Sensor-based analysis of eye drop instillation: effects of bottle stability on instillation success

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Abstract

Proper self-administration of eye drops is essential for glaucoma management, yet many older adults struggle with technique, leading to missed doses, wasted medication, and bottle-tip contamination. We developed a bottle-mounted inertial sensing approach to quantify the motion of eye-drop instillation using three-dimensional stability metrics that extend beyond conventional planar measures. Eighty-eight healthy older adults (mean age 74.7±6.0 years) completed 18 instillation trials across standing, sitting, and supine postures, yielding 1,699 attempts. Motion data from a bottle-mounted sensor were used to define the instillation period and compute movement magnitude, directional, and trajectory-dispersion metrics, as well as bottle tilt and instillation duration. Directional metrics were calculated in four reference frames: bottle-fixed, world-vertical, principal component analysis-based, and velocity-defined. Associations of posture and reference frame with stability metrics were evaluated using generalized estimating equations, and posture-stratified logistic models tested associations between stability metrics and three instillation outcomes: drop reaching the eye, bottle-tip contamination, and single-versus multiple-drop dispensing. All reference-frame-dependent metrics differed across frames, indicating that axis definition materially affects directional and planar stability measures. Associations with instillation outcomes were posture-specific. Predictors of successful drop delivery were concentrated in the supine posture, where greater movement magnitude and dispersion were associated with lower odds of success. Multiple-drop dispensing was consistently associated with longer instillation duration across all postures and with greater total excursion in sitting and standing. In upright postures, greater bottle tilt was associated with a lower risk of bottle-tip contamination. These findings support the use of three-dimensional bottle-motion metrics for objective monitoring of eye-drop technique and highlight the importance of consistent reference-frame definition when interpreting directional stability features.

Introduction

Glaucoma is a degenerative optic nerve disease that predominantly affects older adults and can lead to irreversible blindness if left untreated [1]. Medicated eye drops are the primary treatment; however, their efficacy depends on proper self-administration. Many patients experience difficulty with correct instillation techniques, leading to inadequate drug absorption, medication waste, and potential increased periocular side effects, and eye drop bottle contamination [2–7]. Although previous research indicates that targeted patient education and training significantly improve eye drop instillation [8–11], no widely adopted standardized systems exist for training or objectively monitoring patient technique [12, 13]. Traditional evaluations of eye drop instillation technique rely on observational methods, considering factors such as the number of drops dispensed, whether the drops successfully enter the eye, and whether the bottle tip comes into contact with the eye or nearby skin [12, 14–16]. These outcomes are essential for judging performance, but they are coarse, discrete summaries of the task and can depend on rater judgment and viewing conditions. Recent studies have used inertial measurement units (IMUs) to measure upper-limb movements and fine motor skills, including pediatric hand coordination and task performance in neurorehabilitation settings [17, 18]. IMUs provide a low-cost, quantitative method for capturing movement data that can be used to quantify features important for assessing motor control and task steadiness. IMUs and other instrumented smart bottles have been employed to monitor real-world medication use. For example, Tabuchi et al. [19] developed a cloud-connected eye drop bottle sensor that detected instillation events and transmitted data to an AI-driven system for adherence monitoring. However, this method depends on the bottle reaching a fully inverted position to register an event, which may limit its ability to detect instillation attempts performed with different bottle orientations or techniques.Nishimura et al. [20] employed a deep learning model trained on IMU data from a sensor attached to the eye drop bottle to identify instillation events and their durations. Nonetheless, this approach also faces the limitation of requiring the user to position the bottle in a desired manner. Additionally, Payne et al. [21] introduced an eye drop bottle-mounted sensing system that combines IMU-based motion tracking with capacitive liquid-level sensing, enabling healthcare providers to monitor adherence and dosing behaviors remotely. However, these tools mainly focus on monitoring instillation events rather than analyzing instillation quality or the stability of bottle motion during instillation. In this study, we aim to investigate the relationship between eye drop instillation success and bottle stability during instillation. However, no studies have quantified three-dimensional (3-D) bottle stability or systematically examined its association with instillation outcomes across postures using inertial measurement units (IMUs). We utilize IMUs to objectively measure the motion (linear acceleration and angular velocity) of eyedrop bottles while participants instill eye drops in three postures (standing, sitting, and supine). Because the calculation of stability metrics is sensitive to the reference frame in which bottle motion is resolved, we compare the sensitivity of bottle stability metrics across four reference frames (a bottle-fixed frame, a frame defined by principal components analysis, a velocity-defined frame, and an inertial frame). We hypothesize that (1) stability metrics are sensitive to reference frame choice, (2) posture influences bottle stability, and (3) bottle stability is significantly related to instillation success. By establishing an objective method to quantify bottle stability during instillation and evaluating its relationship with instillation success, we aim to provide actionable insights to inform teaching eye drop instillation techniques or inform alternative approaches to glaucoma management among those with

Materials and methods

Participant Recruitment

We recruited healthy older adults from communities local to the University of Michigan from January 24, 2024 through April 25, 2024. We used the University of Michigan participant recruitment registry umhealthyresearch.org for recruitment, and we placed advertisements for study participation at local clinics, geriatric centers, and senior centers. Exclusion criteria included current prescription eye drop use, cognitive impairments such as dementia, known allergies to artificial tears, recent changes in vision, persistent eye irritation lasting more than 72 hours, and age >65 or <100 years. The study was conducted in accordance with the ethical standards of the Institutional Review Board and followed the tenets of the Declaration of Helsinki. All participants provided written informed consent, and confidentiality was strictly maintained throughout the study. This study was approved by the University of Michigan IRB (HUM00162357).

Instrumentation

The study used a single IMU (Movella DOT; Movella, Enschede, The Netherlands) secured to the base of a bottle of artificial tears (Refresh Tears, 15mL; AbbVie Inc., North Chicago, Illinois, U.S.A.) using a custom 3D-printed TPU (thermoplastic polyurethane) fitting, as shown in Fig 1. The IMU accurately captures linear acceleration (±16 g), angular velocity (±2000°/s), and magnetic field data (±8 Gauss) [22]. Orientation estimates are provided by Movella's Kalman filter core algorithm (XKFCore) [23, 24]. The IMU captured data at a sampling rate of 120 Hz.

Experimental Protocol

Data collections were conducted in a controlled lab environment to ensure consistent testing conditions. Participants completed a total of 18 eye drop instillation trials, which varied by posture (standing, sitting, or supine) and eye (left or right); each posture/eye combination was repeated three times (3 postures x 2 eyes x 3 trials = 18 total trials). The order of postures was randomized for each participant. Participants were allowed to choose their preferred hand for instillation in each trial. To aid our evaluation of eye drop instillations, we distinguished between instillation trials and attempts. We defined a trial as the time between when the participant was instructed to instill a drop into their eye and when they indicated that they felt they had successfully instilled a drop. We defined an attempt as the time between when the participant brought the bottle to their eye and tipped it to dispense a drop, and when the participant turned the bottle upright and/or moved it away from the eye. In this definition, one trial may include multiple attempts, as the participant may need several attempts to instill an eye drop successfully. Each trial was video recorded to determine eye drop instillation success. Two reviewers examined each video to count the number of drops dispensed, determine whether a drop entered the eye, and check whether the participant contaminated the bottle by touching the tip to any other surface (e.g., the ocular surface, eyelashes, or skin) for each instillation attempt. When reviewers disagreed on their video assessments, a third reviewer adjudicated to establish a gold-standard result. Study data were collected and managed using the Research Electronic Data Capture (REDCap) tool hosted at the University of Michigan. Data from each attempt to instill eye drops were recorded in REDCap.

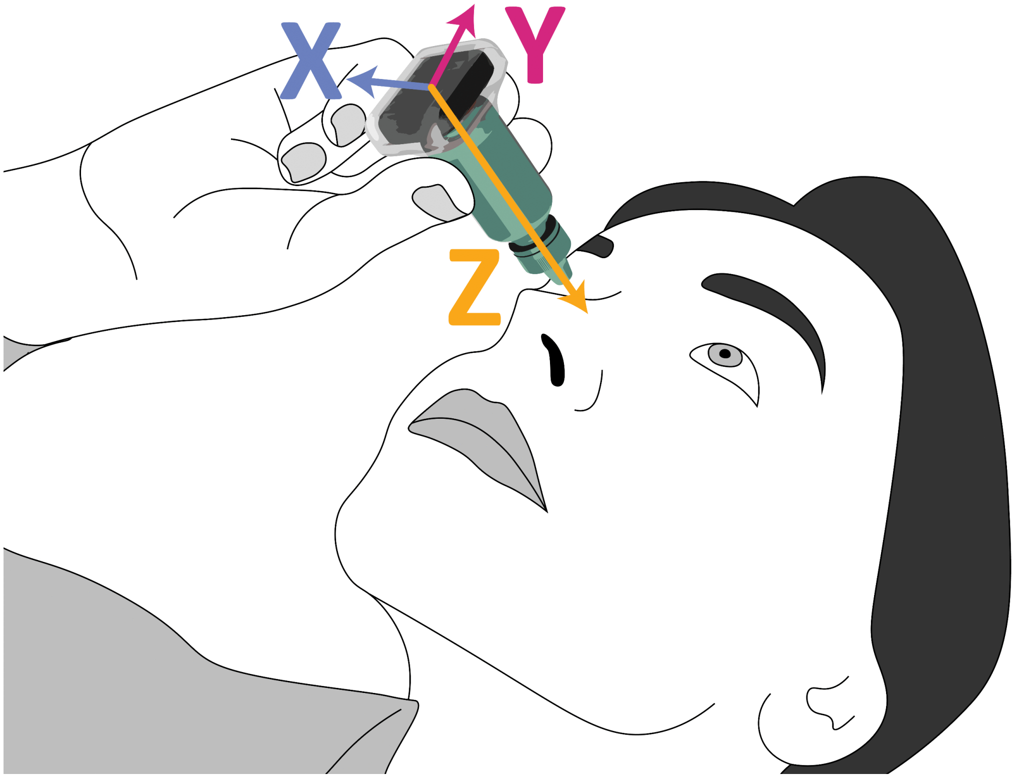

Fig 1. Eyedrop Instillation. Illustration of an eyedrop instillation showing the inertial measurement unit (IMU) mounted at the bottom of the eye drop bottle, with its local, sensor-fixed, coordinate frame. The axes represent the sensor's orientation relative to the bottle, with the Z-axis aligned with the longitudinal axis of the bottle.

