Journal of Epidemiology and Public Health (2026), 11(02): 197-209
Master's Program in Public Health, Universitas Sebelas Maret

Original research

Open Access

Determinants of Type 2 Diabetes Mellitus among Adults in Urban and Rural Areas of Sragen Regency, Central Java, Indonesia

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Received: January 17, 2026; Accepted: March 23, 2026; Available online: April 16, 2026

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a non-communicable disease with increasing prevalence in both urban and rural areas. Differences in sociodemographic characteristics and health behaviors between urban and rural populations are suspected to influence the clinical profile and demographic characteristics of T2DM patients. This study aims to analyze differences in T2DM patient characteristics in adults in urban and rural areas of Sragen Regency, Indonesia, and identify the most dominant factors differentiating these two groups.

Subjects and Method: This was a comparative observational analytical study with a cross-sectional design conducted in six health centers in Sragen Regency representing urban and rural areas. Research subjects were adult patients with T2DM who met inclusion criteria. Variables examined included age, sex, educational level, income, occupation, and physical activity. Data were collected using structured questionnaires and medical records. Bivariate analysis was performed using the Chi-square test, while multivariate analysis used binary logistic regression.

Results: Significant differences were found between T2DM patients in urban and rural areas based on age (p=0.035), educational level (p=0.007), income (p=0.011), occupation (p=0.016), and physical activity (p=0.005). No significant difference was found in sex distribution between the two areas (p=0.078). Binary logistic regression analysis showed that physical activity was the most dominant factor differentiating T2DM patient characteristics in urban and rural areas (OR=2.326; p=0.007). Patients with low physical activity had 2.326 times higher odds of residing in urban areas compared to those with moderate or high physical activity.

Conclusion: Physical activity is the most dominant factor differentiating T2DM patient characteristics between urban and rural areas. Area-specific T2DM prevention and control strategies should prioritize physical activity improvement with approaches tailored to local community characteristics.

Keywords: type 2 diabetes mellitus, urban and rural, physical activity, health determinants.

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Cite this as:
Wandansari NE, Sukamto IS, Rahardjo SS, Cahyanto EB, Novika RGH (2026). Determinants of Type 2 Diabetes Mellitus among Adults in Urban and Rural Areas of Sragen Regency, Central Java, Indonesia. *J Epidemiol Public Health*. 11(2): 197-209. https://doi.org/10.26911/jepublichealth.2026.11.02.07.

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BACKGROUND

The global epidemiological landscape has undergone significant transition, marked by a gradual shift in disease burden from communicable to non-communicable diseases (NCDs). According to the World Health Organization (WHO), non-communicable diseases cause approximately 41 million deaths annually, representing nearly 74% of all deaths worldwide (WHO, 2022). Cardiovascular disease remains the leading cause of death with 17.9 million deaths per year, followed by cancer (9.3 million), chronic respiratory diseases (4.1 million), and diabetes mellitus with its complications, such as chronic kidney disease (2 million) (WHO, 2022). This epidemiological transition places increasing pressure on health service systems, particularly in low- and middle-income countries that still face infrastructure limitations.

Type 2 diabetes mellitus (T2DM) has become one of the most important public health challenges of the 21st century. WHO estimates that the global prevalence of diabetes mellitus will reach approximately 230 million cases, with an annual increase of about 3%, equivalent to 7 million new cases each year (WHO, 2020). In Indonesia, the number of T2DM cases has increased significantly from 8.4 million in 2000 and is projected to reach approximately 21.3 million cases by 2030 (WHO, 2020). As the type of diabetes that accounts for approximately 90% of all diabetes cases worldwide, T2DM primarily occurs in adult populations and is strongly associated with modifiable lifestyle risk factors, such as physical inactivity, unhealthy dietary patterns, and obesity (International Diabetes Federation, 2021).

At the regional level, Central Java Province recorded 635,945 residents as targets for diabetes services in 2024, with service coverage reaching 103.8% (National Institute of Health Research and Development, 2018). In Sragen Regency, 21,732 residents were diagnosed with diabetes mellitus in 2024, with standard service coverage reaching 100% (Sragen District Health Office, 2024). Although service coverage has reached the target, diabetes mellitus ranks third among the ten diseases with the highest mortality rates in hospitalized patients, with a total of 108 deaths in Sragen Regency (Sragen District Health Office, 2024). These data indicate that T2DM not only causes high morbidity and mortality but also increases the need for health services. Furthermore, T2DM is a major risk factor for life-threatening diseases such as coronary heart disease, stroke, and heart failure.

