

Associations of Traumatic Injury with Abnormal Glucose Metabolism: A Population-Based Prospective Cohort Study

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Purpose: Empirical data on the association between traumatic injury and abnormal glucose metabolism risk is limited. This study aimed to investigate the association between traumatic injury and abnormal glucose metabolism.

Patients and Methods: This study included 153,162 participants in the Kailuan Study from 2006 to 2013. Participants with abnormal glucose metabolism at baseline were excluded. All participants were monitored every two years until December 31, 2019. During follow-up, 1915 subjects with a first traumatic injury (defined as a physical injury caused by an external force) were identified. For each subject with traumatic injury, one control subject was randomly selected and matched for age (± 3 years) and sex. A total of 3830 subjects were included in the final analysis. Cox proportional hazards models were used to examine the association between traumatic injury and the subsequent risk of abnormal glucose metabolism.

Results: During a median follow-up of 6.91 (3.57–9.41) years, 990 abnormal glucose metabolism events occurred. After adjustment for demographics, lifestyle behaviors, and traditional risk factors, those who had traumatic injury compared to controls were 32% more likely to develop any abnormal glucose metabolism (hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.16–1.49), including impaired fasting glucose (IFG) (HR 1.29; 95% CI 1.12–1.48) and diabetes (HR 1.37; 95% CI 1.10–1.70). The risks for abnormal glucose metabolism, IFG, and diabetes in subjects with moderate-severe injury were higher than in subjects with mild injury for the 1-year follow-up period, while the association was not significantly different by injury severity for the whole follow-up period.

Conclusion: Traumatic injury was associated with an increased risk of abnormal glucose metabolism. However, the risks of outcome events decreased as the follow-up period extended. Improved short- and long-term prevention and management strategies for controlling glucose are needed for individuals with traumatic injury.

Keywords: traumatic injury, glucose metabolism, diabetes, impaired fasting glucose, cohort study

Introduction

Abnormal glucose metabolism is a common metabolic disorder characterized by elevated blood glucose levels, mainly including diabetes and prediabetes status.¹ Currently, diabetes is one of the fastest growing global health emergencies of the 21st century. According to statistics from the International Diabetes Federation, more than half a billion people suffer from diabetes worldwide, and this number is increasing rapidly at an alarming rate. There will be 643 million adults living with diabetes by 2030 and 783 million by 2045.² Diabetes and its complications not only seriously affect the quality of life for people but also result in a huge economic burden for individuals and countries.^{3,4} Prediabetes, an intermediate state of altered glucose metabolism between normal glucose levels and diabetes, indicates an increased risk of developing type 2 diabetes and related complications in the future.^{5,6} According to the definition of the American

Diabetes Association, it is defined as a condition of elevated blood sugar that has not yet reached the clinical diagnostic criteria.⁷ In recent decades, the prevalence of prediabetes has also risen globally. There will be an estimated 370 million adults with impaired fasting glucose (IFG) in 2030, and an estimated 441 million adults are projected to have IFG in 2045.² Considering that abnormal glucose metabolism is a major challenge across the globe, it is important to identify risk factors associated with abnormal glucose metabolism.

In addition to the traditional risk factors (such as obesity and dyslipidemia) that could cause abnormal glucose metabolism, traumatic injury may also be a potential risk factor.^{8–10} Traumatic injury, defined as physical injury caused by an external force, is one of the leading causes of death and disability, accounting for more than five million deaths annually.^{11–13} Exposure to potentially traumatic events is common.¹⁴ Approximately 70% of individuals suffer from traumatic experiences at least once in their lifetime, and these experiences may increase adverse health outcomes.^{15,16} Emerging data indicate that traumatic injury plays an important role in the development of chronic disease.¹⁷ For example, combat-related traumatic injury is associated with an increased prevalence of metabolic syndrome (MetS) and arterial stiffness.¹⁸ Childhood physical abuse increases the risk of MetS and the number of MetS symptoms increases as the severity of abuse increases.¹⁹ Some studies indicate that a history of physical trauma exposure is associated with higher risks of type 2 diabetes, cardiovascular disease, and all-cause mortality.^{20–24} In the absence of studies with longer follow-up periods, evidence revealed that the deregulation of glucose metabolism in burn injury survivors may persist up to three years post-injury.^{25–27} However, these existing studies mainly estimated the health consequences of a specific period or populations who underwent common trauma, including disaster, childhood/adolescence physical abuse, burn injury, etc., rather than traumatic injury among general people. What's more, data on the long-term risk of developing abnormal glucose metabolism among the general population have been lacking.

In preventive settings, long-term risks have been preferable by clinicians and patients for risk communication and estimation over short-term risks.²⁸ It is a highly worthwhile question to explore that whether traumatic injury has long-term effects on glucose metabolism and how long the effects could be maintained. More population-based evidence is needed to explore the long-term effects of trauma on glucose metabolism. Therefore, our study aimed to investigate the association of traumatic injury with abnormal glucose metabolism among the general population based on a large prospective cohort study, so as to provide a guide to the development of public health initiatives geared toward prevention and risk reduction.

