BMJ Open Diabetes Research & Care

Years of potential life lost in pre-diabetes and diabetes mellitus: data from a 40-year follow-up of the Israel study on Glucose intolerance, Obesity and Hypertension

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To cite: Rapoport M, Chetrit A, Cantrell D, *et al*. Years of potential life lost in pre-diabetes and diabetes mellitus: data from a 40-year follow-up of the Israel study on Glucose intolerance, Obesity and Hypertension. *BMJ Open Diab Res Care* 2021;**9**:e001981. doi:10.1136/bmjdrc-2020-001981

► Supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2020-001981).

Received 30 October 2020
Revised 23 January 2021
Accepted 16 February 2021

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ABSTRACT

Introduction We examined years of potential life lost (YPLL) associated with pre-diabetes as compared with either normoglycemia or diabetes, using data of the Israel cohort of Glucose intolerance, Obesity and Hypertension 40-year follow-up.

Research design and methods Men and women (N=2844, mean age 52.0±8.2 years) who underwent oral glucose tolerance test and anthropometric measurements, during 1976–1982, were followed for mortality until May 2019. Multiple imputation procedures for missing mortality dates and multivariable regression mixed models were applied.

Results At baseline, 35.8%, 48.8% and 15.4% individuals were found with normoglycemia, pre-diabetes, and diabetes, respectively. The average difference in YPLL associated with pre-diabetes as compared with normoglycemia was 4.3 years (95% CI 3.3 to 5.2; p<0.001). YPLL were 1 year higher in women with pre-diabetes than in men with pre-diabetes. These differences persisted mainly in individuals younger than 60 years, and those with body mass index (BMI) <25 kg/m^2, at baseline. Adjusting for age, sex, country of origin, smoking status, BMI, and blood pressure, the average difference in YPLL associated with pre-diabetes as compared with normoglycemia was 2.0 years (95% CI 1.2 to 2.8; p<0.001). Significant reductions of 5.9 years (95% CI 4.8 to 7.0) on average were observed for diabetes as compared with pre-diabetes and 7.9 years (95% CI 6.7 to 9.1) as compared with individuals with normoglycemia.

Conclusions This study reveals that life expectancy of middle-aged individuals with pre-diabetes is shorter than of normoglycemic ones. These findings are especially relevant in view of the rising worldwide prevalence of pre-diabetes within younger age groups and underscore the crucial importance of interventions by either lifestyle modification or drug therapy capable of delaying progression from pre-diabetes to diabetes to reduce the YPLL in this high-risk group.

Significance of this study

What is already known about this subject?

- Pre-diabetes is a risk factor for mortality but the number of years of potential life lost associated with its presence is not known.

What are the new findings?

- In adult men and women, when comparing with normoglycemia, over a 40-year follow-up: (1) pre-diabetes is associated with a loss of 2 years of potential life; (2) diabetes is associated with a loss of 8 years of potential life; (3) although 42% of individuals with pre-diabetes deteriorated to diabetes over a midterm follow-up, 34% remained with pre-diabetes and 24% improved back to normoglycemia with an improved prognosis.

How might these results change the focus of research or clinical practice?

- Clinicians should be aware of the significant loss of potential life years associated with pre-diabetes, clarify its underlying mechanisms, and take protective measures to prevent its occurrence and the progression from pre-diabetes to diabetes.

INTRODUCTION

It has long been established that hyperglycemia contributes significantly to mortality, and that more intensive control reduces mortality in diabetes.[1] Pre-diabetes is the preceding condition of diabetes, and in most of the cases, this ultimately leads to the development of diabetes if left untreated.[2] The prevalence of pre-diabetes is gradually increasing. In the USA, about one of five adolescents and one of four young adults have pre-diabetes.[3] The adjusted prevalence of pre-diabetes is higher in male individuals and in people with obesity.[3] Individuals with pre-diabetes also present an unfavorable cardiometabolic risk profile, putting them both at increased risk for type 2 diabetes, chronic kidney disease, and cardiovascular diseases.[3]

The association between diabetes and early mortality has been established[4] and a recent systematic review with meta-analysis showed an association between pre-diabetes and all-cause mortality (relative risk (RR)=1.13, 95% CI 1.10 to 1.17) as well as cardiovascular morbidity (RR=1.15, 95% CI 1.11 to 1.18).[5]

Years of potential life lost (YPLL) are an estimate of the average years a person would have lived if he or she had not died prematurely.[6] This standard measure is used to compare the relative magnitude of different causes of premature death within a population and prioritize preventive measures accordingly.