Differences in T2DM prevalence between urban and rural areas have been reported in various studies. Data in Indonesia show that of approximately 133 million Indonesian residents aged over 20 years, T2DM prevalence reaches 14.7% in urban areas, while in rural areas it is 7.2% (Statistics Indonesia, 2003). By 2030, the population in this age group is estimated to increase to approximately 194 million, so it is projected that approximately 28 million T2DM patients will be in urban areas and 13.9 million in rural areas (Statistics Indonesia, 2003). These differences can be explained through the Nutrition Transition Model proposed by Popkin (1999), which states that urbanization process drives significant lifestyle changes, including reduced physical activity, increased consumption of energy-dense foods, and higher sedentary behavior, which ultimately increases the risk of obesity and T2DM. Sragen Regency, which has 25 health centers comprising 3 urban and 22 rural health centers, is a representative area to study this phenomenon (Sragen Regency Decision, 2022). Furthermore, the health determinants

framework proposed by H.L. Blum (1974) and the Social Determinants of Health model from WHO (WHO, 2010) support the view that age, sex, educational level, income, occupation, and physical activity are factors that play a role in shaping T2DM patient characteristics in various living environments.

Although various studies have identified risk factors for T2DM, most research still focuses on disease occurrence determinants rather than comparing socio-demographic and behavioral characteristics of T2DM patients between urban and rural areas. Information regarding these differences, particularly in Sragen Regency, remains limited, thus hindering the development of T2DM prevention and control strategies tailored to each area's characteristics. Therefore, this study was conducted to analyze differences in T2DM patient characteristics between urban and rural areas in Sragen Regency, Indonesia, and identify the most dominant factor differentiating patient characteristics in these two areas.

SUBJECTS AND METHOD

1. Study design

This study was a comparative observational analytical research with a cross-sectional design. The study was conducted in six health centers in Sragen Regency, Central Java Province, consisting of three urban health centers (Karangmalang, Sragen, and Gemolong Health Centers) and three rural health centers (Sambirejo, Gondang, and Sambungmacan II Health Centers). Data collection was conducted from February to March 2026. This research design was selected because it is suitable for comparing variable characteristics or distribution between groups at a single observation time (Murti, 2020).

2. Population and sample

The target population consisted of adults diagnosed with T2DM living in urban and rural areas of Sragen Regency. The source population consisted of patients receiving diabetes services at six purposively selected health centers representing both geographic settings, comprising three urban and three rural health centers. Participant selection was conducted using a two-stage sampling procedure. First, health centers were purposively selected based on the official classification established by Sragen Regency Government. Second, eligible participants were recruited sequentially until the required sample size was achieved. A total of 200 adult T2DM patients were included, with approximately 33-34 participants recruited from each health center to ensure balanced representation between urban and rural populations. Study inclusion criteria were T2DM adult patients aged ≥18 years, patients receiving health services at one of the selected health centers, ability to read and write, and willingness to be research subjects. Exclusion criteria were patients with other types of diabetes (type 1, other types, gestational diabetes) and diabetic patients with emergency conditions.

3. Study variables

The dependent variable in this study was residential area of T2DM patients, categorized into urban and rural areas based on the official classification of health center service areas established by Sragen Regency Government. Individual-level independent variables included age, sex, income, occupation, education, and physical activity. These variables were selected based on health determinants theory and previous epidemiological research showing their association with T2DM and possible differences between urban and rural populations.

4. Operational definition of variables

Type 2 diabetes mellitus (T2DM) was defined as a diagnosis of T2DM confirmed by a physician and documented in the patient's medical record.

Age was defined as the respondent's age at the time of data collection and was categorized into younger adults (18–44 years) and older adults (45–59 years).

Sex was defined as the respondent's biological sex and was categorized as male or female.

Educational level was defined as the highest level of formal education completed by the respondent and was categorized as ≤ senior high school and > senior high school.

Monthly income was defined as the total household income received per month and was categorized as below the Sragen Regency Regional Minimum Wage (< IDR 2,182,200) or at or above the Regional Minimum Wage (≥ IDR 2,182,200).

Occupation was defined as the respondent's employment status and was categorized as employed or unemployed.

Physical activity was assessed using the International Physical Activity Questionnaire–Short Form (IPAQ-SF) based on activities performed during the previous seven days and was categorized as low or moderate/high physical activity.

