family history with their extended family; these patients are again asked about their family history at subsequent follow up appointments. The format of the questions asked has remained unchanged since the year 2000.

This study examined the 11,467 individuals with type 2 diabetes who were seen at the Centre between 2000 and 2015. Patients were stratified into five distinct age of diabetes diagnosis strata: 15-<30 years, 30-<40 years, 40-<50 years, 50-<60 years and 60-<70 years. The proportion of patients reporting a maternal, a paternal or a combined parental history of type 2 diabetes were compared across the age of diabetes diagnosis strata.

To assess the robustness of our results, a sensitivity analysis was performed. We examined a subset of patients ($n = 6522$) who were first seen at the Diabetes Centre at a time close enough to diagnosis that they were still of an age which fell within their designated age of diabetes onset band (Supplementary Table 1). For this subset of patients, family history was ascertained close to the time of diabetes diagnosis. By ascertaining family history close to time of diagnosis, problems associated with recall bias are reduced. We also assessed the stability of the composition of our patient cohort and their parental history obtained over the 15 years of the study period by analysing the results in 5 year time bands (Supplementary Table 2). In addition, results obtained from three major ethnic groupings (Angloceltic, Non-Angloceltic European, Asian) were also separately examined (Supplementary Table 3).

In addition to the strata-based examination of parental history data described above, we also examined the distribution of age of diagnosis (as a continuous variable) across the mutually exclusive categories of (i) negative parental history, (ii) positive maternal history, (iii) positive paternal history and (iv) positive maternal and positive paternal history.

Finally, within our cohort of patients with young-onset type 2 diabetes who had comprehensive clinical complications data available for analysis, we looked for associations between parental history and the presence of (i) cardio-metabolic risk factors and (ii) diabetic complications after a median of 15 years of diabetes exposure.

Ethics approval was granted by the Sydney Local Health District Ethics Review Committee of the Royal Prince Alfred Hospital Zone.

2.2. Statistical analysis

Data were analysed using NCSS 2007 (NCSS Statistical Software, Kaysville, UT, USA) and SPSS (Version 24, IBM, Armonk, NY, USA). Continuous data were checked for normality and presented as mean ($\pm$ SD) or median (interquartile range). Categorical data are presented as n (%). The Pearson χ^2 test was used to ascertain whether significant differences in the proportion of patients reporting maternal and the proportion of patients reporting paternal history of diabetes were present.

The ratio of maternal history to paternal history of diabetes was calculated for each age of diagnosis strata using two methods. Firstly, the ratio was calculated for the "maternal history total" and "paternal history total" categories [M(total):P(total)]. The ratio was also calculated for the mutually exclusive "maternal history only" and "paternal history only" categories [M(only):P(only)]. The M(only):P(only) ratio is necessary for the Cochrane-Armitage Trend test which was performed to establish the significance of a trend of increasing predominance of maternal history with increasing age of onset of type 2 diabetes.

One-way ANOVA was used to ascertain whether a significant difference existed in the mean age of diagnosis between parental history groups. Pairwise comparison of mean age of diabetes diagnosis between groups was also undertaken; Bonferroni adjustments were made for multiple comparisons.

In the analysis of the young-onset cohort for complication status, the Pearson χ^2 test was used to ascertain whether significant differences in retinopathy, albuminuria and ischaemic heart disease were observed across mutually exclusive parental history groups after a median of 15 years of diabetes exposure. One-way ANOVA was used to ascertain whether significant differences existed in mean body mass index (BMI), systolic blood pressure, cholesterol, HbA1c and serum creatinine across mutually exclusive parental history groups. For all analyses, statistical significance was defined by a p-value <0.05.

3. Results

Overall in our cohort of 11,467 type 2 diabetes patients, 21.2% reported a maternal history, 12.1% reported a paternal history and 6.1% reported both maternal and paternal history of diabetes. There were clear differences in the pattern of parental history of diabetes across the distinct age of diabetes onset strata (Table 1). The 15-<30 years age of onset sub-group had the highest prevalence of positive parental history (60.7%); as age of diagnosis increased, a progressive step-wise decline in the proportion of individuals reporting a parental history of diabetes was observed. The oldest age of onset sub-group (60-<70 years) had the lowest proportion (25.0%) with a positive parental history.

