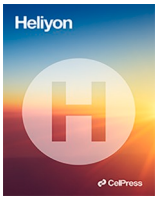
Heliyon 10 (2024) e36912

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

The effect of type 2 diabetes mellitus on lid wiper epitheliopathy and ocular surface parameters

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ARTICLE INFO

Keywords:
Lid wiper epitheliopathy
Diabetes mellitus
Partial blinking rate
Lipid layer thickness
Dry eye

ABSTRACT

Introduction: This cross-sectional study was conducted to investigate the impact of type 2 diabetes mellitus(DM) and its duration on indicators such as lid wiper epitheliopathy(LWE), and to assess the significance of LWE for early diagnosis of dry eye disease(DED) in DM patients.
Methods: A total of 137 subjects with ocular surface disease index(OSDI) score ≥13 were divided into the non-DM group, the short-term DM group (duration <5 years), and the mid-to-long-term DM group(duration ≥5 years). Evaluations were conducted for LWE, OSDI, lipid layer thickness (LLT), partial blinking rate (PBR), fluorescein tear breakup time (FTBUT), corneal fluorescein staining score (CFS), eyelid margin score, and meibomian gland dropout (MGd).
Results: The upper-LWE score and total LWE score in the mid-to-long-term group were higher than those in the non-DM group ($p = 0.008$ and $p = 0.031$, respectively). The lower-LWE scores were more severe than upper-LWE scores in the non-DM and short-term groups ($p = 0.001$ and $p = 0.045$, respectively).
The confirmed diagnosis rate of DEWSII dry eye with LWE as the primary diagnostic indicator was significantly higher than that which utilize FTBUT<5s as the primary diagnostic indicator($p < 0.05$). Compared to the non-DM group, the LLT was thinner and the MGd was more severe in the mid-to long-term group. The upper-LWE score was moderately positively correlated with the MGd, and the lower LWE score was moderately negatively correlated with LLT.
Conclusion: LWE, LLT, and MGd worsen with the progression of diabetes. Additionally, changes in LWE may precede the FTBUT, indicating that LWE could be considered as an important indicator for early diagnosis of DED in diabetic patients.

1. Introduction

The "lid wiper" is defined as the palpebral conjunctiva at the edge of the eyelid margin following the mucocutaneous junction [1,2]. The primary role of the lid wiper is like a “wind-screen wiper”, effectively distributing tears during blinking to ensure the formation of a complete tear film.

Korb et al. introduced the concept of "lid wiper epitheliopathy(LWE)"in 2002, referring to pathological changes in the epithelial layer of the lid wiper region. The development of LWE is primarily due to the increased friction between the lid wiper area and the ocular surface. While the exact mechanism of LWE formation remains unclear, common causes include corneal contact lens [3], tear

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https://doi.org/10.1016/j.heliyon.2024.e36912
Received 16 February 2024; Received in revised form 9 August 2024; Accepted 23 August 2024
Available online 26 August 2024

film abnormalities [4], blinking abnormalities [5], hyperosmolarity [6] and inflammation [7]. The symptoms of LWE are similar to those of dry eye disease(DED), and Korb's scoring method is typically used to grade the severity of LWE from grades 1 (mild) to 3 (severe) [8]. The diagnostic criteria include a staining length ≥2 mm or sagittal width ≥25 % of the lid wiper.

According to Korb and numerous studies, LWE tends to occur in the early stages of DED and correlates with the severity of dry eye [9]. However, diagnosing and treating DED in diabetes mellitus (DM) patients can be more complex, as they often present with mild symptoms but severe clinical signs [10].

Additionally, the severity of dry eye disease is related to the duration of DM [11,12] and glycosylated hemoglobin levels [13]. While research on the correlation between DM and DED is extensive, there has been less focus on LWE in DM patients. Hence, our research delves deeper into this subject. Unlike most previous studies that only concentrated on upper LWE and overlooked lower LWE [14], recent studies have highlighted a significant finding: the severity of lower LWE exceeds that of upper LWE [15]. The suspected etiology of lower LWE includes elevated tear osmolarity [6], which is more frequently observed in DM patients with dry eye. Consequently, this research investigates the variances in upper and lower LWE among DM and non-DM patients.