We examined YPLL associated with pre-diabetes as compared with either normoglycemia or diabetes, using a 40-year follow-up data of a representative cohort of men and women of the Israeli population.

RESEARCH DESIGN AND METHODS

We used data of the Israel study of Glucose intolerance, Obesity and Hypertension (GOH) 40-year follow-up[7] to quantify the number of years lost due to a diagnosis of pre-diabetes as compared with normoglycemia and with diabetes. We hypothesized that adult men and women with pre-diabetes at baseline will have greater number of YPLL as compared with adults with normoglycemia, and smaller number of YPLL as compared to those with diabetes. The population of the current study is a representative sample of the original GOH cohort, which was randomly selected during 1967 from the Israel population registry, stratified by sex, age (three age categories of 10 year of birth between 1912 and 1941) and four ethnic groups according to country of origin (European/American, North African, Yemenite, and other Middle Eastern).[7] During 1976–1982, 2844 participants underwent medical interviews on lifestyle habits and health status, physical examinations, blood testing for fasting glucose, and 2-hour oral glucose tolerance test (OGTT), at regional medical centers. All subjects were home interviewed and their weight, height and blood pressure were measured by trained nurses. Of the original sample (N=5711), non-participation was mainly due to technical reasons, namely shortage of funds (25%), as well as unreported change of address (15%), death during the 10 years of follow-up (6%), and refusals (4%). No major differences in the age–sex–ethnic origin distributions of the study group compared with the original cohort were noted. During 1999–2004, a subcohort of 1013 survivors was followed up for glycemic status according to the baseline protocol.

Laboratory tests

Diagnosis of pre-diabetes was made according to impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) as defined below. The OGTT was performed by ingesting a 100-gram glucose load in order to enhance the insulin responsiveness.[8] The facilities of Sheba Medical Center were used for laboratory examinations. Plasma glucose was determined by an automated Technicon Autoanalyzer II method (Technicon Instruments Corp, Tarrytown, New York, USA), using potassium ferrocyanide reduction.

Exposure, endpoints and covariates

Normoglycemia was defined as fasting plasma glucose <5.55 mmol/L (100 mg/dL) and, when available, 2-hour post-OGTT plasma glucose <140 mg/dL and no reporting of diabetes or of using anti-diabetes medications. Diabetes and pre-diabetes were defined according to American Diabetes Association's glucose cut-point criteria.[9] Pre-diabetes was defined as fasting plasma glucose 5.55–6.94 mmol/L (100–125 mg/dL) and, when available, 2-hour post-OGTT plasma glucose 7.77–10.54 mmol/L (140–199 mg/dL) and no reporting of having diabetes or of using anti-diabetes medications. Diabetes was defined as fasting plasma glucose >6.94 mmol/L (125 mg/dL) or 2-hour post-OGTT plasma glucose >10.54 mmol/L (199 mg/dL) or reporting of having diabetes or of using anti-diabetes medications.

Hypertension was defined as mean systolic blood pressure ≥140 mmHg and mean diastolic blood pressure ≥90 mmHg, or a self-reported history of hypertension.

Linkage of the study file with the National Population Registry, updated until May 2019, by a unique identification number assigned to each Israeli citizen, enabled a complete vital status assessment.

Statistical methods

The X^2 test was used for comparison of categorical variables and the one-way analysis of variance test for continuous variables between the three study groups (normoglycemia, pre-diabetes and diabetes). Survival time was defined as starting from the date of plasma glucose test to the date of death or date of last follow-up, whichever occurred first. Survival was assessed for the three study groups using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Median survival time or 25% survival and 95% CIs were presented for the study groups by sex and the three birth periods.