Within each of the age of diabetes diagnosis strata, more individuals reported a maternal history of diabetes than a paternal history of diabetes. However, the relative difference between maternal and paternal history of diabetes increased with increasing age at diagnosis. The maternal(total):paternal(total) [M(total):P(total)] ratio was smallest in the young-onset group (1.15) and highest in the oldest age of onset group (2.02) [Table 1]. A similar pattern was observed for the maternal(only):paternal(only) [M(only):P(only)] with a ratio of 1.27 in the young-onset group and a ratio of 2.34 in the oldest age of onset group (Table 1). A Cochrane-Armitage Trend test confirmed the significance of the trend of increasing maternal predominance with increasing age of diabetes onset ($p < 0.001$). The same general pattern of results was observed in our sensitivity analysis which examined only patients with a recent onset of diabetes (Supplementary Table 1). When analysis was conducted across 5 year time bands or three major ethnic groupings, the same general pattern of results was again observed (Supplementary Tables 2 and 3). A Cochrane-Armitage Trend test confirmed a significant trend of increasing maternal predominance for the 2000–

Table 1
Parental history and age of onset of type 2 diabetes.

Age of diabetes onset (years)	n	Maternal history total (%)	Paternal history total (%)	Maternal + Paternal history (%)	Negative parental history (%)	M(total):P(total)[a]	Maternal history only (%)	Paternal history only (%)	M(only):P(only)[b]
15-<30	557	40.9	35.5	15.8	39.3	1.15	25.1	19.7	1.27
30-<40	1551	39.1	29.8	11.7	42.8	1.31	27.4	18.1	1.51
40-<50	3030	31.0	21.9	7.4	54.5	1.42	23.6	14.5	1.63
50-<60	3698	23.8	14.2	4.0	65.9	1.68	19.8	10.2	1.94
60-<70	2631	18.2	9.0	2.1	75.0	2.02	16.1	6.9	2.34
Total cohort	11467	27.3	18.2	6.1	60.6	1.50	21.2	12.1	1.75

Cochrane Armitage Trend Test, M(only):P(only) (increasing predominance of maternal history with increasing age of diabetes onset): $p < 0.0001$.
[a] M(total):P(total) obtained by dividing Maternal History Total (%) by Paternal History Total (%).
[b] M(only):P(only) obtained by dividing Maternal History Only (%) by Paternal History Only (%).

2004 and 2005–2009 periods ($p < 0.01$ and <0.001, respectively). A non-significant trend was observed for the post-2010 period ($p = 0.32$).

Examination of age of diabetes onset in patients across mutually exclusive parental history groups revealed a pattern of decreasing mean age of diagnosis with increasing strength of family history and with paternal history (Table 2). ANOVA confirmed that there is a statistically significant difference in mean age of diabetes onset between the parental history groups ($p < 0.001$). Pairwise comparison of parental history groups with Bonferroni adjustments for multiple comparisons revealed statistically significant differences in mean age of diabetes onset between each of the parental history groups (Table 3). The negative parental history group demonstrated the highest mean age of diabetes onset at 52.3 years. The maternal history group (48.3 years) demonstrated a higher mean age of onset than the paternal history group (46.2 years). The combined maternal and paternal history group demonstrated the earliest mean age of diabetes onset at 43.0 years.

A subset of 234 individuals from the cohort of 557 individuals with young-onset type 2 diabetes who were referred for comprehensive clinical and diabetes complications assessment had data available for analysis. In this group, a positive parental history of diabetes was not associated with any difference in mean body mass index, systolic blood pressure, lipid profile, HbA1c or serum creatinine after a median diabetes exposure of 15.0 (IQR: 6.9–24.7) years ($p > 0.45$ for all variables, Table 4). Additionally, a positive parental history of diabetes was not associated with an increased rate of either retinopathy ($p = 0.28$) or ischaemic heart disease ($p = 0.89$). A marginally significant association between positive parental history and an increased rate of microalbuminuria was observed ($p = 0.04$, Table 4).

4. Discussion

Over the course of recent decades our understanding of the pathogenesis of type 2 diabetes has greatly improved. However, because of its complex nature, the chronicity of its natural history and the interaction of genetic and environmental factors, it is still not possible to accurately predict if and/or when an individual will develop type 2 diabetes. For clinical investigators and epidemiologists alike, analysis of carefully collected family history data can act as an aid to further our understanding of type 2 diabetes. Family history data used in this study were obtained in direct face-to-face interviews conducted by health care professionals. Therefore, a key strength of this study lies in the systematically and prospectively collected data that was available for analysis.