Moreover, clinical studies suggest that diabetes not only impairs tear film stability [16,17] and corneal epithelial barrier function [18] but also leads to abnormal blinking due to associated peripheral neuropathy and corneal hypoesthesia [19–21]. However, blinking can stimulate continuous secretion of meibum, thereby replenishing the lipid layer thickness(LLT) by squeezing the meibomian glands [22]. Diabetes may also contribute to meibomian gland dysfunction (MGD) by inhibiting the proliferation and lipid metabolism of human meibomian gland epithelial cells [23,24]. Concurrently, diabetes-induced inflammation can intensify eyelid margin hyperemia [21], potentially exacerbating LWE and perpetuating a detrimental cycle of dry eye.

This study assessed LWE and dry eye related parameters such as blink rate, partial blinking rate (PBR), fluorescein tear breakup time (FTBUT), corneal staining, eyelid margin score and meibomian gland dropout(MGd) in DM and non-DM patients. The aim was to evaluate the effects of DM and its duration on LWE and the tear film, and to further assess the significance of LWE as a diagnostic index of dry eye in DM patients.

2. Methods

2.1. Study population

This study selected 137 patients with OSDI (Ocular Surface Disease Index)scores ≥13 at Peking University First Hospital from March 2021 to December 2021. The sample size of this study was was informed by previous diabetes-related studies [12]. Patients were divided into the non-DM group, the short-term DM group (duration <5 years), and the mid-to-long-term DM (duration ≥5 years) group based on diagnosed DM and its duration.

Inclusion criteria were as follows: (1) aged between 20 and 90 years; (2) OSDI scores ≥13. Exclusion criteria were: (1) eye infections or inflammation; (2) use of eye drops other than artificial tears within 6 months; (3) use of artificial tears within 4 h prior to examination; (5) history of eye trauma or surgery; (6) corneal contact lens wear within the past year. This study was approved by the Ethics Committee of Peking University First Hospital, and informed consent was obtained from all patients. All examinations were conducted by the same ophthalmologist, and the data from the right eye were used.

2.2. Study Protocol

2.2.1. Examination of OSDI [25]

The OSDI questionnaire survey was administered under the guidance of the same physician. It comprises 12 questions, with scores ranging from 0 to 100. An OSDI score ≥13 suggests potential clinical symptoms of dry eye disease [26].

2.2.2. Examination of LLT and PBR [27,28]

Tthe LipiView I ocular interferometer (Johnson & Johnson Vision Care Inc., Santa Ana, CA) was used to conduct a 10-s examination to record the mean LLT and PBR, the latter being the ratio of incomplete to total blinks. The reliabilityof these measurements must exceed 0.80.

2.2.3. Examination of eyelid margin score [29,30]

A slit-lamp microscope was utilized to evaluate four parameters of the eyelid margin: vascular engorgement, obstructed meibomian gland orifices, displacement of the mucocutaneous junction (anterior or posterior), and lid margin irregularity. Each parameter was scored as 1 point if present and 0 if absent, with a maximum score of 4 points.

2.2.4. Examination of FTBUT [31]

Approximately 0.1 ml of physiological saline was applied to a fluorescein sodium strip (1.0 mg fluorescein sodium) (Beijing Mingxintech Development, Tianjin, China), which was then touched to the subject's lower lid conjunctiva. After blinking several times, the subject was instructed to keep their eyes open. The examiner, using a cobalt blue filter, timed the interval until the first dry spot or tear film disruption appeared, known as the FTBUT. This process was repeated thrice to calculate the average value.

2.2.5. Examination of corneal fluorescein staining score(CFS) [32]

To evaluate the CFS, the cornea was divided into four quadrants: upper, lower, temporal, and nasal, Each quadrant received a score

from 0 to 3, with the total score ranging from 0 to 12. Scoring criteria were as follows: 0 indicated no fluorescein staining; 1 indicated 1 to 30 punctate stains; 2 indicated more than 30 punctate stains without fusion; 3 indicated fused punctate staining, filamentary staining, or corneal ulceration.