Residential area was defined according to the administrative catchment area of the primary healthcare center where the respondent received healthcare services and was categorized as urban or rural.

5. Instrumen Penelitian

Research data were obtained from two sources. Primary data were collected directly from respondents using structured questionnaires containing information about age, sex, educational level, income, occupation, and residential area. Physical activity was measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF), an internationally standardized and validated instrument widely used in epidemiological research (Craig et al., 2003). The IPAQ-SF measures vigorous, moderate, and walking activities during the past seven days, then calculated in MET-minutes per week and classified into low, moderate, or high categories according to IPAQ guidelines. For binary logistic regression analysis purposes, moderate and high physical activity categories were combined into one group (moderate/high) to avoid small sample sizes in each category and improve analysis stability.

Secondary data on T2DM diagnosis status based on fasting blood glucose examination results or doctor's diagnosis were obtained from patient registers and health center medical records. Variables age, sex, educational level, income, occupation, and residential area were demographic data that were factual in nature, thus not requiring validity or reliability testing (Murti, 2020). Meanwhile, physical activity was measured using IPAQ-SF that had been internationally validated and was used without modification, thus additional validity and reliability testing was not conducted (Craig et al., 2003).

6. Analisis Data

Data analysis was conducted in three stages. Univariate analysis was used to describe the frequency distribution of each research variable. Bivariate analysis was performed using Chi-square test at 95% confidence level ($p<0.05$) to identify differences in T2DM patient characteristics between urban and rural areas. Subsequently, multivariate analysis was conducted using binary logistic regression with Stata version 17 software to identify the most dominant factor differentiating T2DM patient characteristics between urban and rural areas. Analysis results were

presented in the form of Odds Ratio (OR) with 95% Confidence Interval (CI).

7. Etika Penelitian

This study was conducted in accordance with research ethics principles. Ethical approval was obtained from the Health Research Ethics Committee of RSUD dr. Soehadi Prijonegoro Sragen with Number 299/Ethics-CRSSP/III/2026. All respondents were provided with explanations regarding study objectives, procedures, benefits, and data confidentiality, and expressed their willingness to participate through written consent before data collection. The study was conducted in accordance with ethical principles for research involving human subjects.

RESULTS

1. Sample Characteristics

A total of 200 adults with type 2 diabetes mellitus (T2DM) were included, with equal representation from rural and urban areas (50.0% each). Overall, the majority of participants were older adults aged 45–59 years (67.0%), female (73.5%), had an educational level below senior high school (51.5%), earned less than the regional minimum wage (53.0%), were unemployed (52.5%), and reported low levels of physical activity (52.0%) (Table 1).

Table 1. Sample characteristics

Variables	Category	n	%
Residential Area	Rural	100	50.00
	Urban	100	50.00
Age	Young adult (18–44 years)	66	33.00
	Older adult (45–59 years)	134	67.00
Sex	Male	53	26.50
	Female	147	73.50
Educational Level	Above Senior High School (> SHS)	97	48.50
	Senior High School or below (≤ SHS)	103	51.50
Income	≥ Sragen Minimum Wage	94	47.00
	< Sragen Minimum Wage	106	53.00
Occupation	Employed	95	47.50
	Unemployed	105	52.50
Physical Activity	Moderate/High	96	48.00
	Low	104	52.00

2. Bivariate Analysis

Bivariate analysis comparing participant characteristics between rural and urban adults with T2DM revealed significant differences in age (p=0.035), educational level (p=0.007), monthly income (p=0.011), employment status (p=0.016), and physical activity (p=0.005). Compared with rural participants, those living in urban areas were more likely to be older adults, have higher educational attainment, earn at least the regional minimum wage, be employed, and report lower levels of physical activity. In contrast, no statistically significant difference was found in sex distribution between the two residential areas (p=0.078) (Table 2).