Instillation Period

The raw IMU data were processed using a Zero Velocity Update (ZUPT) algorithm, which effectively corrects linear velocity and position drift in inertial navigation systems [25, 26]. Specifically, the ZUPT algorithm first uses the calculated orientation to resolve the measured linear acceleration into an inertial reference frame. Once the measured linear acceleration is expressed in an inertial frame, the gravitational component can be subtracted, yielding the free acceleration (the sensor's acceleration in an inertial frame). Starting from an initial condition of known zero velocity, defined as periods when the bottle was stationary on a table, we integrated this acceleration forward in time until the velocity again reached zero, either during instillation or when the bottle was returned to rest on the table. Zero velocity points were identified using thresholds of less than 1 m/s^2 for linear acceleration magnitude and 10 degrees/s for angular velocity magnitude. Drift caused by sensor integration was then quantified and removed, assuming linear drift from accelerometer bias. The instillation period was defined as the interval during which the bottle's linear velocity magnitude fell below 5% of its peak velocity, as previously established in reaching and pointing studies [27, 28]. The instillation period for an example attempt is illustrated in Fig 2.

Instillation Stability Metrics

The stability of the bottle during the instillation period was quantified using metrics similar to those used in postural sway analysis [29], as detailed in Table 1.

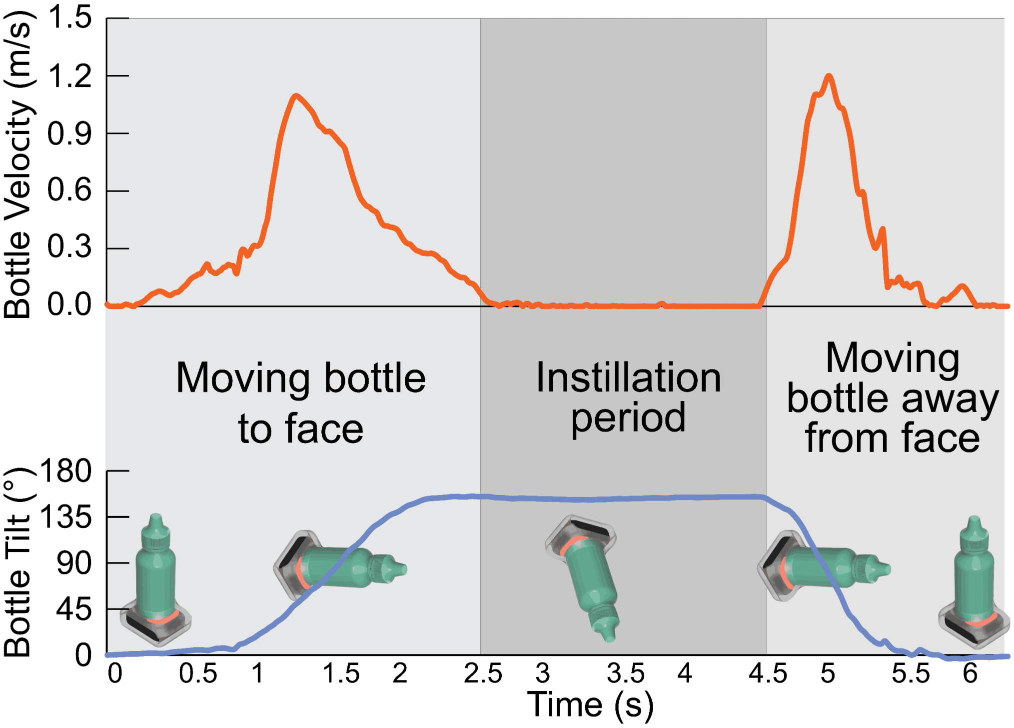

Fig 2. Instillation Period. Graphic showing the timeline of an eye drop instillation. Top: Bottle linear velocity magnitude [m/s] versus time. Bottom: Bottle tilt [degrees] versus time, where 0° indicates an upright bottle and 180° indicates a fully inverted bottle.

Importantly, whereas postural stability is often summarized using planar (2D) descriptors, we extend these sway-based measures to full three-dimensional (3D) bottle motion. This 3D formulation is central to our approach because bottle handling during instillation is not constrained to a single anatomical or laboratory plane; out-of-plane motion can occur and would be underestimated or missed by a purely 2D analysis. Accordingly, our primary stability descriptors were computed as 3D measures from the IMU free-acceleration signal (linear acceleration with the gravitational component removed). To facilitate interpretation and enable direct comparison with conventional planar/axial summaries, we also report component-wise versions of each metric: along the principal axis (Z) and within the orthogonal plane (XY), defined in each reference frame used for calculations. To quantify bottle stability, we computed summary measures of movement magnitude, excursion, smoothness, and dispersion. Movement magnitude was captured using the mean free-acceleration magnitude (MACC) and the root-mean-square free-acceleration magnitude (RACC), which reflect the overall intensity of bottle motion during an instillation attempt. Spatial excursion of the bottle's free-acceleration trajectory was quantified using total excursion (TOTEX), defined as the cumulative path length of the free-acceleration vector over the attempt, with larger values indicating greater overall variability. Movement smoothness was quantified using mean jerk magnitude (MJERK), where jerk is the time derivative of free acceleration, and higher values indicate more abrupt, less smooth handling. Timing was captured using Duration, defined as the length of the instillation attempt interval. In addition, we calculated the maximum free acceleration (amax) and the mean frequency of acceleration signals (MFREQ). Dispersion of the acceleration trajectory was characterized using geometric properties, including the 95% confidence circle and ellipse areas (AREA_{CC} and AREA_{CE}), the 95% confidence sphere and ellipsoid volumes ($\text{VOLUME}_{\text{CS}}$ and $\text{VOLUME}_{\text{CE}}$), and the acceleration trajectory area per unit time (AREA_{SW}). Finally, we quantified the mean tilt of the bottle relative to vertical by converting IMU quaternions into direction cosine matrices and computing the tilt angle with respect to the vertical axis of the inertial frame. The computed stability metrics for each participant are provided in S3 Dataset.

Table 1. Description and components of instillation stability metrics used to quantify bottle motion during instillation. Each metric characterizes different aspects of bottle stability using the free acceleration data (measured sensor linear acceleration with the gravity component removed). Metrics are computed in three dimensions (3D), within an orthogonal plane (XY), or along the principal axis (Z), depending on the context. Tilt and duration are derived from orientation and temporal data, respectively.

Stability Metric Acronym	**Description [units]**	**Components**
MACC	Mean acceleration $\left[m/s^2\right]$	3D, XY, Z
RACC	Root mean square of acceleration $\left[m/s^2\right]$	3D, XY, Z
TOTEX	Total excursions of acceleration $\left[m/s^2\right]$	3D, XY, Z
MJERK	Mean sway jerk $\left[m/s^3\right]$	3D, XY, Z
AREA_{CC}	95% confidence circle area $\left[(m/s^2)^2\right]$	XY
AREA_{CE}	95% confidence ellipse area $\left[(m/s^2)^2\right]$	XY
$\text{VOLUME}_{\text{CS}}$	95% confidence sphere volume $\left[(m/s^2)^3\right]$	3D
$\text{VOLUME}_{\text{CE}}$	95% confidence ellipsoid volume $\left[(m/s^2)^3\right]$	3D
AREA_{SW}	Area of the acceleration trajectory per unit of time $\left[m^2/s^5\right]$	XY
MFREQ	Mean frequency $[rad/s]$	3D
amax	Maximum acceleration $\left[m/s^2\right]$	3D, XY, Z
Tilt	Mean bottle tilt relative to world vertical $[degrees]$	NA
Duration	Instillation duration $[s]$	NA

In contrast to postural stability, in which the center of pressure of the body on the ground is constrained to a horizontal plane, the motion of a bottle is unconstrained, and therefore stability can be assessed in three-dimensional space. Because the bottle's movement during instillation is not equivalent in all directions, instillation stability metrics will be sensitive to the choice of reference frame.