2.2.6. Examination and grading of the LWE [8,33,34]

To assess LWE, a single drop of saline (approximately 0.1 mL) was used to moisten a lissamine green paper strip (Tianjin Jingming Electronic Materials, China). The moistened portion was gently applied to the inferior palpebral conjunctiva, avoiding damage to the conjunctival or lid wiper tissue. This procedure was repeated once after a 3-min interval with another new strip, during which patients were instructed to keep their eyes closed. One minute later, LWE was observed under a slit-lamp microscope at 10x magnification, and staining was graded using Korb's method. Scores were averaged between horizontal length and sagittal width, with 0.25–1.0 indicating mild LWE(Grade 1); 1.25 to 2.0 indicating moderate LWE(Grade 2); and 2.25 to 3.0 indicating severe LWE(Grade 3). Upper and lower LWE were scored separately. The grading was shown in Fig. 1.

2.2.7. Meibomian gland dropout(MGd) [35]

MGd was evaluated using a comprehensive eye surface analyzer (Oculus, Germany) to capture digital images of the meibomian glands.The MGd was assessed on a scale where 0 indicated no gland dropout, grade 1 was given for an MGd ratio of less than 1/3, grade 2 for a ratio of 1/3 to 2/3, and grade 3 for a ratio of >2/3. Both upper and lower eyelids were scored accordingly.

2.3. Statistical analysis

Statistical Analysis Data were analyzed using SPSS 25.0 software. The Kolmogorov-Smirnov test determined that the data did not follow a normal distribution, leading to the use of median and quartiles (M (Q1, Q3)) for metric variables. Categorical variables were compared using the Chi-square test, while the Mann-Whitney *U* test was applied for ordinal and continuous variables. Spearman's correlation analysis assessed the relationship between the upper and lower LWE, and the Wilcoxon signed-rank test was used to conduct paired comparison of LWE scores between the upper and lower LWE. The McNemar test evaluated differences between diagnostic criteria, with p-values <0.05 considered statistically significant.

3. Results

3.1. Demographics

The study included 137 participants: 67 without diabetes mellitus (DM) and 70 with DM, of which 42 had DM for ≤5 years, and 28 for ≥5 years. Gender distribution did not significantly differ between the non-DM group and the two groups with different durations of

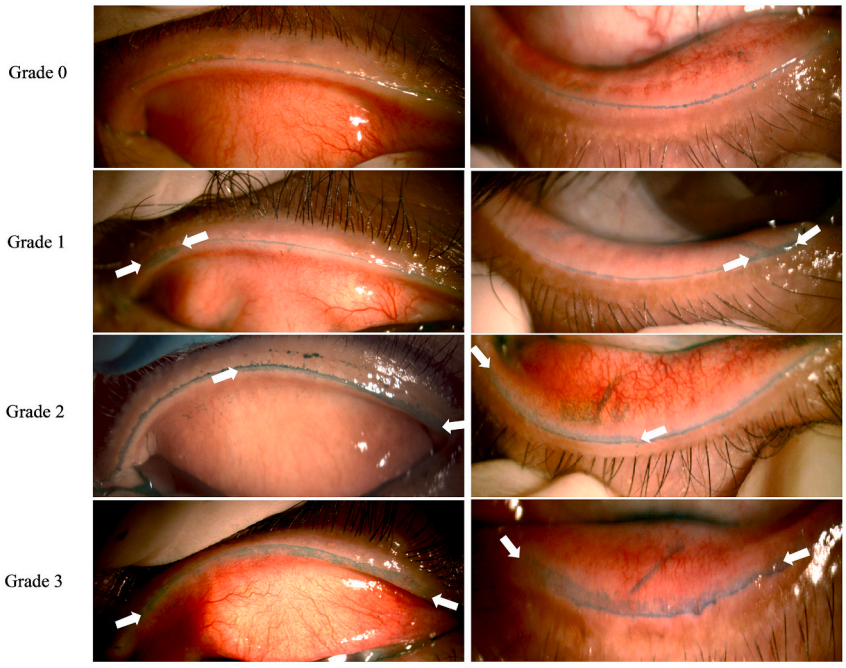

Fig. 1. The figure shows examples of LWE grading for the upper and lower LWE using Korb's method, which includes Grade 0–3. The area indicated by the white arrow represents the region stained for LWE.

DM ($\chi 2 = 1.072$, $p = 0.585$). Furthermore, there were no significant differences in age between the non-DM group and the groups with short or mid-to-long durations of DM (51.00(27.00,70.00), 58.50(50.00,65.00), 60.00(57.00,66.25), respectively, $H = 3.418$, $p = 0.181$,degree of freedom = 2).