Table 2. Differences in variables between urban and rural T2DM patients

Variables	Rural		Urban		p
	n	%	n	%	
Age group					
Young adult (18–44 years old)	40	40.0	26	26.0	0.035
Older adult (45–59 years old)	60	60.0	74	74.0	
Sex					
Male	32	32.0	21	21.0	0,078
Female	68	68.0	79	79.0	
Educational Level					
>Senior high school	39	39.0	58	58.0	0,007
≤Senior high school	61	61.0	42	42.0	
Income					
≥Minimum regional wage	38	38.0	56	56.0	0,011
<Minimum regional wage	62	62.0	44	44.0	
Employment					
Employed	39	39.0	56	56.0	0,016
Unemployed	61	61.0	44	44.0	
Physical activity					
Moderate-high	58	58,0	38	38,0	0,005
Low	42	42,0	62	62,0	

3. Multivariate Analysis

Binary logistic regression analysis showed that physical activity was the most dominant factor in differentiating T2DM patient characteristics between urban and rural areas (OR = 2.326; 95% CI = 1.259-4.298; p = 0.007). T2DM patients in urban areas with low physical activity had 2.326 times higher odds of residing in urban areas compared to patients with moderate or high physical activity. In addition to physical activity, age (OR= 1.987; p= 0.042) and employment status (OR= 0.511; p = 0.030) also showed significant associations with residential area. Meanwhile, educational level (OR= 0.516; p= 0.037) and income (OR = 0.527; p= 0.039) were significantly associated with lower odds of residing in urban areas, indicating that these characteristics were more frequently found in T2DM patients living in rural areas. Conversely, sex showed no significant association with residential area (OR = 1.687; p = 0.145).

Table 3. Binary logistic regression analysis of T2DM patient characteristics by residential area

Independent variables	OR	95% CI		p
		Lower limit	Upper limit	
Age group (45–59 years old)	1.99	1.03	3.85	0.042
Sex (female)	1.69	0.84	3.41	0.145
Education (≤Senior high school)	0.52	0.27	0.96	0.037
Income (<minimum regional wage)	0.53	0.29	0.97	0.039
Occupation (unemployed)	0.51	0.28	0.94	0.030
Physical activity (low)	2.33	1.26	4.30	0.007

DISCUSSION

1. Age Differences in T2DM Patients Between Urban and Rural Areas

This study found significant differences in age distribution between T2DM patients in urban and rural areas of Sragen Regency, with a higher proportion of older adults (45-59 years) in urban areas (74%) compared to rural areas (60%). This finding is consistent with various studies showing that increasing age is one of the major risk factors for T2DM. With advancing age, progressive decline occurs in metabolic function, insulin sensitivity, and pancreatic beta-cell capacity, thus increasing susceptibility to impaired glucose tolerance (De Tata, 2014; Chandler-Laney et al., 2010).

The higher proportion of older-aged T2DM patients in urban areas is likely related to differences in lifestyle characteristics between urban and rural populations. Urban residents generally have lower levels of physical activity due to predominance of sedentary work, better-developed transportation infrastructure, and daily routines requiring less physical activity compared to rural residents (Htet et al., 2016; Chandran and Shah, 2025). Sedentary behavior accelerates accumulation of metabolic risk factors, including insulin resistance, thereby worsening the decline in metabolic function occurring from aging processes. Additionally, urbanization is associated with increased environmental stress exposure and sedentary lifestyle patterns contributing to T2DM development in older adults (Cheema et al., 2014).

These findings reinforce evidence that the relationship between age and T2DM is not solely caused by biological aging processes but is also influenced by differences in lifestyle risk factor exposure and socioeconomic conditions in different residential environments.

2. Sex Distribution Differences in T2DM Patients Between Urban and Rural Areas

This study found no significant differences in sex distribution between T2DM patients in urban and rural areas. Multivariate analysis also showed that sex had no significant association with residential area. Nevertheless, female patients dominated in both areas, constituting 79% in urban areas and 68% in rural areas. This finding indicates that T2DM patient sex distribution in Sragen Regency is relatively similar, regardless of residential area characteristics.

This study result is consistent with various studies in several countries. Research in Iran showed slightly higher T2DM prevalence in women (15.5%) compared to men (11.8%). Although T2DM prevalence in urban areas was slightly higher than rural areas (14.5% vs. 12.3%), this difference was no longer significant after controlling for other factors (Ghassab-Abdollahi et al., 2023). Similarly, a meta-analysis in Pakistan reported slightly higher T2DM prevalence in women but without statistically significant differences by sex, while urban-rural variations differed across study periods (Umar Hasan & Rehman Siddiqui, 2024). Research in West Africa also reported T2DM prevalence of 6.2% in urban and 2.5% in rural areas, but found no significant differences by sex (Issaka et al., 2023). Overall, these results indicate that environmental and lifestyle factors have greater influence on T2DM distribution than biological differences by sex.