Coordinate Frames

To analyze how different reference frames impact metrics of bottle stability during eye drop instillation, we evaluated four reference frames, as shown in Fig 3. Reference frame choice affects stability measures calculated in the XY plane (planar stability) and along the Z axis (axial stability).

The bottle-fixed frame uses the IMU's built-in reference frame, which is aligned with the sensor-fixed coordinate frame. The local Z-axis (aligned with the bottle's length) serves as the primary reference direction. We selected this reference frame because it requires no mathematical transformation of the sensor data into a new reference frame. The principal component analysis (PCA) frame provides a custom coordinate frame based on the measured linear acceleration. We analyze the acceleration data to find the three directions in which motion varies the most. The first two principal components define the plane of most movement (XY-plane), and the third (Z-axis) captures the direction of least motion. This frame is beneficial when movement does not align with traditional axes; it adapts to the data. The velocity vector frame is built from the direction of the linear bottle velocity just before the

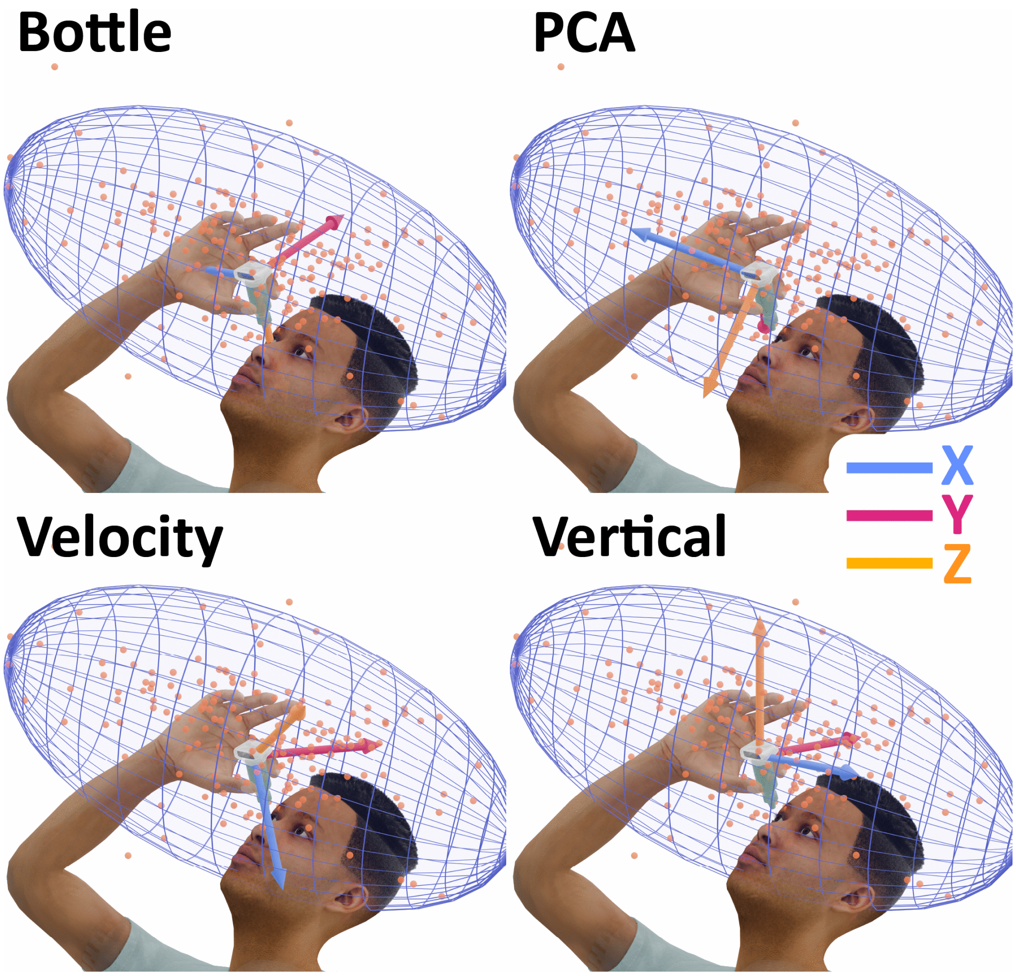

Fig 3. Illustration of the four coordinate frames used to analyze bottle motion during eye drop instillation. Each panel displays a representation of the bottle's linear acceleration cloud (orange points with 95% confidence interval ellipsoid) and principal axes (X: blue, Y: pink, Z: orange) aligned with a different coordinate frames: Bottle (sensor's local axes), PCA (data-driven axes defined by applying principal component analysis to bottle linear acceleration during the instillation period), Velocity (Z-axis aligned with the bottle's approach direction toward the eye), and Vertical (aligned with gravity, also known as an inertial frame).

instillation period, when the bottle is approaching the face. We calculate the average direction of the velocity vector and use it to define the Z-axis. The X-axis is defined by projecting a vertical vector onto a plane perpendicular to the linear velocity vector. The Y-axis is calculated so that the three axes form a right-handed frame. The details on the calculation can be found in S1 File. In the vertical frame, we resolve the measured linear acceleration and angular velocity into components in an inertial reference frame, with the positive Z-axis pointing straight up (toward the ceiling) in line with gravity. This reference frame allows us to distinguish between vertical motion (up and down) and horizontal motion.

Statistics

All statistical analyses were performed in R (version 4.5.2, including geepack [30] and emmeans [31] packages; R Foundation for Statistical Computing, Vienna, Austria) [32]. Stability metrics were categorized into two groups: 1) reference frame independent (MACC, RACC, TOTEX, MJERK, $\mathrm{VOLUME_{CE}}$, $\mathrm{VOLUME_{CS}}$, MFREQ, amax, Tilt, Duration) and 2) reference frame dependent ($\mathrm{MACC_{XY}}$, $\mathrm{MACC_{Z}}$, $\mathrm{RACC_{XY}}$, $\mathrm{RACC_{Z}}$, $\mathrm{TOTEX_{XY}}$, $\mathrm{TOTEX_{Z}}$, $\mathrm{MJERK_{XY}}$, $\mathrm{MJERK_{Z}}$, $\mathrm{AREA_{CC}}$, $\mathrm{AREA_{CE}}$, $\mathrm{AREA_{SW}}$, $\mathrm{amax_{XY}}$, $\mathrm{amax_{Z}}$). First, to assess the effects of the reference frame on bottle stability, reference frame-dependent bottle stability metrics were modeled as continuous outcomes using linear generalized estimating equation (GEE) models (identity link) with the reference frames as a categorical predictor. GEE models were used to account for the dependency of repeated trials within a participant. Overall reference-frame effects were evaluated using Wald tests, and pairwise differences between reference frames were obtained from estimated marginal means with pairwise contrasts. Marginal means provide the estimated baseline of each metric within posture, complementing pairwise contrasts by indicating the direction and relative ordering of postures. Reference frame-independent bottle stability metrics were excluded from this analysis because they are invariant to reference rotations by definition. Second, to evaluate associations between posture (Supine, Sitting, Standing) and bottle stability, separate linear GEE models were fit for each stability metric within each reference frame. Wald tests assessed overall posture effects, and pairwise posture contrasts were obtained from estimated marginal means. Separate models were fitted for each stability metric and each frame, and robust standard errors (SEs) were obtained for inference. Estimates and 95% confidence intervals (CIs) for posture were reported. Lastly, we assessed associations between eye drop instillation success outcomes (drops got in the eye [yes vs no], number of drops [one vs multiple drops], and bottle tip contamination [yes vs no]) and bottle stability metrics using GEE with a logit link (logistic regression) and an exchangeable working correlation structure to account for multiple eye drop instillation from the same participant. Separate models were fitted for each bottle stability metric, and models were stratified by posture and reference frame. Model results are reported as odds ratios (ORs) with 95% CIs. All stability predictors were z-standardized (mean 0, standard deviation 1) within posture; thus, linear model estimates or logistic model ORs reflect the change per one standard deviation increase in the predictor. To control the family-wise error rate across the many metric tests, p-values were adjusted within each outcome family using Holm's method; adjusted p-values < 0.05 were considered statistically significant. Because our goal in this study was to characterize associations between bottle-handling stability and instillation outcomes, rather than to develop a predictive model, we report (i) associations that remained statistically significant after controlling for multiple comparisons and (ii) nominal (uncorrected) associations ($p<0.05$) that did not remain significant after correction. We present these nominal findings explicitly as exploratory to show the broader pattern of potential relationships across metrics and postures and to support hypothesis generation for future confirmatory studies.

Results

A total of 88 participants were enrolled in the study, with an average age of 74.7±6.0 years (range 65-87), and 37.5% were male (n=33/88). Participants completed 1699 attempts (range 18-32 per participant) across the three postures (34.3% sitting, 33.3% standing, 32.4% supine). Across all attempts, 88.07% successfully had a drop instilled into the eye, 72.1% had only a single drop dispensed (2.0% dispensed no drops and

23.8%dispensed >1 drop), and in 59.95% of attempts, the bottle was not contaminated by touching the eye, eyelashes, or skin. Descriptive statistics for all bottle stability metrics computed in the bottle reference frame are summarized in S2 File Table 1.