Methods

Source of Data

The Kailuan study was a population-based prospective cohort study conducted in the Kailuan community in Tangshan city, China. The participants were employees and retirees aged 18 years or older in the Kailuan community. The study design and procedure have been previously described in detail.²⁹ At baseline, 101,510 participants were recruited, underwent clinical and laboratory examinations, and completed a questionnaire interview at 11 hospitals affiliated with the Kailuan Group. Subsequent examinations occurred approximately biennially after baseline until December 31, 2019 (2008/09, 2010/11, 2012/13, 2014/15, 2016/17, and 2018/19). All the questionnaire information and health examination data were entered at a Kailuan General Hospital terminal, and an Oracle 10.2 g database was created by uploading them to a server in Kailuan General Hospital. The study was performed according to the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of the Kailuan General Hospital. All the participants agreed to take part in the study and provided written informed consent.

Study Population

Figure 1 shows the selection process for the study population. For our study, participants were eligible if they attended at least one of the four health examinations between 2006 and 2013. A total of 55,772 participants were excluded based on the following criteria: those who were without subsequent follow-up ($n = 19,796$), with a prior diagnosis of abnormal glucose metabolism before cohort entry ($n = 18,744$), with a history of traumatic injury ($n = 15,070$), with missing information on important covariates or fasting blood glucose (FBG) ($n = 1814$), and with a history of malignant tumors

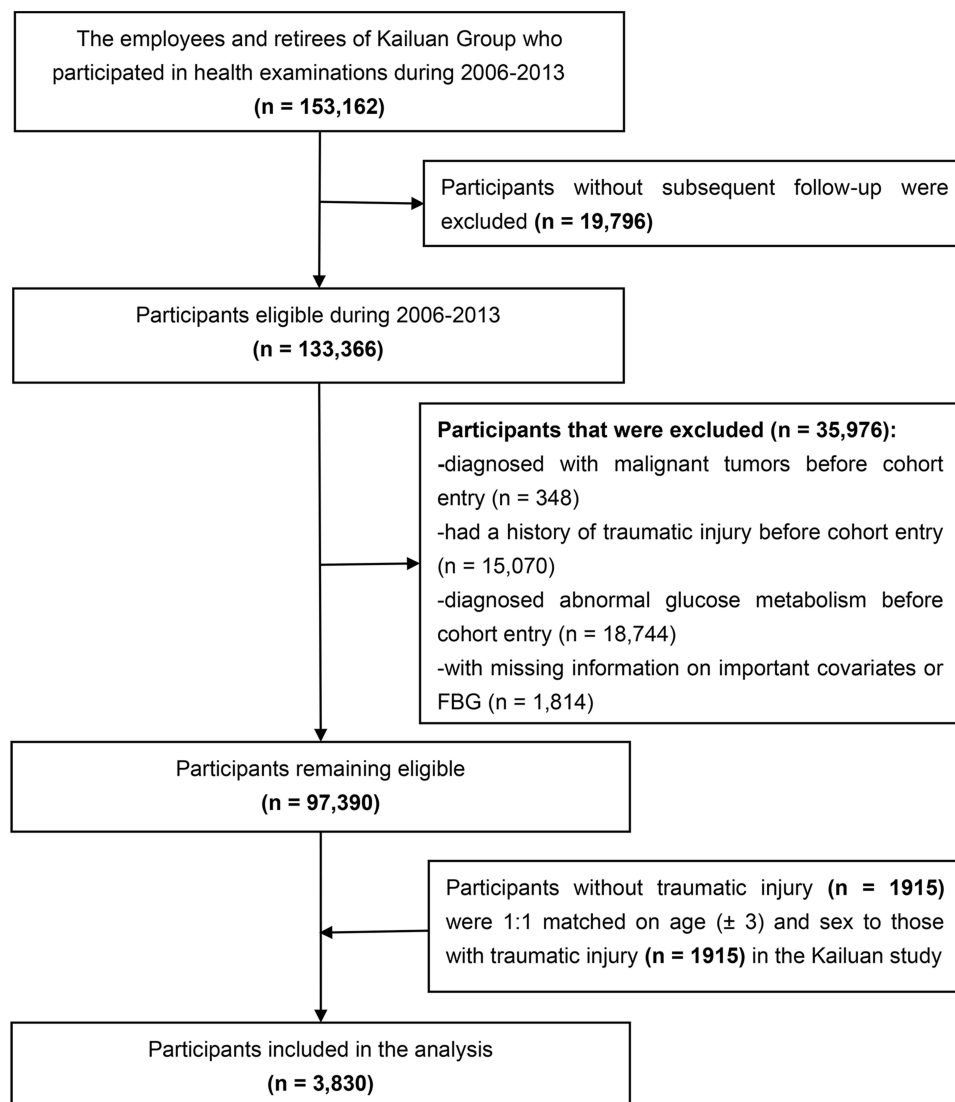


Figure 1 Flowchart of the current study.
Abbreviation: FBG, fasting blood glucose.

