Age of obesity onset, cumulative obesity exposure over early adulthood and risk of type 2 diabetes

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Abstract

Aims/hypothesis Obesity is a risk factor for type 2 diabetes, yet little is known about how timing and cumulative exposure of obesity are related to disease risk. The aim of this study was to examine the associations between BMI trajectories, age of onset of obesity and obese-years (a product of degree and duration of obesity) over early adulthood and subsequent risk of type 2 diabetes.

Methods Women aged 18–23 years at baseline ($n = 11,192$) enrolled in the Australian Longitudinal Study on Women's Health (ALSWH) in 1996 were followed up about every 3 years via surveys for up to 19 years. Self-reported weights were collected up to seven times. Incident type 2 diabetes was self-reported. A growth mixture model was used to identify distinct BMI trajectories over the early adult life course. Cox proportional hazards regression models were used to examine the associations between trajectories and risk of diabetes.

Results One hundred and sixty-two (1.5%) women were newly diagnosed with type 2 diabetes during a mean of 16 years of follow-up. Six distinct BMI trajectories were identified, varying by different initial BMI and different slopes of increase. Initial BMI was positively associated with risk of diabetes. We also observed that age at onset of obesity was negatively associated with risk of diabetes (HR 0.87 [95% CI 0.79, 0.96] per 1 year increment), and number of obese-years was positively associated with diabetes (p for trend <0.0001).

Conclusions/interpretation Our data revealed the importance of timing of obesity, and cumulative exposure to obesity in the development of type 2 diabetes in young women, suggesting that preventing or delaying the onset of obesity and reducing cumulative exposure to obesity may substantially lower the risk of developing diabetes.

Keywords Age of obesity onset · Cumulative obesity · Diabetes · Obese-years · Obesity · Type 2 diabetes · Weight trajectory

Abbreviations

BIC Bayesian information criterion

GMM Growth mixture model

MET Metabolic equivalents

hs-CRP High-sensitivity C-reactive protein

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Introduction

The prevalence of type 2 diabetes has increased dramatically during the past several decades. Currently, more than 500 million adults are living with diabetes worldwide [1]. The increase in type 2 diabetes prevalence is closely related to the upsurge in obesity. At present, more than 2.1 billion people (nearly 30% of the world's population) are either obese (BMI ≥ 30 kg/m²) or overweight (25 kg/m² $\leq$ BMI < 30 kg/m²) [2]. In 2017, almost two-thirds (63%) of adults in Australia were overweight or obese, and 28% were obese [3].

Research in context

What is already known about this subject?

- Obesity is a risk factor for type 2 diabetes

What is the key question?

- Are earlier age at onset of obesity and greater cumulative obesity exposure over young adulthood associated with risk of type 2 diabetes?

What are the new findings?

- Age at onset of obesity was negatively associated with risk of type 2 diabetes in a cohort of women aged 18–23 years at baseline
- Obese-years (a measure of cumulative obesity exposure) was positively associated with type 2 diabetes in this cohort

How might this impact on clinical practice in the foreseeable future?

- Our data reveal the importance of timing of, and cumulative exposure to, obesity in the development of type 2 diabetes in young women, suggesting that preventing or delaying the onset of obesity and reducing cumulative exposure may substantially lower the risk of developing diabetes

Although obesity is a well-established risk factor for type 2 diabetes [4], little is known about the relationships between age of onset of obesity and cumulative exposure to obesity and risk of diabetes, especially among young adults. In most previous studies, exposures (obesity status or weight change) have relied on only one or two measures of weight [5]. As a result, researchers have been unable to account for the dynamic changes of weight over time, or to assess whether timing of weight change over the life course makes a difference to the risk of developing type 2 diabetes.

A few studies have examined the association between the duration of general or central obesity and the risk of diabetes but results are mixed [6–9]. Some studies reported that duration of obesity was associated with the risk of diabetes independently of baseline BMI [7, 9], while others reported that the association between diabetes and duration of obesity was largely determined by current BMI [6, 8].

Obese-years is a construct that accounts for both how long a person has been obese and the magnitude of their obesity (no. of BMI units above 30 kg/m² × no. of years at that BMI) and has been shown to be a better predictor of diabetes risk than duration of obesity or level of BMI alone [10]. However, few studies have examined the relationship between the cumulative exposure to obesity and risk of diabetes.