The widely accepted definition of YPLL limits life span according to an upper age cut-points: 75, 80 or 90 years,[6] determined according to the life expectancy of the population under study. This method allows including only those who died at a younger age than these age limits, most probably leading to an underestimation of YPLL. In the present study, 27.7% were still alive by the end of the follow-up (May 2019). We applied multiple 10 times imputation of age at death using the Weibull distribution with parameters defined by parametric survival model.[10] After imputations, we compared the life span between the normoglycemia, pre-diabetes, and diabetes groups, with and without adjustment for potential covariates (sex, age, origin, smoking, body mass index (BMI), and blood pressure), by corresponding linear models in each of the 10 data sets. Final results were obtained using Rubin's rule

Table 1 Baseline characteristics (%) of the study sample by glycemic status; 1979–1982

	Total N=2844	Normoglycemia N=1019	Pre-diabetes N=1388	Type-2-DM N=437
Sex				
Men	49.5	43.2	53.2	52.6
Women	50.5	56.8	46.8	47.4
Age (years) mean±SD	52.0±8.2	50.0±8.0	52.4±8.0	55.0±8.0
Range	28–69	31–69	35–69	28–69
Ethnic origin				
Europe/America	30.6	31.1	31.7	26.1
Middle East	24.7	25.2	25.3	21.7
North Africa	20.3	20.1	19.2	24.0
Yemen	24.4	23.6	23.8	28.2
BMI* (kg/m^2) mean±SD	26.2±4.2	25.1±3.8	26.4±4.1	27.9±4.8
<25.0	42.9	23.2	39.1	30.7
25.0–26.9	20.0	20.2	20.6	17.5
27.0–29.9	21.3	17.1	23.7	23.3
30.0+	15.9	9.5	16.6	28.5
Blood pressure (mmHg)				
Systolic, mean±SD	133.3±22.4	127.1±19.7	133.4±21.5	147.3±24.3
Diastolic, mean±SD	84.5±11.6	82.2±11.1	85.1±11.5	88.2±11.8
% hypertensive	34.5	25.0	34.7	56.3
Smoking				
Current or past	41.3	41.1	41.6	40.7
Never	58.7	58.9	58.4	59.3
Mortality	72.3	60.1	74.4	94.1

*Missing BMI—38.
BMI, body mass index; DM, diabetes mellitus.

of correcting variance of the estimated parameters after multiple imputations. As a sensitivity analysis, we calculated YPLL using the non-imputed data set excluding those still alive by the end of follow-up. All calculations were done using the LIFEREG, Mixed models and MIANALYZE SAS 9.4 software procedures.

RESULTS

Out of the 2844 cohort members, 49.5% were men, with a mean age of 52.0±8.2 years, with the highest proportion, 31%, from European/American origin and the lowest, 20%, from North Africa. The majority of the cohort had a normal BMI of <25.0 (43%), 41% were former or past smokers, and 34% were classified as hypertensive. In total, 72% have died during the 40-year follow-up.

At baseline, 35.8%, 48.8% and 15.4% individuals had normoglycemia, pre-diabetes, and diabetes, respectively (table 1), with female predominance in the normoglycemia group. Of those with pre-diabetes, 1005 (72.4%) had IFG, 102 (7.3%) had IGT, and 281 (20.2%) had both IFG and IGT. The three study groups differed according to age, BMI, blood pressure levels and proportion of subjects with hypertension, with those diagnosed as having diabetes presenting with the worst indices and individuals with normoglycemia with the most favorable ones. Major differences were observed in mortality, where 94% of the diabetes group died by the end of follow-up, compared with 74% and 60% in the pre-diabetes and the normoglycemia groups, respectively.

Figure 1 and online supplemental table S1 are presenting the results of the survival analysis according to the three glycemic groups. As expected, the lowest median survival was observed in the group with diabetes in both sexes and in the first birth cohort (1912–1921). Compared with normoglycemia, pre-diabetes conferred a worst survival in both men and women and according to the three birth decades. The age-adjusted and sex-adjusted median survival of individuals with normoglycemia, individuals with pre-diabetes and those with diabetes was 34 years (95% CI 34 to 36), 30 years (95% CI 28 to 31) and 17 years (95% CI 16 to 18), respectively. The advantage of normoglycemia over both pre-diabetes and diabetes was evident in terms of YPLL, where 4.3 and 14.2 years were lost for pre-diabetes and diabetes compared