Female patient dominance in both areas in this study likely reflects higher utilization of primary health services by women in Indonesia. Additionally, hormonal changes occurring during menopause are known to increase the risk of T2DM in

women (De Paoli et al., 2021; Ministry of Health Republic of Indonesia, 2018).

3. Educational Level Differences in T2DM Patients Between Urban and Rural Areas

This study found significant differences in educational level between T2DM patients in urban and rural areas (p=0.007). T2DM patients in urban areas more frequently had educational level above Senior High School (58%) compared to rural patients (39%). This difference likely reflects better access to educational facilities and opportunities to pursue higher education in urban areas. Conversely, rural communities still face various barriers in accessing higher education, so the proportion of population with lower educational level remains higher (WHO, 2010; Ministry of Health Republic of Indonesia, 2018).

The relationship between educational level and T2DM has been extensively demonstrated in various studies. A study in Korea showed that individuals with higher education had approximately 50% lower odds of experiencing T2DM compared to those with only basic education (OR=0.49), after controlling for age, healthy lifestyle behaviors, and obesity (Lee et al., 2024). A prospective cohort study in the Netherlands also reported that low educational level was associated with 24% increased T2DM incidence (OR=1.24), even after controlling for lifestyle, body mass index, and income (Duan et al., 2022). Other studies in Telangana (India), China, and the United States showed that rural populations tend to have lower educational levels and health literacy. These conditions limit patients' ability to understand T2DM management, receive diabetes self-management education, and participate in structured diabetes management programs (Boswell et al., 2024).

These findings indicate that health literacy improvement interventions related to T2DM need to be adapted to the educational level characteristics of communities in both urban and rural areas of Sragen Regency.

4. Income Difference in T2DM Patients between Rural and Urban Areas

This study found significant differences in income level between T2DM patients in urban and rural areas (p=0.011). T2DM patients in urban areas more frequently had income equal to or above Sragen Regency's Minimum Wage (56%) compared to rural patients (38%). This finding is consistent with Indonesian society's socioeconomic conditions, showing that urban areas offer more diverse formal employment opportunities with relatively higher income levels, while rural communities remain dependent on agriculture and informal sectors that generally have lower and less stable income (Statistics Indonesia, 2023).

WHO emphasizes that low socioeconomic status is an important risk factor for non-communicable diseases because it can limit access to health-supporting resources while increasing exposure to various behavioral risk factors (WHO, 2010). Research in the United States showed that low-income rural communities more frequently delayed or failed to obtain treatment due to cost constraints (Gaffney et al., 2022). Research in Pakistan also showed that low socioeconomic status in rural communities was associated with worse health outcomes compared to urban communities. Meanwhile, research in China showed that health disparities between urban and rural areas were largely influenced by differences in chronic disease prevalence associated with socioeconomic status, age, and quality of life (Gaffney et al., 2022).

These findings indicate that income disparities between urban and rural areas are reflected in T2DM patients' socioeconomic characteristics in Sragen Regency. Therefore, socioeconomic aspects need to be considered in developing more equitable and appropriate health service programs for community needs in each area.

5. Occupation Differences in T2DM Patients Between Urban and Rural Areas

This study found significant differences in employment status between T2DM patients in urban and rural areas. T2DM patients in urban areas had higher proportion of employed respondents (56%) compared to rural patients (39%). This finding reflects greater diversity and abundance of formal employment opportunities in urban areas, particularly in industry, commerce, and services sectors, compared to rural areas where residents' livelihoods still dominated by agriculture and informal work (Statistics Indonesia, 2023).

This research finding is consistent with Bujawati et al. (2021) findings, reporting that proportion of employed T2DM patients was higher in urban than rural areas. Higher employment rates in urban areas are also related to employment activity characteristics. Most urban work consists of sedentary activities, such as office work, desk-based positions, and commerce/service sectors, generally involving low levels of physical activity. This condition is one important risk factors for T2DM (Roglic, 2016; Indonesian Society of Endocrinology, 2021).

Conversely, high proportion of unemployed T2DM patients in rural areas (61%) may reflect different forms of vulnerability, namely lower income, limited access to health services, and dependence on agricultural work. Although agricultural work traditionally requires high physical activity, increasing agricultural mechanization has made some work activities more sedentary than before. Overall, these occupational characteristic differences indicate close relationships between employment status, physical activity, and metabolic risk in both urban and rural communities.