Reference frame differences in stability metrics

All frame-dependent stability metrics differed significantly by reference frame (all p<0.0001). Pairwise contrasts showed consistent, directional shifts. Relative to the Bottle frame, the PCA frame produced lower XY metrics (MACC$_{\text{XY}}$: -0.29, RACC$_{\text{XY}}$: -0.33, TOTEX$_{\text{XY}}$: -0.18, MJERK$_{\text{XY}}$: -0.28, AREA$_{\text{CC}}$: -0.27, AREA$_{\text{CE}}$: -0.22, AREA$_{\text{SW}}$: -0.23, amax$_{\text{XY}}$: -0.19; all p<0.0001) and higher Z metrics (MACC$_{\text{Z}}$: +0.34, RACC$_{\text{Z}}$: +0.37, TOTEX$_{\text{Z}}$: +0.25, MJERK$_{\text{Z}}$: +0.37, amax$_{\text{Z}}$: +0.21; all p<0.0001). In contrast, the Velocity frame tended to have the opposite effect relative to Bottle, such that the Velocity frame produced higher XY metrics (MACC$_{\text{XY}}$: +0.20; RACC$_{\text{XY}}$: +0.18; TOTEX$_{\text{XY}}$: +0.06,; MJERK$_{\text{XY}}$: +0.10; AREA$_{\text{CC}}$: +0.12; AREA$_{\text{CE}}$: +0.20; AREA$_{\text{SW}}$: +0.14; amax$_{\text{XY}}$: +0.25; all p 0.0002) and lower Z metrics(MACC$_{\text{Z}}$: -0.25; RACC$_{\text{Z}}$: -0.25; TOTEX$_{\text{Z}}$: -0.09; MJERK$_{\text{Z}}$: -0.15; amax$_{\text{Z}}$: -0.32; all p 0.0013). The largest differences were typically between Velocity and PCA, with substantial separation in both the XY and Z components. Relative to the PCA frame, the Velocity frame had higher XY metrics (MACC$_{\text{XY}}$: +0.50, RACC$_{\text{XY}}$: +0.51, TOTEX$_{\text{XY}}$: +0.25, MJERK$_{\text{XY}}$: +0.38, AREA$_{\text{CC}}$: +0.39, AREA$_{\text{CE}}$: +0.42, AREA$_{\text{SW}}$: +0.38, amax$_{\text{XY}}$: +0.44; all p<0.0001) and lower Z metrics (MACC$_{\text{Z}}$: -0.59, RACC$_{\text{Z}}$: -0.61, TOTEX$_{\text{Z}}$: -0.34, MJERK$_{\text{Z}}$: -0.52, amax$_{\text{Z}}$: -0.53; all p<0.0001). Differences between Vertical and Bottle frames were generally smaller and metric-specific. Relative to the Bottle frame, the Vertical frame tended to have higher XY metrics and lower Z metrics; several were significant (MACC$_{\text{XY}}$: +0.13; RACC$_{\text{XY}}$: +0.11; AREA$_{\text{CE}}$: +0.10; AREA$_{\text{SW}}$: +0.06; amax$_{\text{XY}}$: +0.18; MACC$_{\text{Z}}$: -0.13; RACC$_{\text{Z}}$: -0.13amax$_{\text{Z}}$: -0.19; all p 0.0334), whereas others were not (TOTEX$_{\text{XY}}$: +0.02; TOTEX$_{\text{Z}}$: -0.03; MJERK$_{\text{XY}}$: +0.04; MJERK$_{\text{Z}}$: -0.05; AREA$_{\text{CC}}$: +0.05; all p>0.05). Detailed results are provided in S2 File Table 2.

Posture differences in stability metrics

For frame-independent metrics, significant differences in stability metrics by posture effects were observed for MACC (p=0.0002), RACC (p=0.0300), and Tilt (p<0.0001), while MFREQ showed borderline evidence of posture dependence (p=0.0597). Specifically, marginal means (standardized scale) indicated that standing had higher acceleration magnitudes than the other postures (MACC: supine -0.11, sitting -0.04, standing 0.13; RACC: supine -0.07, sitting -0.04, standing 0.11). Pairwise contrasts confirmed that MACC was higher in standing than in supine (estimate = +0.24, p<0.0001) and in standing than in sitting (+0.17, p=0.0007), and RACC was higher in standing than in supine (+0.17, p=0.0051) and in standing than in sitting (+0.15, p=0.0034). Tilt showed the strongest posture separation, with marginal means indicating substantially higher tilt in supine (0.59) than in sitting (-0.24) or standing (-0.30); pairwise contrasts showed sitting was lower than supine (estimate=-0.83, p<0.0001)and standing was lower than supine (-0.89, p<0.0001), while sitting and standing did not differ (standing-sitting = -0.06, p=0.3618). MFREQ marginal means were lower in standing (-0.10) than in supine (0.09) and sitting (0.06), consistent with standing being lower than supine (-0.19, p=0.0086) and lower than sitting (-0.16, p=0.0062). No overall posture effects were observed for TOTEX, VOLUME$_{\text{CE}}$, VOLUME$_{\text{CS}}$, amax, or Duration (all overall p 0.118). Detailed results are provided in S2 File Table 3. For frame-dependent metrics, posture effects were mostly evident in acceleration component measures, particularly the XY components. In the Bottle frame, marginal means again showed higher acceleration components in standing (e.g.,

$MACC_{XY}$: supine -0.11, sitting -0.03, standing 0.14; $RACC_{XY}$: supine -0.07, sitting -0.04, standing 0.11), and $MACC_{XY}$ differed by posture (overall $p=0.0002$) with standing higher than supine (+0.25, $p<0.0001$) and higher than sitting (+0.16, $p=0.0009$). Similar standing–supine differences were observed for $MACC_Z$ (supine -0.09, sitting -0.04, standing 0.12; overall $p=0.0219$; +0.20, $p=0.0009$) and $RACC_{XY}$ (overall $p=0.0359$; +0.18, $p=0.0029$). In the PCA frame, marginal means showed the same ordering (e.g., $MACC_{XY}$: supine -0.09, sitting -0.04, standing 0.13; $MACC_Z$: supine -0.12, sitting -0.03, standing 0.13), and significant differences in standing relative to supine posture were evident for $MACC_{XY}$ (overall $p=0.0025$; estimate = +0.21, $p=0.0002$), $MACC_Z$ (overall $p=0.0002$; +0.24, $p<0.0001$), and $RACC_{XY}$ (overall $p=0.0285$; +0.17, $p=0.0069$), with standing also higher than sitting for $MACC_{XY}$ (+0.17, $p=0.0006$) and $RACC_{XY}$ (+0.15, $p=0.0020$). Detailed results are provided in S2 File Table 4. In the Velocity and Vertical frames, marginal means highlighted larger posture separation for some component metrics. For example, $MACC_{XY}$ marginal means were lowest in supine (Velocity -0.22; Vertical -0.22) and highest in standing (Velocity 0.17; Vertical 0.18), consistent with significant overall posture effects (both $p<0.0001$) and standing–supine contrasts (Velocity +0.39, $p<0.0001$; Vertical +0.40, $p<0.0001$). Z-component patterns were also reflected in marginal means in these frames (e.g., Velocity $amax_Z$: supine 0.27, sitting -0.18, standing -0.07; Vertical $amax_Z$: supine 0.26, sitting -0.14, standing -0.10; both overall $p<0.0001$). In contrast, excursion metrics ($TOTEX_{XY}$ and $TOTEX_Z$) showed limited posture dependence across frames (both overall p 0.1218), with marginal means near zero and small posture separation. Detailed results are provided in S2 File Table 3 and S2 File Table 4.

Eye Drop Instillation and Stability Metrics Independent of Reference Frame

Eye drop administered in the eye (Yes vs No)

In the supine posture, higher MACC (OR = 0.57, adjusted $p=0.0001$), RACC (OR = 0.62, adjusted $p=0.0001$), MJERK (OR = 0.59, adjusted $p=0.0098$), $VOLUME_{CE}$ (OR = 0.83, adjusted $p=0.0131$), and $VOLUME_{CS}$ (OR = 0.83, adjusted $p<0.0001$) measures were associated with lower odds of successfully administering a drop into the eye (S2 File Table 5). For example, a one–standard–deviation increase in MACC corresponded to a 43% decreased odds of administering the drop into the eye. A nominal association was also observed for Tilt, such that larger tilt was associated with increased odds of the drop being administered into the eye (OR = 1.36, unadjusted $p=0.0249$). In the sitting posture, higher Tilt was associated with largely greater odds of successfully administering the drop in the eye (OR = 2.08, adjusted $p=0.0074$). A nominal association was observed for $VOLUME_{CE}$, such that larger values were associated with decreased odds of successful instillation into the eye (OR = 0.71, unadjusted $p=0.0051$). In the standing posture, no frame-independent predictors of success remained significant after p-value adjustment for multiple comparisons. However, nominal associations included increased $VOLUME_{CE}$ (OR = 0.77, unadjusted $p=0.0114$), $VOLUME_{CS}$ (OR = 0.78, unadjusted $p=0.0302$), and amax (OR = 0.78, unadjusted $p=0.0478$) associated with decreased odds of administering a drop into the eye, whereas increased Tilt (OR = 1.52, unadjusted $p=0.0185$) was associated with increased odds. Detailed results are provided in S2 File Table 5.