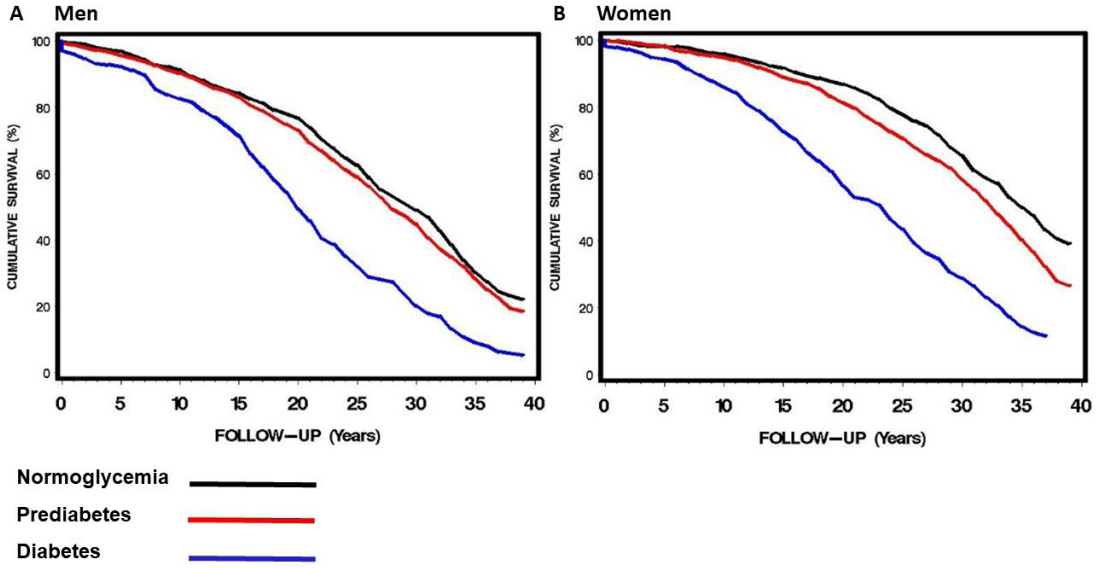

Figure 1 Age-adjusted Kaplan-Meir survival curves of 1409 men (A) and 1435 women (B) by glycemic status.

with normoglycemia (table 2). These YPLL differences were all highly statistically significant. YPLL was higher in women than men, but lower in the oldest age group category (>60 years) than in the younger two groups. In terms of ethnic background, the highest differences were seen in the Middle Eastern-originating individuals, reaching 5.5, 11.8 and 17.3 years for pre-diabetes versus normoglycemia, diabetes versus pre-diabetes, and diabetes versus normoglycemia. YPLL did not differ according to smoking status. Obese individuals (BMI >30 kg/m^2) had lower YPLL than non-obese individuals (4.2, 8.0, and 12.2 years for pre-diabetes vs normoglycemia, diabetes vs pre-diabetes, and diabetes vs normoglycemia). Hypertension was also associated with a lower YPLL.

Using multiple regression mixed models (table 3), controlling for sex, age, origin, smoking, BMI and blood pressure, the average difference in YPLL associated with pre-diabetes as compared with normoglycemia was 2.0 years (95% CI 1.2 to 2.8; p<0.001). Significant reductions of 5.9 years on average (95% CI 4.8 to 7.0) were observed for diabetes as compared with pre-diabetes and 7.9 years (95% CI 6.7 to 9.1) as compared with individuals with normoglycemia.

A sensitivity analysis, restricting the sample to those who actually died by the end of follow-up (table 3), shows similar findings of YPLL between the study comparison groups. While marginal differences are noted for the diabetes versus both pre-diabetes and normoglycemia groups, the non-statistically significant YPLL reduction of 0.6 years observed in the fully adjusted model for pre-diabetes versus normoglycemia (p=0.2) is probably attributed to the higher survival (40%) of the normoglycemic group.

For a subcohort of 1013 individuals who were alive during 1999–2004, we could assess progression of the glycemic state during 1976–1982 and follow-up (online supplemental figure S1). Of those who presented with pre-diabetes at baseline, 42.1% deteriorated to diabetes, 33.9% remained with pre-diabetes and 24.0% became normoglycemic. Progression from pre-diabetes to diabetes occurred among 37.2% when defined by IFG (n=146/392); 51.7% when defined by IGT (n=15/29); and 61.9% when defined by both IFG+IGT (n=52/85). Within this group with pre-diabetes, the rate of mortality was the highest (64.8%) among those who progressed to diabetes and lowest (44.6%) for those who reverted to normoglycemia (the majority of whom were IFG at baseline). As expected, the highest mortality rate was observed among those who remained with diabetes since baseline (75.0%) whereas those who remained with normoglycemia had the lowest mortality rate (37.7%).