(n = 348). A total of 97,390 remained eligible, among which 1915 subjects had traumatic injury. The control subjects were randomly selected as the participants without traumatic injury by matching study subjects according to age (± 3 years), sex and the year of health examination at a 1:1 ratio from the Kailuan study. Ultimately, data from 1915 subjects with traumatic injury and 1915 age- and sex-matched control subjects were analyzed. The index date of the injured subject was the traumatic injury date. For each control subject, the index date was the traumatic injury date for the injured subject to which they were matched. The follow-up period started from the baseline index date. For example, if the traumatic injury was first diagnosed in a 40-year-old male participant in 2008, then a male without traumatic injury who was 37–43 years old and underwent an examination in 2008 was randomly selected from the study population, and then, both subjects were monitored since 2008.

Definition of Traumatic Injury

Traumatic injury is defined as any physical damage to the body caused by an exchange with environmental energy that is beyond the body's resilience.^{30–32} In the present study, traumatic injury was diagnosed based on ICD-10 external cause of injury codes (Codes: V01 - X59 and Y85 - Y86 [except W65 - W74 for drowning and X40 - X49 for poisoning]) by

hospital professional panel review. The diagnosis codes were ascertained from the medical records of all 11 Kailuan hospitals. The expert panel was made up of senior clinicians from the emergency department, orthopedics, and general surgery. Then, according to the injury condition, including injury characteristics, vital signs and the need of each injured person to the level of medical services at admission, the subjects with traumatic injury were categorized into 3 grades by the expert panel. Grade I (mild) injury involved skin and soft tissue injuries or distal limb closed fracture, without important body parts and organs (eg, brain, thoracic cavity, and abdominal cavity) of the patients damaged, the vital signs were stable, and the condition could not be life-threatening without treatment during a short period (such as more than a few hours, etc.). Grade II (moderate) injury was defined as damage to the important body parts or organs of the patients, for example, thoracic organ damage, abdominal organ damage, long bone fractures, multiple rib fractures, and pelvic and corresponding organ damage, and the situation was relatively stable or slowly progressive. The vital signs were relatively stable, and the condition is not life-threatening in a short period but is potentially life-threatening when the injury develops and deteriorates. Grade III (severe) injury was defined as the important body parts or organs of the patients being severely damaged, for example, severe hemorrhage (including visible external hemorrhage and internal hemorrhage caused by organ damage) or severe brain laceration. The patients had a potential death risk and if there were no effective and timely treatments, this condition would be exacerbated quickly and even become life-threatening.

Measurements and Definitions

Demographic characteristics (age, sex), lifestyle behaviors (smoking status, alcohol drinking status, physical activity), and medical history (diabetes, family history of diabetes [FHD], and hypoglycemic drugs) were collected via a standard questionnaire interview and updated every 2 years thereafter, as detailed elsewhere.²⁹ Smoking and alcohol drinking statuses were classified as “never”, “former”, or “current” according to self-reported information. Physical activity was defined as aerobic exercise ≥ 3 times/week for ≥ 30 min/session. Subjects with FHD were defined as those who had either a father, mother, brother, or sister with diabetes.³³ Weight, height, waist circumference, hip circumference, and blood pressure were measured using standard instruments and protocols by trained physicians. The body mass index (BMI) was estimated by dividing the body weight (kg) by the square of the height (m). The waist-to-hip ratio (WHR) was estimated by dividing waist circumference (WC) (cm) by hip circumference (HC) (cm).³⁴ All participants fasted for at least 8 h, and 5 mL of fasting venous blood taken from the antecubital fossa was collected into EDTA vacuum tubes at 7–9 AM on the day of the physical examination. The levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were measured using a Hitachi 7600 autoanalyzer.

Definition of Study Outcomes

In our study, the primary outcome was the development of abnormal glucose metabolism (IFG and/or diabetes). The secondary outcome was the occurrence of IFG or diabetes. Abnormal glucose metabolism events were ascertained from the Municipal Social Insurance Institution that covered all study participants, medical records of all 11 Kailuan hospitals, and a questionnaire survey (biennially since 2006). The medical records of participants in the Kailuan study are held within the Municipal Social Insurance Institution in China, and potential events of abnormal glucose metabolism before cohort entry were found by querying this institution. This is mainly to reduce self-reported recall bias. For the categorization of individuals according to the 1999 World Health Organization guidelines, individuals with FBG levels >7.0 mmol/L or treatment with hypoglycemic drugs were diagnosed with diabetes. Individuals with FBG levels of >6.0 and <7.0 mmol/L were diagnosed with prediabetes.³⁵ Of note, prediabetes is a dynamic state between normoglycemia and diabetes. Venous blood samples were collected from subjects after they had fasted for at least 8 h. Levels of fasting blood glucose were measured using enzymatic methods with a 7600–210 automatic analyzer (Hitachi, Tokyo, Japan) in a certified clinical laboratory. All subjects were monitored until the first occurrence of abnormal glucose metabolism, death, loss to follow-up, or the end of follow-up (December 31, 2019). The occurrence date of abnormal glucose metabolism was defined as the median date between the date of the test for the first report of IFG or diabetes and the date of the last test of the participant with normal fasting glucose.