We used data from the Australian Longitudinal Study on Women's Health (ALSWH) to identify BMI trajectories over the early adult life course. We then examined the relationship between distinct BMI trajectories and risk of type 2 diabetes. Further, we investigated the associations between timing of obesity onset, obese-years and type 2 diabetes. We hypothesise that earlier age at onset of obesity and more obese-years over follow-up would be more strongly associated with type 2 diabetes risk than BMI alone.

Methods

ALSWH

The ALSWH is a longitudinal population-based study of Australian women that was launched in 1996. It was designed to examine the relationships between biological, psychological, social and lifestyle factors and women's physical health, emotional wellbeing, and their use of and satisfaction with healthcare [11]. This study recruited a nationally representative sample of more than 40,000 women in three age cohorts, born in 1921–1926 (aged 70–75 years at baseline), 1946–1951 (aged 45–50 years) and 1973–1978 (aged 18–23 years). Details of the design, recruitment, implementation and progress of the ALSWH study are described elsewhere [11–15]. The study was approved by the Universities of Newcastle and Queensland Ethics Review Committees. All participants provided written informed consent.

Study population

The current study was based on data from the 1973–1978 birth cohort (aged 18–23 years at recruitment, $n = 14,247$). Participants were excluded from the analysis for the following reasons: they reported a history of diabetes at enrolment or reported having type 1 diabetes during follow-up ($n = 247$); they answered only the baseline survey ($n = 2309$); they had missing values for major covariates at baseline including physical activity, income and stress ($n = 133$); or they had no BMI data ($n = 366$). After exclusions, 11,192 women remained in the analytical cohort.

Follow-up

Participants completed survey 2 in 2000 (4 years after baseline) and have been followed up every 3 years thereafter up to 19 years and a total of seven survey administrations. Surveys were completed by mail, and an on-line option has been available since survey 6 in 2012. For the 1973–1978 cohort, the retention rate was low (69%) from wave 1 to wave 2, due to high levels of mobility and inability to contact participants at this stage, but then remained relatively stable thereafter with retention rates of 57–64% [15].

Measurements

Outcome: incidence of type 2 diabetes during follow-up

Incident type 2 diabetes was defined via self-report of new doctor-diagnosed diabetes during follow-up. Self-reported diabetes in the ALSWH has been validated for middle-aged and older cohorts by comparing self-report data with administrative hospital records [16]. There was substantial agreement for diabetes ($\kappa > 0.70$) for both cohorts [16], indicating that self-reported diabetes in the ALSWH may be a reliable indicator of diagnosed diabetes.

Exposure: self-reported weight and height measures across surveys In the ALSWH, height was collected at baseline and weights were self-reported at baseline and at each follow-up survey. BMI was calculated as weight (kg) divided by height (m) squared. Only measures of BMI before the date of diagnosis of type 2 diabetes were included in this analysis.

Accuracy of BMI estimated from self-reported height and weight has been validated in the ALSWH [17]. There was substantial agreement (84%) between BMI categories derived from self-reported and measured height and weight data; agreement for healthy-weight women was 94%. This suggests that the self-reported data on weight and height obtained from mailed surveys in the ALSWH can be used to estimate BMI with reasonable accuracy [17].

Covariates Participants' sociodemographic characteristics (age, educational attainment, income adequacy), lifestyle factors (physical activity, smoking, alcohol use), gestational diabetes history, and psychosocial factors (a stress score) measured at baseline were considered as potential confounders. Table 1 presents detailed information about covariate categories and scores. Income adequacy was assessed by an item asking 'how do you manage on the income you have available?' Physical activity data was collected by asking for the amount of time spent in the last week on different activities including walking briskly, moderate leisure activity and vigorous leisure activity and converting to metabolic equivalents (MET)/week (continuous). Perceived stress was measured continuously as a sum

across items in specific life domains: own health, health of other family members, work/employment, living arrangements, study, money, relationship with parents, relationship with partner/spouse, relationships with children and relationship with other family members. The score has been demonstrated to be reliable and valid [15].