CONCLUSIONS

The current analysis provides a quantitative estimate of the premature mortality associated with pre-diabetes and diabetes. It reveals that adjusted life expectancy of middle-aged individuals with pre-diabetes, and diabetes, is 2 and 8 years shorter than of individuals with normoglycemia, respectively. YPLL was greater in women, in younger individuals (<60 years) and in those with moderate overweight. As expected, diabetes was associated with the highest YPLL in this long-term cohort study when compared with individuals with normoglycemia.

The main outcome of this study, namely that pre-diabetes is associated with a shorter life span as compared with normoglycemia but higher as compared with overt diabetes, is supported by other reports, although some differences exist. In line with our findings, the National Health Interview Survey (NHIS) sample reveals that American women lost more life years than men in both white and black individuals with diabetes.[11] In a Canadian population, diabetes was also found to be associated with a greater loss of life expectancy in women than in men.[12] In addition, life years lost associated with diabetes declined with older age. We found YPLL to be 10 years

Table 2 Year difference of life lost between phase-2 glycemic groups, according to demographic and anthropometric characteristics

	Pre-diabetes versus normoglycemia (1388 vs 1019)	Diabetes versus normoglycemia (437 vs 1019)	Diabetes versus pre-diabetes (437 vs 1388)
Total (N=2844)			
Estimate (years)	4.3	14.2	9.9
95% CI	3.3 to 5.3	12.8 to 15.5	8.6 to 11.2
Sex			
Male (n=1409)			
Estimate (years)	3.3	12.2	8.8
95% CI	1.9 to 4.8	10.2 to 14.1	7.1 to 10.7
Female (n=1435)			
Estimate (years)	4.4	15.5	11.1
95% CI	3.0 to 5.7	13.6 to 17.3	12.9 to 9.3
Age at baseline (years)			
<50 (n=1191)			
Estimate (years)	2.5	10.8	8.2
95% CI	1.2 to 3.8	8.4 to 13.1	5.9 to 10.6
50–59 (n=1033)			
Estimate (years)	2.5	10.4	7.9
95% CI	1.1 to 4.0	8.5 to 12.3	6.2 to 9.6
60–69 (n=620)			
Estimate (years)	2.1	6.7	4.6
95% CI	0.3 to 3.9	4.6 to 8.7	2.8 to 6.4
Origin			
Yemen (n=693)			
Estimate (years)	4.6	12.3	7.6
95% CI	2.7 to 6.6	9.7 to 14.8	5.2 to 10.1
Middle East (n=703)			
Estimate (years)	5.5	17.3	11.8
95% CI	3.5 to 7.4	14.5 to 20.1	9.1 to 14.5
North Africa (n=577)			
Estimate (years)	3.2	15.3	12.1
95% CI	0.98 to 5.4	12.5 to 18.2	9.4 to 14.9
Europe/America (n=871)			
Estimate (years)	3.7	12.3	8.6
95% CI	1.8 to 5.5	9.6 to 15.0	6.1 to 11.2
Smoking			
Current and past (n=1174)			
Estimate (years)	4.5	14.0	9.5
95% CI	2.9 to 6.1	11.9 to 16.2	7.4 to 11.5
Never (n=1670)			
Estimate (years)	4.0	14.3	10.2
95% CI	2.8 to 5.3	12.5 to 16.0	8.5 to 11.9
BMI (kg/m^2)			
<25 (n=1203)			
Estimate (years)	3.7	14.2	10.5

Continued

Table 2 Continued

	Pre-diabetes versus normoglycemia (1388 vs 1019)	Diabetes versus normoglycemia (437 vs 1019)	Diabetes versus pre-diabetes (437 vs 1388)
95% CI	2.2 to 5.3	11.7 to 16.7	8.0 to 12.9
25–26.9 (n=561)			
Estimate (years)	4.7	15.9	11.2
95% CI	2.4 to 6.9	12.7 to 19.1	8.2 to 14.3
27–29.9 (n=597)			
Estimate (years)	4.4	13.6	9.2
95% CI	2.3 to 6.5	10.8 to 16.5	6.7 to 11.8
30+ (n=445)			
Estimate (years)	4.2	12.2	8.0
95% CI	1.6 to 6.8	9.3 to 15.1	5.6 to 10.4
Blood pressure			
Normotensive (n=1862)			
Estimate (years)	3.5	13.2	9.7
95% CI	2.3 to 4.7	11.3 to 15.1	7.9 to 11.5
Hypertensive (n=982)			
Estimate (years)	3.4	10.4	7.0
95% CI	1.7 to 5.1	8.4 to 12.4	5.3 to 8.7