Statistical Analyses

To contrast the profiles of those with traumatic injury and those without traumatic injury, descriptive statistics were used. Continuous variables are presented as the mean \pm SD, or their distribution was skewed by the median (interquartile range). Categorical variables are presented as percentages. The incidence rates (per 1000 person-years) and cumulative incidence of abnormal glucose metabolism, IFG, and diabetes among subjects with traumatic injury versus control subjects across injury severity were calculated. Relationships between exposure variables and time-to-event outcomes were explored graphically using Kaplan–Meier plots. Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of incident abnormal glucose metabolism, IFG, and diabetes among participants with traumatic injury versus control subjects and the risk of abnormal glucose metabolism across the injury severity. The proportional hazards assumption was tested graphically and by using a statistical test based on the distribution of Schoenfeld residuals.³⁶ Global tests based on Schoenfeld residuals suggested that the proportional hazards assumption was satisfied for all models ($P \geq 0.05$). Since there were few subjects with severe injury in this study, we only analyzed the risk of mild injury and moderate-severe injury. We used a structured adjustment scheme to control confounding effects of risk factors, with attention to whether these adjustments attenuated effect sizes. Specifically, Model 1 was adjusted for age and sex; Model 2 was adjusted for variables in Model 1 and FHD; Model 3 was adjusted for variables in Model 2, lifestyle behaviors (smoking and alcohol drinking status, physical activity) and WHR; and Model 4 was adjusted for variables in Model 3 and other traditional factors (SBP, DBP, TG, LDL-C, HDL-C). Considering the potential collinearity between WHR and BMI and the fact that WHR may be better correlated with body fatness and may more accurately reflect the additional risk associated with obesity, WHR was included as a covariate in model 3.³⁷ In addition, we explored the risk of abnormal glucose metabolism and subgroups for all subjects in the specified follow-up periods (1, 3, 5, and 10 years) after baseline. We used multiple imputations by chained equations to impute a missing value for covariates.³⁸

To assess the robustness of our findings, we performed several sensitivity analyses. Since there were very few subjects ($n = 0$) developed traumatic injuries during follow-up period after baseline, no analysis was performed. First, we excluded people with FHD to reduce the influence of genetic factors on our results. FHD reflects both genetic susceptibility and environmental influences shared by families and is a well-known risk factor for diabetes.³⁹ Second, to further examine the impact of competing risks of death on abnormal glucose metabolism incidence, we performed a sensitivity analysis using the Fine-Gray competing risks model.⁴⁰ All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC) and RStudio (Version 1.4.1103).

Results

Baseline Characteristics

A total of 3830 eligible subjects were included in the present analysis; the mean age was 43.04 ± 9.57 years, and 82.82% were men. Descriptions of the baseline characteristics for all, control, and traumatic injury subjects are presented in [Table 1](#). When compared to the controls, subjects with traumatic injury were more likely to be more current drinkers, have a higher SBP level, and have a higher HDL-C level. The baseline characteristics of subjects according to traumatic injury severity are shown in [Supplementary Tables 1](#) and [2](#).

Association of Traumatic Injury with Abnormal Glucose Metabolism Over the Whole Follow-Up Period

During a median of 6.91 (3.57–9.41) years of follow-up, we documented 990 incident abnormal glucose metabolism events, 824 IFG events, and 337 diabetes events. The incidence rates per 1000 person-years of abnormal glucose metabolism, IFG, and diabetes among subjects with traumatic injury versus control subjects across injury severity are presented in [Table 2](#). We also graphically illustrated the relationships between traumatic injury and time-events (abnormal glucose metabolism, IFG, and diabetes) in [Supplementary Figure 1](#).

Compared with the control subjects, traumatic injury subjects had a 1.30 times (95% CI 1.14–1.47) unadjusted risk of abnormal glucose metabolism. After adjustment for age and sex, traumatic injury was associated with a 1.29-fold (95%