When analysis is performed on the cohort as a whole, results of this study are in keeping with previous reports that have noted a predominance of maternal diabetes.[9–16] However, analysis of parental history across the spectrum of diabetes onset from youth to older adulthood has enabled new insights into age-specific associations to be obtained. The difference in prevalence of maternal and paternal history of diabetes is much less marked in those with young-onset type 2 diabetes. This finding may have been overlooked in previous studies which did not examine family history across a wide range of age of diabetes onset strata.

We observed a decreasing mean age of diabetes diagnosis as strength of parental history of diabetes increased. When directly comparing individuals with maternal and paternal histories of diabetes, the mean age of diabetes onset in our cohort with a paternal history of diabetes was 2 years younger than in those with a maternal history of diabetes. Whether this observation represents a specific effect of paternal inheritance or is a consequence of early exposure to an environment which promotes the development of type 2 diabetes remains to be investigated. Interestingly, a significant difference in age of diabetes onset in those reporting maternal and paternal histories of diabetes was not evident in the TODAY study.[23] However, the population of our study and the TODAY study are not directly comparable. The TODAY study examined a cohort of youth (aged 10–17 years) with type 2 diabetes while the vast majority of our study population were >18 years at the time of their diabetes diagnosis.

The presence of parental diabetes in our cohort diagnosed during young adulthood did not appear to affect their cardio-metabolic risk factor status after a median of 15 years of diabetes exposure. This finding is in general agreement with previous studies in this area.[15,24,25] A borderline association between parental history of diabetes and microalbuminuria was identified, but the difference was very small. Further work will be required to confirm or refute this association in other young-onset type 2 diabetes cohorts.

Our study is observational in design and as such may be subject to reporting bias, censoring bias and selection bias. With respect to reporting bias, we acknowledge that it is possible for an individual to know the medical history of one, but not both of their biological parents. In this regard, it is likely that paternal history would be more unreliable

Table 2
Mean age of diabetes onset according to parental history of diabetes.

Parental history	n	Age of diabetes onset[a]
Negative	6945	52.3 ± 10.7
Maternal only	2437	48.3 ± 11.2
Paternal only	1389	46.2 ± 11.2
Both maternal and paternal	696	43.0 ± 11.2

[a] Data are presented as Mean ± Standard Deviation.

Table 3
Difference in mean age of diabetes onset between the different parental history groups.

Comparison group	Difference in mean age of diagnosis (years)[a]	p value
Negative parental history vs positive maternal history	4.5 (3.9–5.2)	<0.001
Negative parental history vs positive paternal history	6.5 (5.7–7.4)	<0.001
Maternal history vs paternal history	2.0 (1.1–3.0)	<0.001
Paternal history vs positive maternal + positive paternal history	3.2 (1.9–4.5)	<0.001

[a] Data are presented as difference in mean age of diagnosis (95% confidence interval).

Table 4
Clinical and complications data, grouped by family history of diabetes, in those with young onset type 2 diabetes.[‡]

	Maternal only history of diabetes	Paternal only history of diabetes	Positive maternal and positive paternal history of diabetes	Negative maternal and negative paternal history of diabetes	p value
n	61	43	42	88	
Duration of diabetes at complications assessment (years)	15.9 (9.1–28.3)	15.3 (6.5–23.7)	14.7 (6.1–24.7)	14.8 (7.8–23.7)	0.71[*]
Age at complications assessment (years)	42.9 (33.3–52.2)	42.2 (31.1–50.0)	40.5 (32.6–51.0)	42.3 (32.3–51.4)	0.87[*]
Body mass index (kg/m^2)	31.9 (27.1–36.2)	31.9 (27.8–36.4)	29.9 (27.7–35.2)	32.1 (27.0–39.5)	0.58[*]
Systolic blood pressure (mmHg)	120 (110−133)	120 (112−130)	120 (114–130)	120 (116–130)	0.69[*]
Total cholesterol (mmol/L)	4.5 (3.8–5.3)	4.4 (3.9–5.3)	4.5 (3.7–5.0)	4.4 (3.8–5.5)	0.72[*]
LDL cholesterol (mmol/L)	2.7 (2.2–3.4)	2.7 (2.1–3.1)	2.5 (2.0–3.0)	2.5 (2.0–3.1)	0.80[*]
HDL cholesterol (mmol/L)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.1 (0.9–1.2)	0.85[*]
Triglycerides (mmol/L)	1.9 (1.3–3.0)	1.7 (1.3–2.8)	2.0 (1.2–3.3)	1.9 (1.3–2.5)	0.71[*]
HbA1c (%)	8.5 (7.3–9.8)	8.0 (6.8–9.9)	7.8 (6.8–8.9)	7.9 (7.0–9.1)	0.45[*]
Serum creatinine (umol/L)	70 (60–91)	66 (58–86)	70 (63–84)	75 (60–99)	0.75[*]
Elevated urinary albumin to creatinine ratio [n (%)]	28 (46)	27 (62)	24 (57)	30 (34)	0.04[†]
Retinopathy [n (%)]	10 (16)	5 (12)	6 (14)	15 (17)	0.28[†]
Ischaemic heart disease [n (%)]	29 (48)	12 (29)	14 (33)	31 (35)	0.90[†]