BMI, body mass index.

greater in diabetes versus normoglycemia for individuals aged <60 years, but of only 6 years among the older individuals. Narayan *et al*[13] also reported similar findings. In the Japanese NIPPON DATA80 Study, a 7–9 years shorter life expectancy was found in participants with diabetes as compared with those without diabetes, and 2–4 years for participants with IGT compared with those without diabetes.[14] In contrast to our findings of greater YPLL in women with pre-diabetes than in men, Japanese men with IGT had a shorter life expectancy than women with IGT.

Whether the higher YPLL of patients with pre-diabetes is due to their aberrant glycemic state associated with higher morbidity and mortality or emergence of overt diabetes with time is not clear. The Australian Diabetes, Obesity, and Lifestyle Study found increased mortality for patients with IFG and IGT with a median of 5.2 years' follow-up.[15] This relatively short time period suggested that progression to diabetes is a less likely factor for the increased mortality associated with pre-diabetes and underscores the inherent risk of pre-diabetes. Similarly, the Framingham Offspring Study showed that pre-diabetes and especially

Table 3 Unadjusted and fully adjusted models of full cohort and of deceased individuals by end of follow-up

	Full cohort (N=2844)			Only deceased individuals by the end of follow-up (N=2056)		
	Pre-diabetes versus normoglycemia (1388 vs 1019)	Diabetes versus normoglycemia (437 vs 1019)	Diabetes versus pre-diabetes (437 vs 1388)	Pre-diabetes versus normoglycemia (1033 vs 612)	Diabetes versus normoglycemia (411 vs 612)	Diabetes versus pre-diabetes (411 vs 1033)
Unadjusted model						
Estimate (years)	4.3	14.2	9.9	1.3	8.1	6.8
95% CI	3.3 to 5.3	12.8 to 15.5	8.6 to 11.2	0.3 to 2.3	6.8 to 9.3	5.6 to 7.9
Fully adjusted model						
Estimate (years)	2.0	7.9	5.9	0.6*	6.0	5.4
95% CI	1.2 to 2.8	6.7 to 9.1	4.8 to 7.0	−0.4 to 1.5	4.8 to 7.2	4.4 to 6.5

Adjusted for: sex, age, origin, smoking, BMI, and blood pressure.
*P=0.2.
BMI, body mass index.

early-onset pre-diabetes confers increased propensity for death, mainly from cardiovascular causes without ever progressing to diabetes.[16] On the other hand, during the 23 years of follow-up in the Da Qing Diabetes Prevention Study, the higher death rate compared with matched cohort without diabetes of the IGT group was attributed to the high 79% progression rate to diabetes mellitus.[17] This latter finding underscores the great potential for mortality reduction when delaying the onset of diabetes by preventing the progression of pre-diabetes to diabetes. A lifestyle intervention in individuals with pre-diabetes from the Da Qing Diabetes Prevention Study increased life expectancy by an average of 1.44 years.[18]

Taken together, these data suggest that both factors—inherent risk conferred by pre-diabetes per se together with progression from pre-diabetes to diabetes—may play a role in reducing the life span of persons with pre-diabetes. Our midterm analysis performed after 2 decades of follow-up supports this notion, demonstrating increased mortality for the group with pre-diabetes advancing to diabetes and less so for the individuals with stable pre-diabetes. In addition, the observed gradient of progression rate from pre-diabetes to diabetes according to pre-diabetes criteria, that is, IFG, IGT or both, may be associated with differential YPLL. This was not examined in the present study due to the relatively small groups. In the present study, 12% reverted from pre-diabetes, mostly IFG, to normoglycemia, during a 20-year follow-up, with a relatively low mortality rate of 45% by the end of follow-up. Although the cause for this reversion is unknown, the latter finding may be in accordance with lifestyle intervention studies such as the Finnish Diabetes Prevention Study,[19] the Malmo Study[20] and the Diabetes Prevention Program,[21] consistently showing a reduction in diabetes incidence as well as a decrease in cardiovascular risk factors associated with early mortality. Other interventions, such as drug therapy and bariatric surgery, have proven effective in prevention of progression to diabetes.[22–26] Most drugs, excluding metformin, had only modest benefit, with no mortality or cardiovascular advantage.[22–25] Although bariatric surgery had better diabetes prevention rates compared with drugs, it lacks proven mortality/cardiovascular benefit and has a considerable adverse effect profile.[26]