Table 1 Baseline Characteristics of the Subjects

Varieties	Overall (n = 3830)	Control (n = 1915)	Traumatic Injury (n = 1915)
Age, years, mean (SD)	43.04 ± 9.57	43.04 ± 9.56	43.04 ± 9.57
Male, n (%)	3172 (82.82)	1586 (82.82)	1586 (82.82)
Smoke, n (%)			
Current	1516 (39.58)	770 (40.21)	746 (38.96)
Former	180 (4.70)	76 (3.97)	104 (5.43)
Never	2134 (55.72)	1069 (55.82)	1065 (55.61)
Drink, n (%)			
Current	1418 (37.02)	689 (35.98)	729 (38.07)
Former	299 (7.81)	181 (9.45)	118 (6.16)
Never	2113 (55.17)	1045 (54.57)	1068 (55.77)
Physical activity, n (%)			
Yes	389 (10.16)	182 (9.50)	207 (10.81)
No	3441 (89.84)	1733 (90.50)	1708 (89.29)
SBP, mmHg, mean (SD)	126.12 ± 18.50	125.31 ± 17.80	126.93 ± 19.15
DBP, mmHg, mean (SD)	82.44 ± 11.20	82.53 ± 11.19	82.34 ± 11.22
TG, mmol/L, mean (SD)	1.60 ± 1.32	1.57 ± 1.24	1.63 ± 1.40
HDL-C, mmol/L, mean (SD)	1.45 (1.23–1.70)	1.43 (1.21–1.66)	1.48 (1.26–1.74)
LDL-C, mmol/L, mean (SD)	2.39 (1.89–2.85)	2.39 (1.92–2.85)	2.40 (1.85–2.85)
FBG, mmol/L, mean (SD)	5.00 (4.60–5.40)	5.00 (4.62–5.40)	4.96 (4.57–5.37)
Weight, kg, mean (SD)	70.54 ± 10.82	71.06 ± 10.67	70.01 ± 10.94
BMI, kg/m ² , mean (SD)	24.76 ± 3.28	24.84 ± 3.21	24.68 ± 3.34
WC, cm, mean (SD)	86.12 ± 9.77	86.05 ± 9.79	86.19 ± 9.76
HC, cm, mean (SD)	96.78 ± 9.45	96.72 ± 9.37	96.84 ± 9.53
WHR, mean (SD)	0.89 ± 0.07	0.89 ± 0.07	0.89 ± 0.07
FHD, n (%)			
Yes	175 (4.57)	92 (4.80)	83 (4.33)
No	3655 (95.43)	1823 (95.20)	1832 (95.67)

Notes: Data are presented as mean ± SD, median (interquartile range) or percentages.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; FHD, family history of diabetes.

CI 1.14–1.47) increased risk of abnormal glucose metabolism compared with controls. The increased risk of abnormal glucose metabolism was strengthened after further adjustment for FHD, smoking, drinking, WHR, SBP, DBP, TG, LDL-C, and HDL-C (HR 1.32; 95% CI 1.16–1.49) (Table 2). Additional adjustment for other factors only slightly changed effect sizes, with the overall association remaining significant (Table 2). For different injury severities, subjects with moderate-severe injury had a higher risk for abnormal glucose metabolism, with an unadjusted HR of 1.41 (95% CI 1.16–1.72). The increased risk of abnormal glucose metabolism was attenuated after further adjustment for FHD, smoking, drinking, WHR, SBP, DBP, TG, LDL-C, and HDL-C (HR 1.33; 95% CI 1.09–1.62) (Table 2). Similar results were obtained for the subgroup analysis. There was a significant increase for all injury severities, and it was significantly higher in all but moderate-severe injuries for diabetes (Table 2).

Association Between Traumatic Injury and 1-, 3-, 5-, and 10-Year Risk of Abnormal Glucose Metabolism

Figure 2 shows the HR (95% CI) for all subjects among the postmatched subjects in each of the specified follow-up periods. The risks for abnormal glucose metabolism, IFG, and diabetes in subjects with traumatic injury were highest for the 1-year follow-up period. The HR of abnormal glucose metabolism gradually decreased as the follow-up period was extended to 3 and 5 years and then remained relatively constant for the 10-year follow-up period. The risks for abnormal glucose metabolism, IFG, and diabetes in subjects with moderate-severe injury were higher than for mild injury for the 1-year follow-up period. The gap in the HR of abnormal glucose metabolism, IFG, and diabetes decreased in all subjects

Table 2 HR (95% CI) for Incident Abnormal Glucose Metabolism, IFG, and Diabetes Among Subjects with Traumatic Injury versus Controls According to Injury Severity

Outcomes	Injury Severity	Events/Total	Rate ^a	HR (95% CI)				
				Unadjusted	Model 1	Model 2	Model 3	Model 4
Abnormal glucose metabolism	Control	454/1915	34.77	Reference	Reference	Reference	Reference	Reference
	Traumatic injury	536/1915	44.97	1.30 (1.14, 1.47)	1.29 (1.14, 1.47)	1.29 (1.14, 1.47)	1.29 (1.14, 1.46)	1.32 (1.16, 1.49)
	Mild	405/1463	43.82	1.26 (1.10, 1.44)	1.29 (1.13, 1.48)	1.29 (1.13, 1.48)	1.29 (1.12, 1.47)	1.31 (1.15, 1.50)
	Moderate-severe	131/452	48.93	1.41 (1.16, 1.72)	1.30 (1.06, 1.58)	1.30 (1.06, 1.58)	1.29 (1.06, 1.57)	1.33 (1.09, 1.62)
IFG	Control	378/1915	28.13	Reference	Reference	Reference	Reference	Reference
	Traumatic injury	446/1915	35.87	1.28 (1.12, 1.47)	1.28 (1.11, 1.46)	1.28 (1.11, 1.46)	1.26 (1.10, 1.45)	1.29 (1.12, 1.48)
	Mild	337/1463	35.03	1.25 (1.08, 1.45)	1.28 (1.10, 1.48)	1.28 (1.10, 1.48)	1.26 (1.09, 1.46)	1.28 (1.11, 1.49)
	Moderate-severe	109/452	38.75	1.39 (1.12, 1.71)	1.28 (1.03, 1.58)	1.28 (1.03, 1.58)	1.27 (1.02, 1.57)	1.30 (1.04, 1.61)
Diabetes	Control	150/1915	10.35	Reference	Reference	Reference	Reference	Reference
	Traumatic injury	187/1915	13.68	1.33 (1.07, 1.65)	1.33 (1.07, 1.65)	1.33 (1.07, 1.65)	1.35 (1.08, 1.67)	1.37 (1.10, 1.70)
	Mild	142/1463	13.39	1.30 (1.03, 1.63)	1.34 (1.06, 1.68)	1.34 (1.06, 1.68)	1.35 (1.07, 1.70)	1.37 (1.09, 1.73)
	Moderate-severe	45/452	14.68	1.44 (1.03, 2.01)	1.31 (0.93, 1.83)	1.30 (0.93, 1.83)	1.33 (0.95, 1.87)	1.36 (0.97, 1.90)