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables.
[*] p value for ANOVA (Mat Only Hx, Pat Only Hx, Positive Mat + Pat Hx, Negative Mat + Pat Hx).
[†] p value for χ^2 test (Mat Only Hx, Pat Only Hx, Positive Mat + Pat Hx, Negative Mat + Pat Hx).
[‡] Young Onset Type 2 Diabetes defined as type 2 diabetes diagnosed 15-<30 years of age.

than maternal history, both for biological and sociological reasons. However, in our database there are relatively few individuals (between 1 and 2% for each age of diabetes onset group) who report an "unknown" family history of diabetes. This rate of unknown family history is substantially lower than that documented in other studies. For example, Thorand et al[26] identified that 21.2% of respondents in three independent cross-sectional surveys in Germany did not know the diabetes status of their parents. We suspect that the lower rate of unknown family history observed in our study is a result of direct questioning used to collect family history data at our Centre. This approach has resulted in a significant reduction in the number of patients who report an unknown family history of diabetes. We acknowledge that some mothers with gestational diabetes may have been reported as having diabetes and our database does not document this possibility. However, in our analysis of the 5 year time bands, there was no obvious increase in maternal diabetes, suggesting that any confounding effect due to inclusion of gestational diabetes is likely to be small. It is also reasonable to surmise that different ethnicities may have varying patterns of parental diabetes, both for genetic reasons and how they may answer questions about their families. However, our observation of changing maternal and paternal diabetes ratios seems to hold true in the different ethnic groupings that we have studied.

We acknowledge that censoring bias may also explain some difference between maternal and paternal history of diabetes. It is conceivable that a higher mortality rate and earlier age at death for males could reduce the chance of fathers developing diabetes before their death. This would introduce a form of bias which could explain some of the maternal diabetes predominance we and others have observed. However, given improvements in the management of cardiovascular risk factors and macrovascular diseases in general, the earlier mortality seen in males has steadily reduced over recent decades. Certainly, most males in Australia now survive beyond the age that type 2 diabetes usually manifests. Furthermore, data presented in the IDF Diabetes Atlas demonstrates little difference in type 2 diabetes prevalence between the sexes in multiple regions of the world.[1]

In terms of selection bias, our patient cohort all had diabetes associated with a degree of severity that prompted referral by their treating doctors for specialist care. Thus, it is possible that the prevalence of maternal and paternal diabetes in our cohort may be different from the wider population with type 2 diabetes. Patients with a family history of diabetes are presumably more likely to be identified and referred, but it seems unlikely to be a cause of preferentially affecting the prevalence of maternal or paternal diabetes to change their ratio in such a systematic way that we have observed. Nevertheless, it will be important to confirm our findings in other cohorts before concluding that the results are representative of the wider population with type 2 diabetes.

5. Conclusions

Historically type 2 diabetes has predominantly been a disease of older adulthood but today the prevalence of young-onset type 2 diabetes is increasing in many communities throughout the world. Our study suggests that while a maternal history of diabetes is more frequently reported, paternal factors may be almost as important as maternal factors in contributing to the earlier age of diabetes onset that is being observed. As such, a paternal history of type 2 diabetes may in time be used to help identify individuals who are likely to develop type 2 diabetes at an earlier age and therefore stand to benefit from regular screening for diabetes. Early identification of type 2 diabetes will enable opportunities for early treatment and this may help alleviate some of the future burden of complications seen in those with young onset disease.

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Authors contribution

All authors (Timothy Middleton, Belinda Brooks, Maria Constantino, Ted Wu, Jencia Wong and Dennis Yue) have contributed to:

1. Conception or design, or analyses and interpretation of data, or both:
2. Drafting the article or revising it.
3. Providing intellectual content or critical importance to the work described.
4. Final approval of the version to be published.

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