3.2. Comparison of upper and lower LWE scores in three groups

The study revealed that the lower LWE was more severe than the upper LWE in all groups, with significant differences in the non-DM and short-term groups($Z = -3.413$, $p = 0.001$, $Z = -2.008$, $p = 0.045$,respectively) as shown in Fig. 2.

3.3. Comparison of upper LWE scores and lower LWE scores among the three groups

The difference in upper LWE scores among the three groups was statistically significant ($H = 9.585$,$p = 0.008$), with the mid-to-long-term group exhibiting more severe LWE than the non-DM group (1.50(1.00,2.00) versus 1.00(0.50,1.50),$p < 0.05$).However, no significant difference were found in lower LWE scores among the three groups ($H = 2.382$,$p = 0.304$)as shown in Fig. 2, and Table 1.

3.4. Comparison of the diagnosis rates of dry eye and LWE among the three groups

The difference in LWE diagnosis rates among the three groups was not statistically significant with rates of 91.0 %, 95.2 %, and 100 % ($p = 0.222$). Due to the lack of uniform diagnostic criteria for dry eye, the diagnosis rate was calculated using three different standards: the Chinese Dry Eye Consensus(2020) [36] (FTBUT <5s or 5s < FBUT ≤10s and positive corneal sodium fluorescein staining (CSF) (≥5 dots)), Dry Eye Workshop II(DEWSII) [14] (FTBUT <10s), and the Asia Dry Eye Society(ADES) [37] (FTBUT <5s). The difference in diagnosis rates among the groups was not statistically significant ($p = 0.763$,$p = 0.543$ and $p = 0.817$, respectively). The diagnosis rate of DEWSII with LWE as the main diagnostic index was higher than that of the Chinese Dry Eye Consensus and ADES both with FTBUT < 5s as the main diagnostic index, and the difference was statistically significant between the different groups ($p < 0.05$) as shown in Table 2.

3.5. Comparison of LLT and PBR in three groups

The LLT was thicker in the non-DM group than in the mid-to-long-term group, and the difference was statistically significant (((78.00(42.00,94.00) nm versus 53.00(34.50,63.50) nm), $p = 0.025$). The difference in PBR among the three groups was not statistically significant ($H = 4.617$, $p = 0.099$) (shown in Fig. 2 and Table 3).

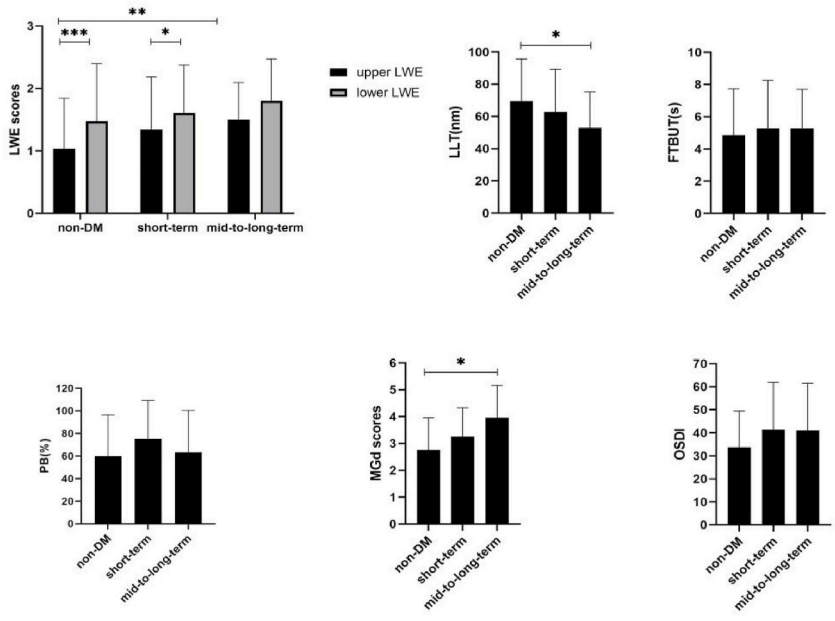

Fig. 2. The figure contains six graphs showing the differences in ocular surface parameters including upper and lower LWE, LLT, FTBUT, PB, MGd, and OSDI between the groups, as well as a comparison of the severity of upper and lower LWE. *p < 0.05; **p < 0.005; ***p ≤ 0.001.