Statistical analysis

First, descriptive statistics were calculated. Second, BMI growth curves (trajectories) over time were examined. We fitted the data by using both linear and quadratic models and compared which of these models fit the data better by looking at whether the z score test was significant for the quadratic growth factor mean. Since the quadratic growth factor mean was significant ($p < 0.05$), we used quadratic models for growth curves.

Third, a growth mixture model (GMM) was used to identify distinct BMI trajectories over time. The GMM allows modelling variables with partially missing data [18]. The optimal number of groups was assessed by the Bayesian information criterion (BIC) [19]. A lower BIC indicates better fit to the data. Once the best-fitting model was identified, participants were assigned to the trajectory groups to which their posterior membership probability was largest. Cox proportional hazards regression models were then used to evaluate the associations between the trajectories and risk of type 2 diabetes. Survival time was defined as time between baseline and the date of newly diagnosed diabetes, censoring due to missing data, death, or end of follow-up at survey 7, whichever came first. For women who reported newly diagnosed diabetes on a survey, we assumed the point of diagnosis was halfway through the period between that survey and the previous survey. The BMI trajectory would end at the previous survey. In the multivariate-adjusted models, potential confounders were included as covariates. We also examined relationships between sociodemographic characteristics, lifestyle and stress and BMI trajectories.

Fourth, since the GMM approach enables us to model BMI trajectories with random variation among individuals within a group, we allowed each individual to have her own BMI trajectory; namely, we predicted BMI trajectory (including intercept, slope and quadratic) for each individual. Using the predicted curve for each individual, we estimated the age of onset of obesity if any, degree of obesity (measured by difference in BMI above obesity [≥ 30 kg/m²]), and duration in years of obesity. Obese-years was estimated by calculating the AUC that was above 30 kg/m² by trapezoid rule [20]. Age of onset of obesity and obese-years were treated as time-varying covariates in Cox models.

We conducted a sensitivity analysis using baseline-only BMI categories to examine HRs for diabetes, with control

Table 1 Comparison of baseline characteristics across BMI trajectories

Variable	Overall (<i>N</i> =11,192)	NW-low stable (13%; <i>n</i> =1558)	NW-low modest increase (21%; <i>n</i> =2329)	NW-mid stable (14%; <i>n</i> =1563)	NW-mid rapid increase (28%; <i>n</i> =3118)	OW-rapid increase (21%; <i>n</i> =2335)	OB-rapid increase (3%; <i>n</i> =289)	<i>p</i> value
Age, years	20.8 ± 1.4	20.7 ± 1.5	20.7 ± 1.4	20.8 ± 1.4	20.8 ± 1.5	20.8 ± 1.5	20.9 ± 1.4	0.2749
Physical activity, MET	19.0 ± 14.1	20.3 ± 14.8	18.5 ± 14.1	20.4 ± 14.2	18.7 ± 13.9	18.4 ± 13.6	17.6 ± 13.6	<0.0001
Mean stress score	0.90 ± 0.6	0.86 ± 0.5	0.88 ± 0.5	0.90 ± 0.5	0.89 ± 0.6	0.94 ± 0.6	0.92 ± 0.6	0.0003
Smoking								<0.0001
Never	5828 (59.8)	975 (65.7)	1415 (63.5)	690 (63.0)	1610 (56.8)	990 (53.3)	148 (61.7)	
Former	1630 (16.7)	243 (16.4)	315 (14.1)	177 (16.1)	487 (17.2)	366 (19.7)	42 (17.5)	
Current: <10 cigarettes/day	1006 (10.3)	138 (9.3)	232 (10.4)	116 (10.6)	296 (10.4)	208 (11.2)	16 (6.7)	
Current: 10–19 cigarettes/day	749 (7.7)	88 (5.9)	158 (7.1)	69 (6.3)	252 (8.9)	162 (8.7)	20 (8.3)	
Current: ≥20 cigarettes/day	529 (5.4)	40 (2.7)	109 (4.9)	44 (4.0)	189 (6.7)	133 (7.2)	14 (5.8)	
Alcohol intake								0.03
Low-risk, non or rarely drinker	10,499 (94.7)	1595 (95.7)	2400 (95.5)	1193 (93.7)	3066 (94.6)	1977 (93.6)	268 (95.0)	
Risky drinker (3–4 drinks per day)	523 (4.7)	65 (3.9)	104 (4.1)	71 (5.6)	154 (4.8)	115 (5.4)	14 (5.0)	
High-risk drinker (≥5 drinks per day)	64 (0.6)	6 (0.4)	9 (0.4)	9 (0.7)	20 (0.6)	20 (0.9)		
Education								<0.0001
High school or lower	7809 (69.8)	1199 (71.3)	1727 (68.2)	881 (68.5)	2273 (69.4)	1535 (72.0)	194 (67.8)	
Technical training	1993 (17.8%)	219 (13.0%)	454 (17.9%)	189 (14.7%)	645 (19.7%)	410 (19.2%)	76 (26.6%)	
University degree or higher	1390 (12.4)	263 (15.6)	352 (13.9)	216 (16.8)	357 (10.9)	186 (8.7)	16 (5.6)	
Income adequacy								<0.0001
Difficult always	1921 (17.2)	214 (12.7)	378 (14.9)	177 (13.8)	592 (18.1)	495 (23.2)	65 (22.7)	
Difficult sometimes	3665 (32.7)	497 (29.6)	815 (32.2)	418 (32.5)	1078 (32.9)	748 (35.1)	109 (38.1)	
Not too bad	4100 (36.6)	653 (38.8)	981 (38.7)	489 (38.0)	1205 (36.8)	684 (32.1)	88 (30.8)	
It is easy	1506 (13.5)	317 (18.9)	359 (14.2)	202 (15.7)	400 (12.2)	204 (9.6)	24 (8.4)	
Gestational diabetes, yes	275 (2.5)	25 (1.5)	39 (1.5)	15 (1.2)	104 (3.2)	80 (3.8)	12 (4.2)	<0.0001