6. Physical Activity Differences in T2DM Patients Between Urban and Rural Areas

This study showed significant differences in physical activity levels between T2DM patients in urban and rural areas. Low physical activity was significantly more common in urban T2DM patients (62%) compared to rural patients (42%). This finding is consistent with various studies showing physical activity disparity between urban and rural populations due to more sedentary urban lifestyle, better-developed transportation infrastructure, and dominance of minimal-activity work in urban areas.

Physical activity plays an important role in glucose metabolism and insulin sensitivity. Skeletal muscle contraction during physical activity can increase glucose uptake by cells independently of insulin signaling pathways, thus helping lower blood glucose levels and improve insulin resistance (Borghouts & Keizer, 2000). Conversely, sedentary behavior promotes visceral fat accumulation, increased free fatty acid levels, and impaired insulin signaling pathways (Indonesian Society of Endocrinology, 2021). Therefore, WHO recommends moderate-intensity aerobic physical activity of at least 150 minutes per week or vigorous-intensity activity of at least 75 minutes per week as T2DM prevention and control strategies (Roglic, 2016). 2018 Basic Health Research data consistently showed T2DM prevalence was higher in individuals with low physical

activity levels (Ministry of Health Republic of Indonesia, 2018).

Htet et al. (2016) research also confirmed that urban populations tend to have lower physical activity levels compared to rural populations. Research in Indonesia showed that low physical activity was one important risk factor for T2DM, particularly in urban communities, and each increase in moderate to vigorous physical activity duration was associated with decreased diabetes odds (Kurniawan et al., 2024). Research among elderly in China also found that prevalence of physical inactivity and diabetes was higher among elderly living in urban than rural areas (Zhao et al., 2023). Overall, these findings strengthen the notion that physical activity differences between urban and rural areas represent important modifiable characteristics in T2DM patient profiles in Sragen Regency.

7. Physical Activity as the Most Dominant Differentiating Factor

Binary logistic regression analysis showed that physical activity was the most dominant factor differentiating T2DM patient characteristics between urban and rural areas in Sragen Regency, after controlling for age, sex, educational level, income, and occupation. T2DM patients with low physical activity levels had 2.326 times higher odds of living in urban areas compared to patients with moderate or high physical activity. This result is consistent with bivariate analysis showing physical activity was the variable with the most notable difference between the two areas.

Although educational level showed significant differences between urban and rural areas, it was not the most dominant factor in the multivariate model. Educational level influences T2DM risk through various intermediate pathways, such as occupation, income, and health behaviors, not directly on glucose metabolism processes. Conversely, physical activity is a behavioral determinant acting directly on metabolic processes, thus becoming a stronger differentiating factor between T2DM patient characteristics in urban and rural areas.

This finding is supported by H.L. Blum's (1974) health determinants theory, which places behavioral factors, including physical activity, as major health determinants alongside environmental factors, health services, and hereditary factors. This study's physical activity dominance reinforces the view that health behaviors have very substantial influence on metabolic health. These results also align with WHO (2022), identifying physical inactivity as one major risk factor for non-communicable diseases, as well as Bujawati et al. (2021) research reporting that low physical activity was more commonly found in T2DM patients in Indonesian urban areas.

The present study has several limitations. First, its cross-sectional design precludes the establishment of causal relationships between the study variables and the observed urban–rural differences among patients with T2DM. Second, the study was conducted in six primary health care centers within a single regency, which may limit the generalizability of the findings to other settings. Third, several potential determinants of T2DM characteristics, such as dietary habits, obesity, smoking status, duration of diabetes, and family history, were not included in the analysis. Despite these limitations, the findings demonstrated significant differences in age, educational level, monthly income, occupation, and physical activity between adults with T2DM living in urban and rural areas of Sragen Regency, while physical activity emerged as the most influential factor distinguishing the two populations. These

findings suggest that T2DM prevention and management strategies should be tailored to the sociodemographic and behavioral characteristics of each residential setting. Health promotion programs in urban areas should prioritize interventions to increase physical activity, whereas educational and community-based strategies should be strengthened in rural areas to improve diabetes prevention and self-management.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to this research, including research conception and design, data collection, data analysis and interpretation, manuscript preparation, critical review of scientific content, and approval of the final manuscript for publication.

FUNDING AND SPONSORSHIP

This study received no external funding.

ACKNOWLEDGMENTS

The researchers thank the Sragen District Health Office, all health centers at the research sites, and all respondents who participated in this study.

CONFLICT OF INTEREST

The researchers declare no conflict of interest in this study.

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