Number of drops (1 drop vs multiple drops [2])

Longer Duration was consistently associated with decreased odds of dispensing exactly one drop in all postures (supine OR = 0.49, adjusted p<0.0001; sitting OR = 0.50, adjusted p=0.0001; standing OR = 0.36, adjusted p<0.0001) (S2 File Table 6). For example, a one–standard deviation increase in Duration while in the standing posture corresponded to 64% lower odds of dispensing exactly one drop. Higher TOTEX was also associated with lower odds of dispensing exactly one drop while sitting (OR = 0.61, adjusted p=0.0489) or standing (OR = 0.46, adjusted p=0.0009) (S2 File Table 6). In the supine posture, TOTEX showed a nominal association (OR = 0.62, unadjusted p=0.0051). Detailed results are provided in S2 File Table 6.

Bottle tip contamination (No vs Yes)

In the sitting posture, higher Tilt was associated with a higher odds of no contamination (OR = 1.89, adjusted p = 0.0002). Higher MACC (OR = 0.63, adjusted p=0.0387), RACC (OR = 0.66, adjusted p=0.0421), and VOLUME$_{\mathrm{CS}}$ (OR = 0.55, adjusted p=0.0225) were each associated with a lower odds of no contamination (i.e., greater contamination risk). Additional nominal associations while sitting included increased MJERK (OR = 0.66, p=0.0084), VOLUME$_{\mathrm{CE}}$ (OR = 0.57, p=0.0034), and amax (OR = 0.83, p=0.0137) associated with decreased odds of contamination. In the standing posture, greater Tilt was associated with a higher odds of no contamination (OR = 1.79; adjusted $p < 0.0001$). Nominal associations included increased RACC (OR = 0.79, p=0.0465), MJERK (OR = 0.77, p=0.0291), and amax (OR = 0.82, p=0.0202) associated with decreased odds of contamination. In the supine posture, no bottle stability metrics remained significant after adjusting p-values for multiple comparisons. However, nominal associations included increased RACC (OR = 0.84, adjusted p=0.0430) associated with decreased odds of contamination and increased MFREQ (OR = 1.27, adjusted p=0.0100) associated with increased odds of contamination. Detailed results are provided in S2 File Table 7.

Eye Drop Instillation and Stability Metrics Dependent on Reference Frame

Eye drop administered in the eye (Yes vs No)

In the supine posture, higher MACC$_{\mathrm{XY}}$ was associated with lower odds of successfully administering a drop in the eye across all frames (Bottle OR = 0.59, adjusted p=0.0002; PCA OR = 0.66, adjusted p=0.0238; Velocity OR = 0.58, adjusted p=0.0001; Vertical OR = 0.56, adjusted p<0.0001). Detailed results are provided in S2 File Table 8. Additional dispersion-based metrics were also significant in the supine posture, particularly in the Bottle, Velocity, and Vertical frames, such that increased AREA$_{\mathrm{CC}}$ (Bottle OR = 0.74, adjusted p=0.0201; Velocity OR = 0.73, adjusted p=0.0057; Vertical OR = 0.71, adjusted p=0.0051), AREA$_{\mathrm{CE}}$ (Bottle OR = 0.75, adjusted p=0.0099; Velocity OR = 0.76, adjusted p=0.0131; Vertical OR = 0.72, adjusted p=0.0002), and AREA$_{\mathrm{SW}}$ (Bottle OR = 0.74, adjusted p=0.0007; Velocity OR = 0.74, adjusted p=0.0002; Vertical OR = 0.71, adjusted p=0.0002) were all similarly associated with decreased odds of administering a drop in the eye. Increases in several acceleration component metrics were also significantly associated with reduced odds of successfully getting a drop in the eye, including RACC$_{\mathrm{XY}}$ (Bottle OR = 0.62, adjusted p=0.0024; Velocity OR = 0.62, adjusted p=0.0013; Vertical OR = 0.60, adjusted p=0.0005) and RACC$_{\mathrm{Z}}$ (Bottle OR = 0.68, adjusted p=0.0148; PCA OR = 0.60, adjusted p<0.0001; Velocity OR = 0.67, adjusted p=0.0091). Jerk metrics were partly robust, such that increased MJERK$_{\mathrm{XY}}$ (Velocity OR = 0.60, adjusted p=0.0169; Vertical OR = 0.59, adjusted p=0.0333) and $\mathrm{MJERK_Z}$ (PCA OR = 0.54, adjusted p=0.0065) were associated with decreased odds of getting a drop in the eye. Several additional stability metrics were nominally associated with getting a drop successfully in the eye for the supine posture, including $\mathrm{MACC_Z}$ (Bottle OR = 0.62, unadjusted p=0.0005; Vertical OR = 0.68, unadjusted p=0.0076), $\mathrm{RACC_{XY}}$ (PCA OR = 0.70, unadjusted p=0.0010), $\mathrm{RACC_Z}$ (Vertical OR = 0.74, p=0.0034), $\mathrm{MJERK_{XY}}$ (Bottle OR = 0.62, unadjusted p=0.0006; PCA OR = 0.69, unadjusted p=0.0154), $\mathrm{MJERK_Z}$ (Bottle OR = 0.61, unadjusted p=0.0019; Velocity OR = 0.63, unadjusted p=0.0055; Vertical OR = 0.70, unadjusted p=0.0197), $\mathrm{AREA_{CC}}$ (PCA OR = 0.85, unadjusted p=0.0289), and $\mathrm{AREA_{CC}}$ (PCA OR = 0.83, unadjusted p=0.0050). All these associations showed that increases in these stability metrics (less stable) were associated with decreased odds of administering a drop into the eye. In sitting or standing postures, no frame-dependent stability metrics were significantly associated with successfully instilling a drop into the eye after adjusting p-values for multiple comparisons. However, multiple nominal associations were observed, primarily involving Z-components and dispersion metrics. When sitting, increased $\mathrm{MACC_Z}$ (Velocity OR = 0.80, unadjusted p=0.0171; Vertical OR = 0.69, unadjusted p=0.0192), $\mathrm{RACC_Z}$ (Velocity OR = 0.81, unadjusted p=0.0308; Vertical OR = 0.70, unadjusted p=0.0242), $\mathrm{TOTEX_Z}$ (Velocity OR = 0.77, unadjusted p=0.0382), $\mathrm{AREA_{CC}}$ (Bottle OR = 0.71, unadjusted p=0.0038; PCA OR = 0.76, unadjusted p=0.0209), $\mathrm{AREA_{CC}}$ (Bottle OR = 0.73, unadjusted p=0.0027; PCA OR = 0.72, unadjusted p=0.0006; Velocity OR = 0.67, unadjusted p=0.0044), and $\mathrm{AREA_{SW}}$ (Bottle OR = 0.78, unadjusted p=0.0483; PCA OR = 0.75, unadjusted p=0.0042) were all associated with reduced odds of instilling a drop into the eye. When standing, some similar nominal associations were found for $\mathrm{MACC_Z}$ (Vertical OR = 0.73, unadjusted p=0.0161), $\mathrm{RACC_Z}$ (Vertical OR = 0.73, unadjusted p=0.0150,), $\mathrm{AREA_{CC}}$ (PCA OR = 0.77, unadjusted p=0.0350), and $\mathrm{AREA_{SW}}$ (PCA OR = 0.77, unadjusted p=0.0315), but nominal associations with $\mathrm{amax_{XY}}$ were additionally observed (Bottle OR = 0.80, unadjusted p=0.0381; Velocity OR = 0.75, unadjusted p=0.0283).

Number of drops (1 drop vs multiple drops [2])

In the standing posture, higher $\mathrm{TOTEX_{XY}}$ was associated with lower odds of dispensing one drop across all frames (Bottle OR = 0.50, adjusted p=0.0128; PCA OR = 0.48, adjusted p=0.0084; Velocity OR = 0.49, adjusted p=0.0150; Vertical OR = 0.45, adjusted p=0.0021). Higher $\mathrm{TOTEX_Z}$ was similarly associated with lower odds of dispensing one drop across all frames (Bottle OR = 0.44, adjusted p=0.0076; PCA OR = 0.47, adjusted p=0.0039; Velocity OR = 0.46, adjusted p=0.0015; Vertical OR = 0.50, adjusted p=0.0180). Detailed results are provided in S2 File Table 9. In the sitting posture, frame-specific associations that remained significant after adjustment for multiple comparisons included $\mathrm{TOTEX_Z}$ in the Bottle frame (OR = 0.57, adjusted p=0.0434) and $\mathrm{TOTEX_{XY}}$ in the Vertical frame (OR = 0.59, adjusted p=0.0295). Additional nominal associations included $\mathrm{TOTEX_{XY}}$ in Bottle (OR = 0.65, unadjusted p=0.0061), PCA (OR = 0.62, unadjusted p=0.0004), and Velocity (OR = 0.61, unadjusted p=0.0030), and $\mathrm{TOTEX_Z}$ in PCA (OR = 0.62, unadjusted p=0.0057) and Velocity (OR = 0.66, unadjusted p=0.0009). In the supine posture, no stability metrics were significantly associated with dispensing one drop after adjustment for multiple comparisons. However, nominal associations were observed for excursion metrics, including $\mathrm{TOTEX_{XY}}$ in the Vertical frame (OR = 0.63, unadjusted p=0.0054) and $\mathrm{TOTEX_Z}$ in multiple frames (Bottle OR = 0.58, unadjusted p=0.0007; PCA OR = 0.63, unadjusted p=0.0020; Velocity OR = 0.62, unadjusted p=0.0020; Vertical OR = 0.62, unadjusted p=0.0059).