Values are expressed as *n* (%) for categorical variables or mean±SD for continuous variables

Participants were grouped according to baseline BMI (NW, normal BMI at baseline; OB, obesity at baseline; OW, overweight at baseline; low, at low end of the category; mid, at middle of the category; high, at high end of the category) and BMI trajectory (growth curves over time: stable, slope <1; modest increase, slope = 1 to <2; rapid increase, slope ≥2)

p value comparisons across class categories are based on χ^2 test for categorical variables; *p* values for continuous variables are based on ANOVA

for the same covariates, to compare HRs to those obtained for weight trajectories.

Finally, we performed a sensitivity analysis by further adjusting for diet data from a food frequency questionnaire [21], including information about total energy intake, fibre intake, dietary glycaemic index and glycaemic load. Statistical analyses were performed using Mplus 8.2 [22] and SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Results

Among 11,192 women who were free of diabetes at baseline, 162 women (1.5%) developed type 2 diabetes during a mean of 16 years of follow-up. The mean BMI increased from 22.8 kg/m² at baseline to 26.9 kg/m² at survey 7. The obesity prevalence rate increased from 6.5% at baseline to 25.7% at survey 7, and the mean obesity-years was 8.4 years (SD 5.2) among the 2008 women who became obese.

We examined different quadratic models with varying number of classes (trajectories) from two to seven, and identified a six-class solution based on the lowest BIC value. We ranked the six classes (Fig. 1) based on their corresponding mean of BMI at baseline from low to high. We then categorised the four classes with baseline BMI <25 kg/m² as normal weight, and labelled them according to their baseline BMI and slope: NW-low stable (slope <1); NW-mid stable; NW-low modest increase (slope 1 to <2); NW-rapid increase (slope ≥2). The remaining two classes were overweight at baseline, with BMI 25 to <30 kg/m² and with a rapid increase in BMI (OW-rapid increase), or obese (BMI ≥30 kg/m²) with a rapid increase (OB-rapid increase).

In the study population, we observed that two classes had stable BMI trajectory over time (27% of women), including NW-low stable and NW-mid stable classes; 21% of women with normal weight at baseline had modest BMI increase, and more than half of the women had a rapid increase of BMI over time, including those in the NW-rapid increase, OW-rapid increase and OB-rapid increase classes. The largest proportion (28%) of women belonged to the NW-mid rapid increase class. The next most frequent categories were the OW-rapid increase group (21%) and NW-low modest increase group (21%). A small group (3%) of women belonged to the OB-rapid increase class, with initial BMI around 33 kg/m².