Notes: Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and FHD. Model 3: Adjusted for age, sex, FHD, smoke, drink, physical activity, and WHR. Model 4: Adjusted for age, sex, FHD, smoke, drink, physical activity, WHR, SBP, DBP, TG, LDL-C, and HDL-C. ^aPer 1000 person-years.

Abbreviations: HR, hazard ratio; CI, confidence interval; FHD, family history of diabetes; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

across mild and moderate-severe injury as the follow-up period was lengthened, except for the diabetes risk in the 3-year follow-up period and IFG risk in the 5-year follow-up period. The diabetes risk in the 3-year follow-up period and IFG risk in the 5-year follow-up period in the subjects with moderate-severe injury were not significant.

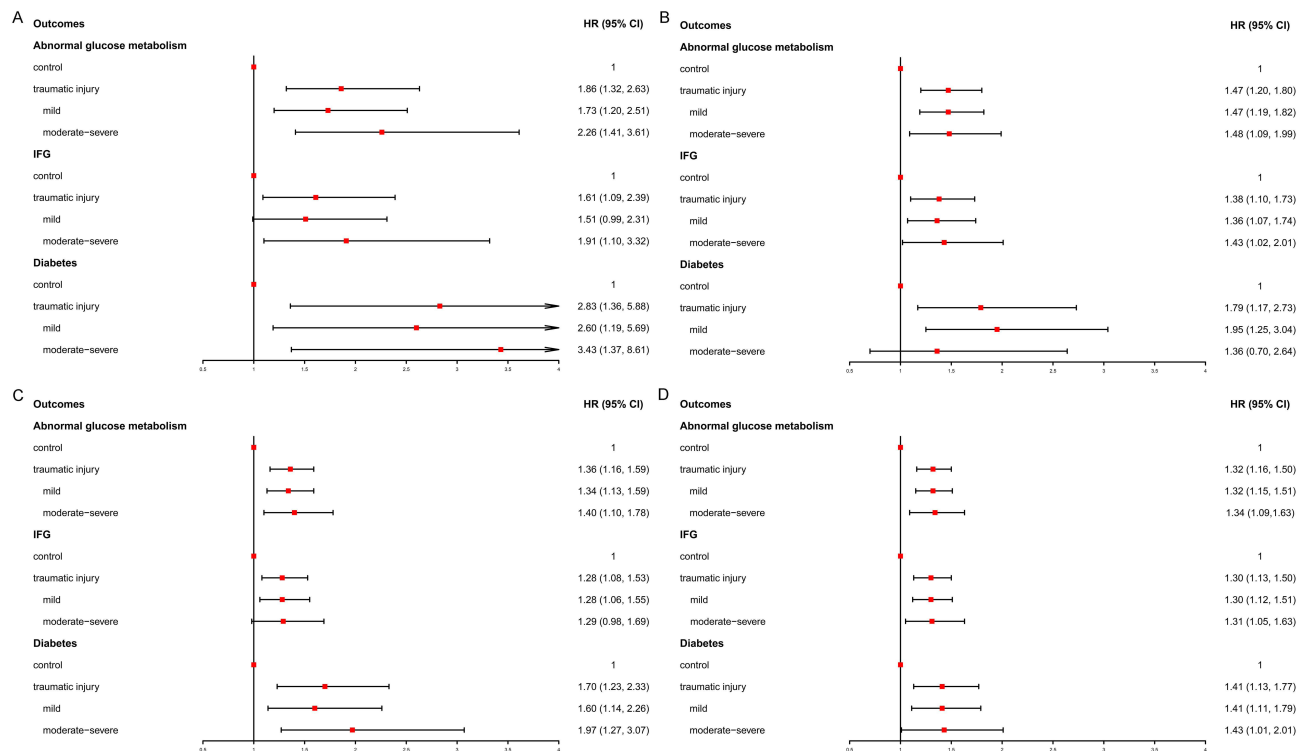


Figure 2 The forest plot for the risk of abnormal glucose metabolism, IFG, and diabetes in the matched subjects for 1 (A), 3 (B), 5 (C), and 10-year (D) follow-up periods after baseline.

Abbreviation: IFG, impaired fasting glucose.