The association of mortality with obesity among people with diabetes is not clear. While previous reports did not find differences in life expectancy between people with diabetes with or without obesity,[27] in this study the largest number of YPLL was observed in the mild-overweight group (BMI 25.0–26.9 kg/m^2) in both individuals with pre-diabetes and diabetes. Our finding is in accordance with the American NHIS 1997–2000 survey demonstrating that the largest YPLL associated with diabetes was found in the overweight for most of the age, sex and race groups.[11] The lowest number of YPLL observed among the obese individuals, when comparing pre-diabetes, diabetes, and normoglycemia, may be a result of other obesity-related comorbidities.

Our study has several limitations. Glycemic state was examined at baseline and may have changed over the years of follow-up until death occurred. Although we performed a midterm analysis, it included only part of the GOH cohort, mainly of survivors. Thus, we were unable to analyze stable pre-diabetes versus that progressing to diabetes and its association with YPLL for the entire cohort. Nevertheless, this midterm analysis most probably reflects an underestimation of the magnitude of the association between dysglycemia and YPLL. Although a 100-gram glucose load was used instead of the standard 75 g, it was found to have little effect on glucose levels.[28] Higher rates of pre-diabetes, of 48% were observed in the present study, compared with other Western population reports of 30%–34%.[17 29] This may affect the external validity to other populations. Cohort ethnic imbalance, including ~25% Yemenites, known for the extremely high proportion of diabetes and pre-diabetes,[30] may explain cohort pre-diabetes proportions. However, the estimated YPLL reported herein were adjusted for ethnic origin, as well as sex, age, smoking, BMI, and blood pressure. Cause-specific mortality could not be examined in the current study due to lack of available data on cause of death. Finally, some of the cohort members were still alive at end of follow-up, and an imputation strategy was applied to allow the use of the full data set while avoiding the risk of survival (selection) bias. Our sensitivity analysis revealed that the estimated YPLL with and without these individuals is showing a similar pattern.

This study has several strengths. While most studies on life expectancy in relation with dysglycemia focused on diabetes, our study reports YPLL in association with both pre-diabetes and diabetes. The data used in the current study were collected and laboratory tests were performed under standard conditions for purposes of a follow-up study, increasing the validity of the data. Availability of information on additional risk factors is another advantage of the present study. In addition, glycemic state definition was based on both fasting and OGTT in accordance with present major guidelines; our cohort is comprised of both men and women and was randomly drawn from the Central Population Registry. Finally, in regard to mortality, the length of follow-up is exceptionally long, providing high event rates (death) and better YPLL assessment.

The exceptionally long 4-decade follow-up of our cohort provided a unique opportunity to determine the association between various stages of dysglycemia and YPLL over an ordinary life span. Our study reveals that adjusted life expectancy of middle-aged individuals with pre-diabetes is shorter than of individuals with normoglycemia. These findings are especially relevant in view of the rising worldwide prevalence of pre-diabetes within younger age groups and underscore the crucial importance of delaying progression from pre-diabetes to diabetes by either lifestyle modification or drug therapy to reduce the YPLL in this high-risk group.

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Acknowledgements The authors would like to acknowledge the late Dr Michaela Modan who was the principal investigator of this cohort study during baseline data collection.

Contributors MR researched data and contributed to discussion. AC ran the statistical analysis, wrote the manuscript and researched data. DC contributed to the discussion and to writing the manuscript. IN contributed to the statistical analysis plan and wrote the statistical methods section. JR reviewed/edited the manuscript. RD collected and researched the data, contributed to the discussion and wrote the manuscript. RD is the guarantor of this paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Informed consent was obtained from each participant and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Sheba Medical Center's human research committee (Sheba Medical Center #1180).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request from RD, the study principal investigator.