Table 1 shows baseline characteristics across the six BMI trajectories. Based on mean baseline BMI from low to high, compared with the lower ranked class, women in the higher ranked classes were more likely to be physically inactive, have higher stress scores, smoke more, be more risky drinkers, have lower education level, have more difficulty in managing on available income and were more likely to have a history of gestational diabetes. Baseline age across classes was not different (Table 1).

Estimated intercept, slope and quadratic parameters for each class are listed in Table 2. Specific growth trajectories are presented in Fig. 1. Compared with women in the NW-low stable class, two groups had significantly higher risk of type 2 diabetes (HR 4.75 [95% CI 2.43, 9.28] for OW-rapid increase class; HR 10.06 [95% CI 4.69, 21.58] for OB-rapid increase class] after adjustment for potential confounders. Initial BMI was significantly and positively associated with risk of type 2 diabetes. Slope was borderline significantly associated with the risk ($p = 0.07$) but the quadratic term was not associated with risk (Table 2).

Fig. 1 BMI trajectories over 19 years of follow-up. The estimated mean BMI in each trajectory is shown. Participants were grouped according to baseline BMI (NW, normal BMI; OB, obese; OW, overweight; low, at low end of the category; mid, at middle of the category) and BMI increase (growth curves over time: stable, slope <1; modest increase, slope 1 to <2; rapid increase, slope ≥2)

Table 2 Estimated means of intercept, slope and quadratic parameters for each BMI class, and HRs for type 2 diabetes incidence

Class/parameter	No. of cases	Intercept	Slope	Quadratic	Multivariable-adjusted model, HR (95%CI) ^a
Class					
NW-low stable (13% of study population) (<i>n</i> = 1558)	10	19.92	0.13 ^b	0.16	1.00
NW-low modest increase (21% of study population) (<i>n</i> = 2329)	21	20.27	1.61	0.07 ^b	1.34 (0.63, 2.85)
NW-mid stable (14% of study population) (<i>n</i> = 1563)	11	22.46	0.03 ^b	0.23 ^b	1.37 (0.50, 3.22)
NW-mid rapid increase (28% of study population) (<i>n</i> = 3118)	32	22.61	3.72	−0.44	1.49 (0.73, 3.04)
OW-rapid increase (21% of study population) (<i>n</i> = 2335)	67	26.56	5.51	−0.79	4.75 (2.43, 9.28)
OB-rapid increase (3% of study population) (<i>n</i> = 289)	21	33.28	7.69	−2.32	10.06 (4.69, 21.58)
Quadratic model parameter					
Intercept					1.12 (1.09, 1.15)
Slope					1.06 (0.99, 1.13)
Quadratic					0.97 (0.83, 1.14)

Participants were classed according to baseline BMI (NW, normal BMI at baseline; OB, obesity at baseline; OW, overweight at baseline; low, at low end of the category; mid, at middle of the category; high, at high end of the category) and BMI trajectory (growth curves over time: stable, slope <1; modest increase, slope = 1 to <2; rapid increase, slope ≥2)

^a Model adjusted for age (continuous), physical activity in (MET/week, continuous), smoking (never, former, current smoker [<10 cigarettes/day, 10–19 cigarettes/day, ≥20 cigarettes/day]), alcohol (low-risk, non or rarely drinker, risky drinker, high-risk drinker), education (high school or lower, technical training, university degree or higher), income adequacy (impossible, difficult always, difficult sometimes, not too bad, it is easy), stress score (continuous) and history of gestational diabetes (no, yes)

^b These estimates were not significant; *p* < 0.05 for all other estimates

Among the 10,521 (94%) women who were not obese at baseline, we observed that women who became obese during follow-up had a threefold (95% CI 2.01, 4.50) risk of type 2 diabetes compared with women who did not become obese. There was a negative association between age at onset of obesity and risk of type 2 diabetes among women who became obese during follow-up (HR 0.87 [95% CI 0.79, 0.96]) (Table 3). Compared with women who did not become obese during the follow-up, women who became obese and had obese-years of <10, 10 to <30 and ≥30 had an HR (95% CI) of 2.18 (1.25, 3.81), 3.01 (1.53, 5.91) and 5.88 (3.15, 10.97), respectively (*p* for trend <0.0001) (Table 3).