Bottle tip contamination (No vs Yes)

Frame-dependent stability metrics were not associated with bottle tip contamination after adjusting for multiple comparisons across posture–frame combinations. However, multiple nominal associations were observed, all indicating that increases in the given stability metrics (lower stability) were associated with reduced odds of keeping the bottle contamination-free. Detailed results are provided in S2 File Table 10. Specifically, in the supine posture, nominal associations included $\mathrm{MACC_Z}$ (Bottle OR = 0.81, unadjusted p=0.0344; Velocity OR = 0.77, unadjusted p=0.0096), $\mathrm{RACC_Z}$ (Bottle OR = 0.83, unadjusted p=0.0256; Velocity OR = 0.81, unadjusted p=0.0204), and $\mathrm{amax_Z}$ (Bottle OR = 0.87, adjusted p=0.0464; Velocity OR = 0.86, unadjusted p=0.0492). In the sitting posture, nominal associations were observed across all frames for $\mathrm{MACC_{XY}}$ (Bottle OR = 0.64, unadjusted p=0.0028; PCA OR = 0.67, unadjusted p=0.0044; Velocity OR = 0.66, unadjusted p=0.0026; Vertical OR = 0.65, unadjusted p=0.0015) and $\mathrm{RACC_{XY}}$ (Bottle OR = 0.66, unadjusted p=0.0033; PCA OR = 0.68, unadjusted p=0.0053; Velocity OR = 0.68, unadjusted p=0.0036; Vertical OR = 0.66, unadjusted p=0.0013). Nominal associations were also observed for Z-components ($\mathrm{MACC_Z}$: Bottle OR = 0.69, unadjusted p=0.0041; PCA OR = 0.65, unadjusted p=0.0019; Velocity OR = 0.79, unadjusted p=0.0239; Vertical OR = 0.73, unadjusted p=0.0150) and ($\mathrm{RACC_Z}$: Bottle OR = 0.71, unadjusted p=0.0032; PCA OR = 0.68, unadjusted p=0.0021; Velocity OR = 0.79, unadjusted p=0.0203; Vertical OR = 0.77, unadjusted p=0.0238). Further nominal associations were observed for $\mathrm{MJERK_{XY}}$ (ORs 0.66–0.68 across frames; unadjusted p=0.0080–0.0122), $\mathrm{MJERK_Z}$ (ORs 0.70–0.72 across frames; unadjusted p=0.0109–0.0290), and dispersion metrics including $\mathrm{AREA_{CC}}$ (Bottle OR = 0.60, unadjusted p=0.0015; PCA OR = 0.66, unadjusted p=0.0022; Velocity OR = 0.64, unadjusted p=0.0022; Vertical OR = 0.62, unadjusted p=0.0003), $\mathrm{AREA_{CC}}$ (ORs 0.63–0.67; unadjusted p=0.0013–0.0064), and $\mathrm{AREA_{SW}}$ (ORs 0.62–0.63; unadjusted p=0.0021–0.0066). Nominal associations were also observed for $\mathrm{amax_{XY}}$ (ORs 0.78–0.81; unadjusted p=0.0028–0.0133) and $\mathrm{amax_Z}$ (Bottle OR = 0.86, unadjusted p=0.0373). In the standing posture, nominal associations included $\mathrm{MACC_{XY}}$ (Velocity OR = 0.78, unadjusted p=0.0269), $\mathrm{MACC_Z}$ (Bottle OR = 0.75, unadjusted p=0.0204), $\mathrm{RACC_{XY}}$ (Velocity OR = 0.78, unadjusted p=0.0211), $\mathrm{RACC_Z}$ (Bottle OR = 0.75, unadjusted p=0.0177; Vertical OR = 0.79, unadjusted p=0.0368), $\mathrm{MJERK_{XY}}$ (Velocity OR = 0.79, unadjusted p=0.0225), $\mathrm{MJERK_Z}$ (Bottle OR = 0.72, unadjusted p=0.0076; PCA OR = 0.72, unadjusted p=0.0032; Vertical OR = 0.76, unadjusted p=0.0329), $\mathrm{AREA_{CC}}$ (Velocity OR = 0.80, unadjusted p=0.0253), $\mathrm{AREA_{SW}}$ (Velocity OR = 0.80, unadjusted p=0.0369), and peak acceleration metrics $\mathrm{amax_{XY}}$ (Bottle OR = 0.81, unadjusted p=0.0141; Velocity OR = 0.83, unadjusted p=0.0289; Vertical OR = 0.81, unadjusted p=0.0239) and $\mathrm{amax_Z}$ (Bottle OR = 0.82, unadjusted p=0.0405; PCA OR = 0.84, unadjusted p=0.0381).

Fig 4 summarizes all statistically significant associations (adjusted $p < 0.05$) between standardized stability metrics, and each eye drop instillation outcome across postures and reference frames. Tilt effects are reported in S2 File tables but are not plotted here because their larger ORs require a different x-axis range.

Discussion

This study first evaluated the influence of posture and reference frame on the stability metrics derived from an eye-drop bottle-mounted IMU during eye-drop instillation. Subsequently, the relationship between these stability metrics and three clinically relevant outcomes for eye drop instillation success was assessed: (1) whether a drop

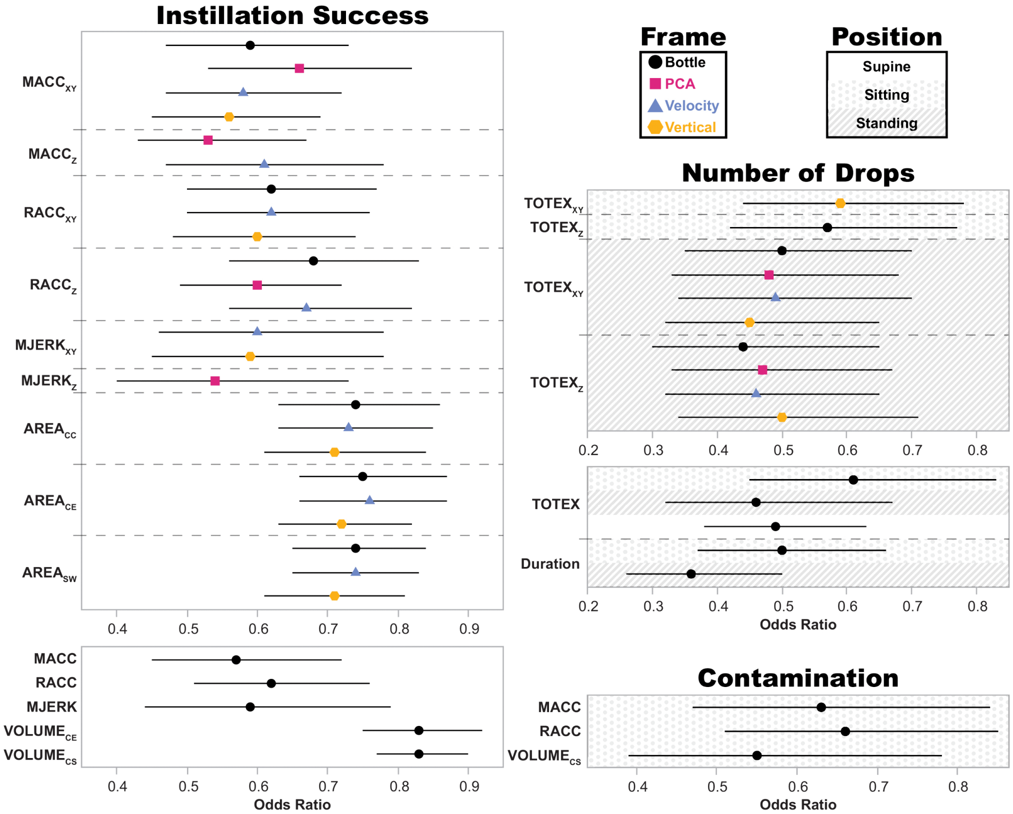

Fig 4. Significant associations between bottle stability metrics and eye drop instillation outcomes. Forest plots show odds ratios (points) and 95% confidence intervals (lines) for eye drop instillation outcomes from GEE logistic regression models relating a 1-SD increase in each stability metric. Results are stratified by posture (background shading) and, for frame-dependent metrics, by reference frame (symbols/colors: Bottle, PCA, Velocity, Vertical). Panels summarize the significant predictors of successfully administering a drop into the eye (versus not), for dispensing a single drop (versus 2 drops), and not contaminating the bottle-tip (vs touching the bottle tip to the eye, lashes, or skin). Only associations remaining significant after adjustment for multiple comparisons are displayed.

reached the eye, (2) whether a single drop was dispensed, and (3) whether the bottle tip remained uncontaminated. An operational definition of an instillation attempt was provided using bottle kinematics, specifically the interval during which the bottle's linear-velocity magnitude fell below 5% of its peak value. Two consistent patterns emerged: posture produced broad shifts in stability and orientation metrics, indicating that the biomechanical demands of the task differ substantially across supine, sitting, and standing positions; and metrics that preserve directional structure (XY/Z components, planar geometry measures, and directional maxima) were strongly affected by reference frame definition, emphasizing that component-level interpretations depend on axis specification. As the objective was to characterize associations rather than to develop a predictive model, both associations that remained significant after multiple-comparison adjustment and nominal (uncorrected) associations ($p<0.05$) are reported as exploratory findings to inform future confirmatory research.