Sensitivity Analysis

In the sensitivity analysis, after excluding subjects with FHD, the risks of abnormal glucose metabolism, IFG, and diabetes among subjects with traumatic injury versus controls remained consistent ([Supplementary Table 3](#)). The results for abnormal glucose metabolism events using Fine-Gray competing risk model are shown in [Supplementary Table 4](#). Compared with the control subjects, traumatic injury subjects had 1.26 times the unadjusted risk of abnormal glucose metabolism (95% CI 1.12–1.43). Mild (HR 1.24, 95% CI 1.09–1.42) and moderate-severe injury subjects (HR 1.34, 95% CI 1.10–1.63) were also at increased risk in the unadjusted model. The estimated risk was not significantly reduced after adjustment for either demographics (Model 1), demographics and genetics (Model 2), or demographics, genetics, and health behavior (Model 3 and Model 4). However, there was attenuation for developing IFG status in moderate-severe injury subjects after the adjusted models. The HR for traumatic injury subjects was essentially unchanged.

Discussion

In this prospective cohort study of 3830 individuals from the Kailuan study, we found an association between traumatic injury and the risk of abnormal glucose metabolism during a median follow-up of 6.91 years. Traumatic injury was also associated with IFG and diabetes. Similar results were also seen in a sensitivity analysis that excluded subjects with FHD. The risk for abnormal glucose metabolism remained elevated for the first 10 years after traumatic injury; in other words, over the follow-up period over 10 years, abnormal glucose metabolism incidence in subjects with traumatic injury remained higher than that of the control subjects, but the gap was narrowed with time.

In this study, traumatic injury was associated with an increased risk of abnormal glucose metabolism compared with control subjects. Similar results were obtained for analyzing the risk of IFG and diabetes. For the whole follow-up period, the risks of abnormal glucose metabolism, IFG, and diabetes for traumatic injury were 32%, 29%, and 37% higher, respectively. This was consistent with previous findings. In a 13-year retrospective cohort study in Taiwan, it was found that the adjusted HR for diabetes was 1.33 times higher in patients with spinal cord injury than in those without spinal cord injury.²⁰ Individuals living with traumatic brain injury are at an increased risk for developing diabetes compared to the non-injured population.⁴¹ In our study, injured subjects were more likely to be more current drinkers and have a higher SBP level. They possessed more risk factors for abnormal glucose metabolism than the controls. In addition, despite adequate control of confounding factors, there may be residual confounding factors that were not available in our study but may impact outcome events including details of the injury site and extent, post-injury social supports and psychological condition, or possibly even a combination of multiple factors.^{42,43} Furthermore, the initial effect appeared to have decreased over time. The risk of abnormal glucose metabolism for the 1-year follow-up period in the subjects with traumatic injury was nearly 86% higher than that in the control subjects and the risk of IFG and diabetes for the 1-year follow-up period in the subjects with traumatic injury was nearly 61% and 183% higher risk than in the control subjects, respectively. The risks all generally fell as the follow-up period increased. Some potentially plausible explanations of the pathophysiology underpinning the results existed. Traumatic injury could activate a series of neuroendocrine reactions with sympathetic excitation and hypothalamic–pituitary–adrenal axis secretion and cause various functional and metabolic changes after the injury factor acts on the human body.⁴⁴ By activating the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, injury causes the release of various stress hormones, such as corticosteroids, catecholamines, glucagon, and growth hormone; at the same time, the renin-angiotensin system is also activated to regulate the function and metabolism of various organs throughout the body and mobilize the body's compensatory ability to counter the damaging effects of injury-causing factors.^{45,46} On the one hand, due to the role of the neuroendocrine system, the body is generally in a catabolic state after injury, which accelerates the decomposition of sugar and increases gluconeogenesis. On the other hand, patients with traumatic injury exhibit altered sensitivity to insulin and glucose control, and symptoms may persist for months to years post-injury and may be permanent in some cases.^{47,48} A series of physiological and pathological changes immediately occur in the body during the short-term after the intense stress state. The traumatic injury condition and physiopathological changes of post-traumatic injury may also persist due to poor health conditions and care challenges. When the stimulus persists, the inflammatory process associated with the traumatic injury and the stress response can continue for a long time, sustaining the persistent

hypermetabolic state. In turn, the recovery phase is not continuous, healing is delayed because of the existence of inflammatory and stress responses, and the two can aggravate each other to form a vicious cycle.⁴⁹ Meanwhile, care and treatments could improve the impact of traumatic injury. In addition, some people after physical trauma may value their physical health more than in the past and were eager to improve their health and physical functioning by making positive personal changes. This may also be one of the potential reasons why this risk diminishes over time.