Table 1
Comparison of upper LWE scores and lower LWE scores among the three groups.

Group	Number	upper LWE scores	lower LWE scores	Z value	*p* value
non-DM	67	1.00(0.50,1.50)	1.50(1.00,2.00)[b]	−3.413	0.001
short-term	42	1.00(1.00,2.00)	2.00(1.00,2.00)[b]	−2.008	0.045
mid-to-long-term	28	1.50(1.00,2.00)[a]	2.00(1.00,2.38)	−1.590	0.112
H value		9.585	2.382		
p value		0.008	0.304		

[a] $p < 0.05$ vs non-DM.
[b] $p < 0.05$ vs upper LWE scores.

Table 2
The diagnosis rate of LWE and the diagnosis rate of dry eye under different diagnostic criteria.

Diagnostic criteria	Non-DM(n)	Short-term(n)	mid-to-long-term(n)	*p* value
DEWSII (LWE positive)	91.0 %(61)	95.2 %(40)	100 %(28)	0.222
DEWSII (FTBUT <10s)	97.0 %(65)	92.9 %(39)	92.9 %(26)	0.763
Chinese Dry Eye Expert Consensus (FTBUT<5s or 5s < FTBUT≤10s and CSF≥5 dots)	70.1 %(47)[a]	64.3 %(27)[a]	71.4 %(20)	0.543
ADES (FTBUT < 5s)	50.8 %(34)[a]	50.0 %(21)[a]	57.1 %(16)	0.817

ADDITIONAL: In the mid-to-long-term group, due to the 100 % diagnosis rate of DEWSII (LWE), it was not possible to perform the McNemar test.
[a] $p < 0.05$ vs DEWSII (LWE positive).

3.6. Comparison of other ocular surface parameters(OSDI, FTBUT and MGd) among the three groups

The research showed the MGd was more severe in the mid-to-long-term group than in the non-DM group ($p < 0.001$). Moreover, OSDI score increased and FTBUT shortened with prolongation of diabetic disease, but there was no statistical difference among the three groups ($p = 0.150$). There was also no statistically significant difference in eyelid margin score or CFS ($p > 0.05$)(shown in Fig. 2).

In addition, there was a moderate positive correlation between the upper LWE score and the MGd ($r = 0.386$, $p < 0.001$) and a weak negative correlation between the LWE score and the LLT ($r = -0.172$, $p = 0.044$).

4. Discussion

In this study, we found that LWE was more severe and LLT was thinner in patients with mid-to-long-term DM compared to the non-DM patients. Additionally, the severity of upper LWE was correlated with the degree of meibomian gland dropout, a finding not previously reported. Furthermore, meibomian gland loss and LLT were more severe in DM patients with longer duration of the disease compared to non-DM patients.

The formation of LWE is primarily due to " tribology-related microtrauma" in the lid wiper area during blinking [38], as well as inflammation and tear film changes. Diabetes destabilizes the tear film, exacerbate the inflammation of the ocular surface and eyelids [39], increases tear osmolarity [18], and produces blinking-related abnormalities [40]. Poor quality of the lipid layer, insufficient mucin secretion, or alterations in mucin tissue structure [41] can lead to a decreased tear film, thereby aggravating LWE. Previous research indicates that tear osmolarity、 lower eyelid pressure and shear stress generated by blinking all play a very important role in the pathology of lower LWE [6,42], which could explain why our study found a more severe degree of lower LWE than upper LWE both in DM-patients with short-term duration and non-DM patients. Moreover, it also has been found that diabetic patients, especially those blood glucose are poorly regulated, exhibit hyperosmolarity on the ocular surface, which produces an inflammatory cascade by activating inflammatory factors [43], thereby exacerbating LWE. However, contrary to our expectations, our study results showed that there was no significant difference in the lower LWE between the diabetes group and the control group. This may be due to the following two reasons: first, the population we included all had symptoms of dry eye, and their LWE was generally severe, so the difference was not significant; second, we only grouped the diabetic patients based on the duration of the disease without considering the blood glucose control situation. Therefore, subsequent research on LWE in DM patients can be grouped based on glycated

Table 3
Comparison of LLT and PBR among three groups.