Reference-frame effects and posture effects on stability metrics

The definition of the reference frame materially changed the values of all frame-dependent stability metrics. In particular, PCA reorientation systematically reduced XY components and increased Z components relative to the Bottle Frame, while the Velocity Frame tended to produce the opposite pattern. The largest differences were typically between Velocity and PCA Frames, indicating that component magnitudes are not directly comparable across frames without careful specification. These findings emphasize that studies reporting component-level metrics must explicitly document reference definitions. Posture effects were also evident. For frame-independent metrics, standing showed higher baseline acceleration magnitudes (less stable), whereas supine showed substantially higher tilt. MFREQ showed a corresponding shift toward lower values in standing (less stable). For frame-dependent metrics, the same posture ordering was observed across multiple acceleration components in each reference frame, whereas excursion components showed comparatively small posture separation and non-significant overall posture differences. Together, these results reinforce that posture establishes distinct baseline movement and orientation states during instillation attempts, supporting posture-aware interpretation of stability metrics and careful reporting of reference conventions whenever directional features are used.

Instillation success

Associations between stability and instillation success were strongest in the supine posture. For frame-independent metrics, greater overall movement magnitude and dispersion (less stable) were robustly linked to lower odds of success, consistent with the idea that supine instillation may be more sensitive to deviations in aim and bottle control. For example, a one standard deviation increase in MACC in supine position corresponded to a 43% decreased odds of successfully instilling a drop into the eye. This quantitative relationship highlights a potential modifiable target for both educators and device designers: training interventions or feedback strategies could be developed with the direct goal of helping users reduce their instillation MACC by one standard deviation, thereby aiming to meaningfully improve their odds of success. For frame-dependent metrics, the supine posture again dominated, and importantly, several effects were stable across reference frames. The clearest example was $\mathrm{MACC}_{\mathrm{XY}}$, which showed very similar odds ratios across all frames. This cross-frame consistency suggests that planar instability during supine instillation, as captured by $\mathrm{MACC}_{\mathrm{XY}}$, is not an artifact of a particular reference choice and could therefore also be considered a practical, modifiable target. A similar pattern held for dispersion metrics ($\mathrm{AREA}_{\mathrm{CC}}$, $\mathrm{AREA}_{\mathrm{CE}}$, and $\mathrm{AREA}_{\mathrm{SW}}$), supporting a coherent interpretation that increased planar spread and instability are associated with reduced success in the supine posture. By contrast, in sitting and standing, no frame-dependent predictors remained significant after adjustment for multiple comparisons, though multiple nominal associations appeared (e.g., Z-component and dispersion metrics), implying that any relationships between directional instability and success in upright postures are weaker, less consistent, or more confounded by factors not directly observed by bottle kinematics (e.g., eye–bottle distance control, eyelid behavior, and squeeze timing). When an association remains stable across frames with similar odds ratios, we recommend using the Bottle-Frame version for reporting. This approach is the easiest to compute and interpret because it relies solely on local axes, without additional spatial transformations. Based on the current findings, the most justifiable “core” stability indicators for supine success are MACC, RACC, MJERK, and VOLUME, as they are independent of the frame. For frame-dependent metrics, specifically in the bottle frame, where effects were consistent in direction and largely reliable across frames, we recommend $\mathrm{MACC}_{\mathrm{XY}}$ and the dispersion measures ($\mathrm{AREA}_{\mathrm{CC}}$, $\mathrm{AREA}_{\mathrm{CE}}$, and $\mathrm{AREA}_{\mathrm{SW}}$). This recommendation does not imply PCA, Velocity, and Vertical frames are invalid; rather, when the effect is not frame-specific, Bottle-frame reporting maximizes simplicity and reproducibility.

Number of drops

Dispensing multiple drops was most consistently associated with time and, secondarily, with excursion. Duration was a robust indicator across all postures. Total excursion was also associated with multi-drop dispensing in sitting and standing, consistent with longer or more unstable attempts contributing to extra drops. For frame-dependent metrics, the strongest and most consistent findings were observed in standing, where both $\mathrm{TOTEX}_{\mathrm{XY}}$ and $\mathrm{TOTEX}_{\mathrm{Z}}$ were significant after multiple comparison adjustment across all reference frames, with very similar ORs. This is a key example in which the association is not meaningfully dependent on the choice of references. In sitting, excursion effects were more frame-specific, and in supine, only nominal excursion associations were observed. Recommended metric and framework for practical multi-drop risk assessment: primarily, use Duration, which applies across all postures. Additionally, use TOTEX specifically for sitting and standing positions. Given that $\mathrm{TOTEX}_{\mathrm{XY}}$ and $\mathrm{TOTEX}_{\mathrm{Z}}$ show consistent ORs across frames, we recommend using the Bottle-frame versions for simplicity, noting that the effect is robust to frame choice in the standing posture.

Bottle-tip contamination

Contamination was most strongly aligned with technique rather than with directional stability. For frame-independent metrics, tilt was the most robust factor in upright postures, with higher tilt associated with a lower odds of contamination in both sitting and standing postures, consistent with the practical idea that a steeper bottle orientation can facilitate drop delivery while keeping the tip farther from periocular surfaces. When sitting, additional frame-independent stability and dispersion measures (MACC, RACC, and $\mathrm{VOLUME}_{\mathrm{CS}}$) were significantly associated with bottle contamination after multiple comparison adjustment, suggesting that unstable handling and spread may increase the risk of contact in that posture.
Frame-dependent metrics were not significantly associated with contamination after adjustment for multiple-comparisons. Still, many nominal associations were observed across frames, particularly in sitting (e.g., $\mathrm{MACC}_{\mathrm{XY}}$ and $\mathrm{RACC}_{\mathrm{XY}}$ were nominally associated across all frames, with similar ORs). The extent of these nominal findings is consistent with a possible relationship between directional instability and contamination, but the lack of corrected significance indicates that these signals are not yet strong enough to support firm inferences without additional confirmatory work. The recommended metric for contamination is Tilt, which applies to both sitting and standing positions. When sitting, the secondary metrics MACC, RACC, and $\mathrm{VOLUME}_{\mathrm{CS}}$ remain reliable after adjustment.

Implications for wearable sensing and feedback design

Across eye drop instillation success outcomes, the results support a step-by-step strategy for IMU-based evaluation, using frame-independent metrics as the default because they are robust to reference conventions and provide consistent signals for clinically relevant behaviors. Specifically, recommended metrics would be duration for single-drop dispensing; MACC, RACC, MJERK, and VOLUME metrics for successfully instilling a drop into the eye while in the supine posture; and Tilt to prevent contamination of the bottle in upright postures. Frame-dependent metrics should be used selectively, focusing on cases where they offer clear benefits or demonstrate consistency across frames. Two particularly useful examples are for the outcome of successfully instilling a drop into the eye while in the supine position, where planar instability or dispersion, such as $\mathrm{MACC_{XY}}$, showed consistent ORs across all frames, validating its role as a posture-specific stability indicator. For administering a single drop outcome while in the standing posture, the directional excursion components ($\mathrm{TOTEX_{XY}}$ and $\mathrm{TOTEX_{Z}}$) were significant across all frames with similar ORs, confirming their reliability for this outcome/posture combination. When the association between a metric and outcome is consistent across frames with approximately similar ORs, we recommend reporting the Bottle-frame version of that metric because it is the simplest implementation. Alternative frames (Vertical, Velocity, PCA) remain useful when the application requires interpretability relative to gravity, motion direction, or principal movement axes, but those benefits should be weighed against added processing and potential sensitivity to estimation choices.

Limitations and future directions

This work is limited by reliance on bottle-mounted kinematics alone; some determinants of performance (eye–bottle distance, head motion, eyelid aperture, and squeeze timing and force) are not directly observed and may explain why several associations were posture-specific and why many upright-posture findings were nominal rather than robust after correction. Nominal patterns, especially the broad set of frame-dependent contamination associations in sitting, should be treated as hypothesis-generating. Future work should integrate multi-sensor context (e.g., head, upper-limb kinematics, and squeeze force), confirm these associations in home settings and clinical glaucoma populations, and test whether targeted feedback focused on tilt and attempt duration can reduce multi-drop dispensing and contamination risk.