The sensitivity analysis using only baseline BMI revealed that individuals with baseline obesity (BMI ≥30 kg/m²) had an HR of 7.07 (95% CI 4.73, 10.57), which is lower than the HR of 10.06 (95% CI 4.69, 21.58) shown in Table 2 for individuals in the obese with rapid increase group. Similarly, individuals shown in Table 2 who were overweight with rapidly increasing BMI had an HR of 4.75 (95% CI 2.43, 9.28), which was higher than the baseline-only overweight group (HR 2.33 [95% CI 1.53, 3.55]).

A sensitivity analysis that further adjusted for the number of children and dietary intake (including total energy intake, fibre intake and dietary glycaemic index or glycaemic load) found similar results (data not shown).

Table 3 Associations between age at onset of obesity, obese-years, and risk of type 2 diabetes incidence among 10,521 (94%) women who were not obese at baseline

	Cases/population	HR (95% CI)
Became obese during follow-up		
No	79/8513	1.00
Yes	38/2008	3.01 (2.01, 4.50)
Age at onset of obesity among women who became obese	38/2008	0.87 (0.79, 0.96) ^a
Obese-years		
Not obese	79/8513	1.00
<10	15/916	2.18 (1.25, 3.81)
10 to <30	10/494	3.01 (1.53, 5.91)
≥30	13/598	5.88 (3.15, 10.97)
<i>p</i> for trend	117/10,521	<0.0001

^a For a 1 year increment in age of obesity onset

Discussion

From this population-based prospective cohort of Australian young adult women with 19 years of follow-up, we identified six distinct BMI trajectories varying by initial BMI and slope. More than half of the women experienced a rapid BMI increase from early (18–23 years old) to middle adulthood (37–42 years old). Our data confirmed that BMI in young adulthood played an important role in the subsequent risk of developing type 2 diabetes during adulthood. We also observed that women who were non-obese at baseline but became obese during follow-up had a higher risk of type 2 diabetes relative to women who stayed non-obese; the younger the age at onset of obesity or the greater obese-years, the higher the risk of type 2 diabetes.

A few previous studies have investigated associations between BMI trajectories and diabetes incidence [23–26], diabetes-related metabolic markers, or inflammatory markers [27–30]. Findings from these studies indicate that risks for diabetes incidence, diabetes-related metabolic markers (i.e. glucose, insulin and HOMA-IR), or elevated hs-CRP (high-sensitivity C-reactive protein) [23, 27–30] are associated with steeper weight gain trajectories, consistent with our findings. Two studies [27, 28] based on a cohort in a similar age group to our study also identified six similar trajectories and observed that a steeper weight gain trajectory was associated with higher risks of metabolic markers of diabetes or greater risk of elevated hs-CRP compared with more moderate weight gain trajectories. A recent study using repeated measurements of BMI from childhood to adulthood observed that the linear slope of BMI change between ages 10 and 19 years was positively associated with adult hyperglycaemia [31]. Another study based on retrospectively recalled weights from age 20 years and weight in middle-aged Japanese men and women found that long-term weight change slope was significantly associated with risk of type 2 diabetes [32]. That is, the steeper slope, the higher the risk of type 2 diabetes. In our study, the association between slope and risk of type 2 diabetes was only borderline significant. This may be due to the small number of women diagnosed with type 2 diabetes over time among this young cohort.

Our data indicated that baseline BMI among young women was significantly associated with risk of developing type 2 diabetes, with women in the overweight or obese BMI trajectories having significantly higher risk of type 2 diabetes compared with women in the NW-low stable group. The results highlight the importance of overweight or obesity in early adulthood as risk factors for adult diabetes, indicating that weight control starting before early adulthood is critical for reducing type 2 diabetes risk in later life.