Group	Number	LLT (nm)	PBR (%)
non-DM	67	78.00(42.00,94.00)	50.00(33.33,100.00)
short-term	42	60.50(38.75,95.50)	100.00(53.33,100.00)
mid-to-long-term	28	53.00(34.50,63.50)[a]	70.00(33.33,100.00)
H value		6.991	4.617
p value		0.030	0.099

[a] $p < 0.05$ vs non-DM.

hemoglobin levels to observe if there are more significant differences and to further explore the formation mechanism of LWE in diabetic patients.

In the current study, there was no significant correlation between DM and PB, aligning with the majority of previous studies [12]. This lack of correlation may stem from confounding factors such as age, psychological factors, and visual display terminal (VDT). Despite the scarcity of relevant studies, the altered corneal nerve sensitivity in DM patients has been linked to the occurrence of partial blinking and its frequency [44]. Therefore, investigating the blinking patterns in DM patients could be valuable for analyzing blinking-related ocular surface damage in this demographic.

Our previous study [45] and Korb's study [8] showed that LWE may precede corneal fluorescein staining and FTBUT, serving as an early indicator for early diagnosis of dry eye. This is the rationale behind the inclusion of LWE as one of the diagnostic criteria for dry eye in DWESII. In this regard, we would like to highlight the particularly crucial role of LWE in patients with DM. Moreover, our study revealed that the diagnostic rate of DEWSII dry eye, using LWE as the primary diagnostic criterion was significantly higher than that of the ADES and the Chinese Dry Eye Consensus, which used FTBUT $<$5s as the main diagnostic index. As advocates for early diagnosis and intervention in dry eye patients, we propose that LWE, as an additional indicator, may be more suitable for screening early-stage dry eye in DM patients compared to FTBUT.

Furthermore, it is interesting to note that our study found more significant changes in LWE compared to FTBUT, which is due to the fact that LWE staining is an objective staining test, which is reproducible and accurate [46], and may be more helpful in the early diagnosis of dry eye. Nonetheless, it should be noted that the detection of LWE presents certain limitations. Studies have shown that variables such as the frequency of dye instillation, the duration of the waiting period post-instillation, the frequency of eyelid eversion, and the use of different lissamine green test strips can introduce confounding factors in LWE detection [34,47,48]. Efforts should be made to minimize these variables in research studies. Additionally, the grading methods currently widely used are highly subjective, which has prompted the development of various semi-automated [49] and fully automated scoring systems [50] in recent years, with the goal of enhancing the objectivity and reproducibility of LWE assessments. Furthermore, this study did not include glycated hemoglobin measurements in diabetic patients, which is a limitation since glycated hemoglobin control is related to the ocular surface condition in DM patients. Our analysis was primarily focused on the duration of DM. Additionally, twhile this study compared FTBUT and LWE as diagnostic indicators, Non-Invasive Tear Break-Up Time (NIBUT) is also clinically relevan [51], so it is worthwhile to be analyzed. Future studies with larger participant numbers are needed to confirm our findings.

Overall, LWE, LLT, and MGd worsen with the progression of diabetes, with LWE not previously reported in DM patients. We considered this is related to tear film instability, inflammatory factors, blinking-related abnormalities, and high osmolarity. Additionally, changes in LWE may precede the FTBUT, indicating that LWE could serve as an important early diagnostic indicator for DED in diabetic patients.

Statement of ethics

For ethics approval: This study was reviewed and approved by The Ethics Committee of Peking University First Hospital with the approval number: [2021-468].

For consent: All patients provided written informed consent to participate in the study and for their data to be published.

Funding sources

This study was not supported by any sponsor or funder.

Data availability statement

All data included in this study are available upon request by contact with the corresponding author.

CRediT authorship contribution statement

Meiting Huang: Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Xiaoming Yan:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuan Gao:** Supervision, Resources, Methodology, Investigation. **Wenjing Song:** Resources, Data curation. **Yu Cheng:** Methodology, Investigation. **Luoying Xie:** Methodology, Investigation. **Yingsi Li:** Resources, Investigation. **Xuecong Zhou:** Methodology, Investigation. **Songlin Yang:** Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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