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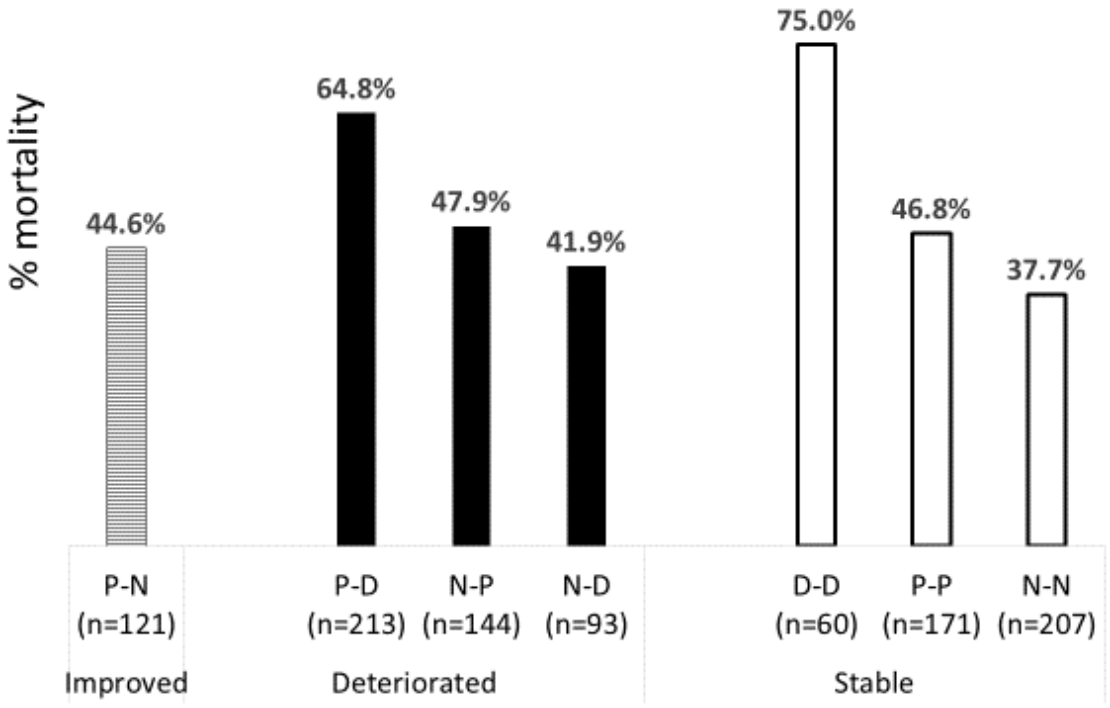
Table S1: Survival of Phase-2 cohort according to glycemic state, sex, and period of birth

	Normoglycemia			Prediabetes			Diabetes		
	n	Median (years), 95%CI	25% (years), 95%CI	n	Median (years), 95%CI	25% (years), 95%CI	n	Median (years), 95%CI	25% (years), 95%CI
Males, Birth years									
1912 -1921	113	18.0, 16 – 22	11.0, 8 - 13	255	19.0, 17 – 20	11.0, 8 – 13	115	15.0, 12 – 17	8.0, 7 – 9
1922 - 1931	159	31.0, 28 – 33	23.0, 19 – 24	260	29.0, 27 – 31	21.0, 17 – 22	74	19.5, 16 – 22	14.0, 9 – 16
1932 - 1941	167	-	35.0, 31 - -	224	-	30.0, 27 – 33	33	29.0, 20 – 34	16.0, 9 – 22
Females, Birth years									
1912 -1921	107	24.0, 21 – 28	15.0, 11 – 19	184	19.5, 18 – 21	13.5, 12 – 15	100	13.5, 11 – 16	8.0, 7 – 10
1922 - 1931	207	35.0, 33 - -	28.0, 25 – 29	255	32.0, 30 – 33	25.0, 23 – 26	81	20.0, 17 – 24	14.0, 12 – 16
1932 - 1941	265	-	36.0, 34 - -	210	-	35.0, 31 – 37	22	34.5, 25 - -	25.0, 9 - 33

Figure S1: Percent mortality among the sub-cohort according to transition in glycemic group between baseline and ~20 years follow up (N=1,013)



	Baseline	-	Follow up
N-N:	Normoglycemia	-	Normoglycemia
N-D:	Normoglycemia	-	Diabetes
P-N:	Prediabetes	-	Normoglycemia
P-P:	Prediabetes	-	Prediabetes
N-P:	Normoglycemia	-	Prediabetes
P-D:	Prediabetes	-	Diabetes
D-D:	Diabetes	-	Diabetes