In addition to initial BMI, we also observed that a higher number of obese-years was associated with higher risk of type 2 diabetes in a dose–response fashion. Unlike measurements

of BMI at one point in time, measurement of obese-years account for the cumulative effect of obesity. A previous study compared different measures of obesity as predictors of diabetes risk and reported that obese-years was a better predictor for type 2 diabetes than duration of obesity or BMI values alone [10]. This may be because obese-years represent the cumulative damage to the body caused by obesity. It is well-accepted that excess adiposity can have deleterious metabolic effects such as increased insulin resistance or increased levels of proinflammatory cytokines [33, 34]. Prolonged duration of excess adiposity may result in additional metabolic changes, leading to the development of diabetes [34, 35]. These results indicate the importance of both duration of obesity and the degree of obesity in the development of type 2 diabetes.

We also observed that older age at onset of obesity was associated with lower risk of type 2 diabetes when compared with younger age at onset. Our finding indicates that early-onset obesity may be particularly deleterious for future diabetes risk in women. We only identified one study that examined age at onset of obesity in relation to the risk of type 2 diabetes [36]. This analysis, based on the Framingham Heart study, found that age of onset may be a useful, practical addition to current BMI in the elderly. One explanation for the finding of higher risk of type 2 diabetes among women who became obese at a younger age may be the prolonged duration of obesity, because women with early onset of obesity will likely also have longer duration of obesity. However, it is possible that obesity during young age may be more deleterious for insulin resistance and diabetes than obesity during older age [37, 38]. Another study has also demonstrated that diabetes risk was particularly high in individuals who were obese as adolescents relative to those with adult-onset obesity [38]. These data highlight the need for early diabetes prevention efforts to prevent or delay the onset of obesity.

Strengths of the study include the long-term follow-up in a large prospective cohort. Several limitations deserve mention. First, weight was self-reported. There is evidence from a previous validation study that self-reported height and weight are reliable [17]; however, the reliability of self-reported weight is better for normal weight women than obese women. Thus, potential misclassification in trajectory assignment may still exist and the fact that the degree of under-reporting in weight is differential with respect to their true weight may lead to an overestimate of the associations between trajectories and diabetes risk. Second, although self-reported diabetes in the cohort has been validated for middle-aged and older cohorts and has been demonstrated to be a reliable indicator of diagnosed diabetes [16], a relatively larger degree of under-diagnosis in the young cohort is possible, which may bias our findings. For example, if diabetes is more likely to be under-diagnosed among obese women than non-obese women, our results may be under-estimated. On the other hand, if diabetes is less likely to be under-diagnosed for obese

women than non-obese women our results may be over-estimated. The prevalence of diabetes we observed (1.5%) was similar to self-reported data from the Australian Bureau of Statistics (ABS) 2014–15 National Health Survey, where the prevalence of diabetes was 1.5% among women aged 18–44 years [39]. Third, the low incidence of diabetes in our young study population during the follow-up period may be a concern for the Cox models, given these can produce unreliable estimates when the outcome is rare. Fourth, BMI data were only collected from baseline; thus, we were unable to calculate the timing of obesity for women who were already obese at baseline. These women had to be excluded from analyses for age at onset and obese-years. This may reduce study power despite the fact that these women accounted for only 6.5% of the study population. Another limitation is that our analysis does not consider the uncertainty of the classification rather than forcing individuals into their most likely trajectory patterns. Finally, the study was conducted among young Australian women. Caution should be taken when generalising our findings to other populations.

In conclusion, our data have shown that more than half of the women experienced a rapid BMI increase from early to middle adulthood, suggesting the importance of monitoring weight change over time. Persons who experience rapid weight gain are at increased diabetes risk independently of baseline BMI status. In particular, our data indicate the importance of timing of obesity and cumulative exposure to obesity measured by obese-years in relation to diabetes risk in young women. The results highlight the importance of preventing or delaying the onset of obesity and reducing cumulative exposure to obesity to substantially lower the risk of developing diabetes. We recommend that people self-monitor weight change over time, and that healthcare providers attend to weight change in addition to static weight as another risk factor for diabetes.

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Data availability Data may be made available to collaborating researchers where there is a formal request to make use of the material. Permission to use the data must be obtained from the Data Access Committee of ALSWH (<https://www.alswh.org.au/how-to-access-the-data/alswh-data>).

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