While the risks of abnormal glucose metabolism, IFG and diabetes in subjects with moderate-severe injury were higher than those with mild injury for the 1-year follow-up period, we also found that different injury severities had a similar risk for abnormal glucose metabolism and subgroups in the whole follow-up period. This may be because subjects with moderate-severe traumatic injury were older, had higher blood pressure and lower HDL cholesterol and were more likely to be drinkers, which created challenges for care and treatment. Moderate-severe injury patients were more likely to be at an increased risk of premature death than those with mild injury. It was not ignored that the small difference observed between mild and moderate-severe injuries also suggested that factors other than the injury and metabolic impact of the injury played a major role, including objective elements related to the patient's physical condition (ie, weight gain, decreased physical activity) and subjective considerations related to the patient's psychological (ie, depression), social (ie, education level), and economic status. Traumatic injury often leads to reduced physical activity levels, which could result in weight gain, depression onset, and an increased risk of chronic diseases.⁵⁰ A recent study indicated that prediabetic adults with more physical activity had a higher degree of insulin sensitivity.⁵¹ One potential reason is that injured subjects reduce their physical activity, which decreases insulin sensitivity and can lead to abnormal blood glucose. In addition, individuals with higher socioeconomic status were likely to have more positive attitudes regarding traumatic injury and self-care and better access to available health care options, which had a direct effect on health.⁵² The management of injured patients is a comprehensive process, and it is necessary to consider multiple factors. Clinical and sociodemographic factors have an impact on a patient's recognition because each individual has unique experiences in the physical, psychosocial, social and environmental domains. This results in different effects on traumatic injury management. Another potential explanation was the inability of our study to detect differences between groups, and our findings need to be confirmed in larger studies. The gap in the risks of abnormal glucose metabolism, IFG, and diabetes decreased in all subjects across mild and moderate-severe injury as the follow-up period lengthened. Our estimates may partly reflect earlier and/or more appropriate interventions for the risk management of traumatic injury and provide a reference for improving long-term outcomes.⁵³

The findings of the current study suggest that preventive measures against abnormal glucose metabolism are needed in individuals with traumatic injury. Over the past few decades, the prevalence of traumatic injury has dramatically increased.⁵³ Traumatic injury often leads to changes in the body's metabolic profile. Thus, appropriate interventions that meet the needs of individuals with traumatic injury are important for short- and long-term outcomes. Our research provides valuable implications in clinical practice for injured individual management.

In this study, an interesting note was the low levels of physical activity of the participants at baseline. A WHR of 0.9 was observed in this cohort, which may be associated with low levels of physical activity. The WHR was an important index to judge central obesity. The frequency of physical activity was associated with central obesity and was lower among those who presented an increased WHR.⁵⁴ In addition, potential for measurement error due to recall bias and discrepancies between researcher and participant definition of physical activity may explain low levels of physical activity in this cohort. A number of individual, social, cultural, environmental, and economic factors could influence physical activity levels.⁵⁵ How physical activity levels vary after trauma and the long-term effects of physical activity interventions on post-trauma glucose metabolic outcomes would require further attention.

The current study has several strengths. This is a large prospective cohort study conducted to investigate the effect of traumatic injury on abnormal glucose metabolism. Second, the Cox proportional hazard models and sensitivity analysis were performed after adjusting for important confounding factors, including WHR, smoking status, drinking status and various blood glucose metabolism-associated factors. We also analyzed the associations of traumatic injury with IFG and diabetes separately. Third, our study was based on the data of injured individuals with a median follow-up of approximately 7 years. Fourth, the entire study population was covered by the Municipal Social Insurance Institution,

the hospitals' discharge register, and biennial medical examinations, which enabled us to track the outcome events in all participants.

However, this study has several potential limitations that must be considered. First, the diagnosis of abnormal glucose metabolism was based on a single measurement of FBG rather than oral glucose tolerance testing or the measurement of hemoglobin A1c; therefore, the incidence of outcome events may be underestimated. Second, the date of occurrence of abnormal glucose metabolism was defined as the median date between the date of the test for the first report of impaired fasting blood glucose or diabetes and the date of the last test of the participant with normal fasting glucose, which slightly differed from the actual age at the occurrence. Third, this study might underestimate the number of trauma patients since very minor injuries may not seek medical care in the hospital. In addition, it involved only a relatively small sample of participants with severe injury. Fourth, we only explored the effect of baseline lifestyle, and modifications in lifestyle post-injury were not considered. The longitudinal effect of lifestyle changes in the follow-up period among individuals with traumatic injury also requires attention. Fifth, a possible methodological limitation is that matching was associated with some risk of selection bias. Matching for too many variables may lead to overmatch, which would result in a loss of statistical efficiency, introduction of bias and an increase in the number of concordant pairs. In general, when a given confounding variable was adjusted, it was also carried out for variables related to it.⁵⁶ Therefore, to avoid the risk of overmatching and maximize the number of informative pairs, we only matched for age and sex. Finally, all participants were employees and retirees of the Kailuan Group, and most of them were men; thus, the generalizability of the results is relatively limited.

Conclusion

In the present study, we observed that traumatic injury was associated with increased risks of abnormal glucose metabolism, IFG, and diabetes. The risk for abnormal glucose metabolism remained elevated for the first 10 years after traumatic injury. However, the risks of these events all decreased as the follow-up period extended. Hence, clinicians should consider short- and long-term prevention and management strategies for controlling glucose in individuals with traumatic injury.

Ethics Approval and Informed Consent

This study was approved by the ethics committees of Kailuan General Hospital. Written informed consent form was obtained from all participants.

Consent for Publication

All authors have consented to publication of this research.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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