Conclusion

Bottle-mounted IMU data measuring stability showed specific associations with posture and the success of eye drop instillation. The most consistent and strong connections depended on posture: success in the supine position decreased as motion magnitude and spread increased (less stable); dispensing a single drop was associated with shorter attempt times and less movement (more stable) when in upright positions; and less risk of bottle contamination in the upright position was closely related to more bottle tilt. While some metrics based on direction and geometry were highly affected by the choice of reference frame, several relationships remained stable across different frames, suggesting they reflect real effects rather than measurement artifacts. For practical reporting and system design, these results support a core metric set that is both interpretable and implementation-friendly: frame-independent metrics (Duration, MACC, RACC, MJERK, VOLUME measures, Tilt) should serve as the default measures to assess eyedrop instillation success because they are robust to reference conventions, while frame-dependent metrics should be used selectively when they show cross-frame consistency. When effect sizes are similar across frames, the Bottle-frame implementation is the most straightforward choice; in this study, $\mathrm{MACC_{XY}}$ provided a robust planar-stability marker for successfully instilling a drop into the eye while in the supine position, and $\mathrm{TOTEX_{XY}}$ and $\mathrm{TOTEX_{Z}}$ provided robust excursion markers for single-drop administration success. Together, these findings provide a posture-aware foundation for standardized IMU-based assessment of eye drop technique and for designing targeted, objective feedback strategies.

Supporting information

S1 File. Velocity vector calculation. Supplementary methods describing the construction of the velocity-defined coordinate frame, including preprocessing of bottle velocity, identification of the pre-instillation approach interval, calculation of the mean approach direction, projection of the vertical reference vector, and assembly of the right-handed rotation matrix used to resolve bottle motion in the Velocity frame.

S2 File. Expanded results tables. Supplementary tables reporting descriptive statistics for bottle stability metrics and complete generalized estimating equation results for coordinate-frame effects, posture effects, and associations between stability metrics and eye drop instillation outcomes, including estimates, odds ratios, 95% confidence intervals, and Holm-adjusted p-values.

S3 Dataset. Computed stability metrics and analysis variables. Comma-separated values file containing the computed bottle-motion stability metrics and associated variables used in the analyses for each participant and instillation attempt.

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References

1. Ehrlich JR, Burke-Conte Z, Wittenborn JS, Saaddine J, Omura JD, Friedman DS, et al. Prevalence of Glaucoma Among US Adults in 2022. JAMA Ophthalmology. 2024 11;142(11):1046-53. doi:10.1001/JAMAOPHTHALMOL.2024.3884.

2. Abdu N, Weldemariam DG, Tesfagaber AG, Tewelde T, Tesfamariam EH. A cross-sectional study on the proper administration of eye medications and its determinants among outpatients attending Brhan Aini Ophthalmic National Referral Hospital in Asmara, Eritrea. BMJ Open. 2024 4;14(4):e084168. doi:10.1136/BMJOPEN-2024-084168.

3. Mehuys E, Delaey C, Christiaens T, Van Bortel L, Van Tongelen I, Remon JP, et al. Eye drop technique and patient-reported problems in a real-world population of eye drop users. Eye. 2020 8;34(8):1392-8. doi:10.1038/s41433-019-0665-y.

4. Gao X, Yang Q, Huang W, Chen T, Zuo C, Li X, et al. Evaluating Eye Drop Instillation Technique and Its Determinants in Glaucoma Patients. Journal of Ophthalmology. 2018 apr 8;2018:1376020. doi:10.1155/2018/1376020.

5. Schwartz GF, Hollander DA, Williams JM. Evaluation of eye drop administration technique in patients with glaucoma or ocular hypertension. Current Medical Research and Opinion. 2013 nov 1;29(11):1515-22. _eprint:

https://doi.org/10.1185/03007995.2013.833898. doi:10.1185/03007995.2013.833898.

6. Hennessy AL, Katz J, Covert D, Protzko C, Robin AL. Videotaped Evaluation of Eyedrop Instillation in Glaucoma Patients with Visual Impairment or Moderate to Severe Visual Field Loss. Ophthalmology. 2010 dec 1;117(12):2345-52. doi:10.1016/j.ophtha.2010.03.040.
7. BURNS E, MULLEY GP. Practical Problems with Eye-drops Among Elderly Ophthalmology Outpatients. Age and Ageing. 1992 may 1;21(3):168-70. doi:10.1093/ageing/21.3.168.
8. Davis SA, Carpenter DM, Blalock SJ, Budenz DL, Lee C, Muir KW, et al. A randomized controlled trial of an online educational video intervention to improve glaucoma eye drop technique. Patient Education and Counseling. 2019 may 1;102(5):937-43. doi:10.1016/j.pec.2018.12.019.
9. Gonzalez-Salinas R, Jimenez-Roman J, Lazcano-Gomez G, Castillejos A, Kahook M. Videographic Assessment of Glaucoma Drop Instillation. Journal of Current Glaucoma Practice. 2015 8;9(2):47-50. doi:10.5005/jp-journals-10008-1183.
10. Lee TE, Cho Y, Yoo HH. The effects of self-video feedback on the eyedrop instillation techniques of glaucoma patients: a prospective randomized controlled trial. International Ophthalmology. 2024;44(1):7. doi:10.1007/s10792-024-02941-0.
11. Newman-Casey PA, Weizer JS, Heisler M, Lee PP, Stein JD. Systematic Review of Educational Interventions to Improve Glaucoma Medication Adherence. Seminars in ophthalmology. 2013 5;28(3):191-201. doi:10.3109/08820538.2013.771198.
12. Davis SA, Sleath B, Carpenter DM, Blalock SJ, Muir KW, Budenz DL. Drop instillation and glaucoma. Current opinion in ophthalmology. 2018 3;29(2):171-7. doi:10.1097/ICU.0000000000000451.
13. Carpenter DM, Sayner R, Blalock SJ, Muir KW, Hartnett ME, Lawrence SD, et al. The Effect of Eye Drop Technique Education in Patients With Glaucoma. Health communication. 2016 8;31(8):1036-42. doi:10.1080/10410236.2015.1020263.
14. Tatham AJ, Sarodia U, Gatrad F, Awan A. Eye drop instillation technique in patients with glaucoma. Eye (Basingstoke). 2013 8;27(11):1293-8. Publisher: Nature Publishing Group PMID: 23970024. doi:10.1038/EYE.2013.187.
15. Gupta R, Patil B, Shah BM, Bali SJ, Mishra SK, Dada T. Evaluating Eye Drop Instillation Technique in Glaucoma Patients. Journal of Glaucoma. 2012 3;21(3):189. doi:10.1097/IJG.0b013e31820bd2e1.
16. Inter-Rater Agreement in the Assessment of Video Recordings of Eye Drop Instillation by Glaucoma Patients | PLOS One;. [Online; accessed 2026-03-09]. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0145764. Available from: `https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0145764`.
17. Bisi MC, Stagni R. Sensor-Based Quantitative Assessment of Children's Fine Motor Competence: An Instrumented Version of the Placing Bricks Test. Sensors. 2024 1;24(7):2192. Number: 7. doi:10.3390/s24072192.

18. Repnik E, Puh U, Goljar N, Munih M, Mihelj M. Using Inertial Measurement Units and Electromyography to Quantify Movement during Action Research Arm Test Execution. Sensors. 2018 9;18(9):2767. Number: 9. doi:10.3390/s18092767.

19. Tabuchi H, Nishimura K, Akada M, Ishikami T, Shirakami T, Kamiura N, et al. Real-world evaluation of novel eye drop bottle sensors: Cloud-based AI support for eye drop adherence. Heliyon. 2024 jul 30;10(14):e34167. doi:10.1016/j.heliyon.2024.e34167.

20. Nishimura K, Tabuchi H, Nakakura S, Nakatani Y, Yorihiro A, Hasegawa S, et al. Evaluation of Automatic Monitoring of Instillation Adherence Using Eye Dropper Bottle Sensor and Deep Learning in Patients With Glaucoma. Translational Vision Science & Technology. 2019 jun 27;8(3):55. doi:10.1167/tvst.8.3.55.

21. Payne N, Gangwani R, Barton K, Sample AP, Cain SM, Burke DT, et al. Medication Adherence and Liquid Level Tracking System for Healthcare Provider Feedback. Sensors (Basel, Switzerland). 2020 apr 24;20(8):2435. doi:10.3390/s20082435.

22. Xsens. Xsens DOT User Manual; 2022. https://www.xsens.com/hubfs/Downloads/Manuals/Xsens%20DOT%20User%20Manual. Available from: `https://www.xsens.com/hubfs/Downloads/Manuals/Xsens%20DOT%20User%20Manual.pdf`.

23. Paulich M, Schepers M, Rudigkeit N, Bellusci G. Xsens MTw Awinda: Miniature Wireless Inertial-Magnetic Motion Tracker for Highly Accurate 3D Kinematic Applications.

24. Vydhyanathan A, Bellusci G. The Next Generation Xsens Motion Trackers for Industrial Applications.

25. Bai L, Pepper MG, Wang Z, Mulvenna MD, Bond RR, Finlay D, et al. Upper Limb Position Tracking with a Single Inertial Sensor Using Dead Reckoning Method with Drift Correction Techniques. Sensors. 2023 1;23(1):360. Number: 1. doi:10.3390/s23010360.

26. Wahlström J, Skog I. Fifteen Years of Progress at Zero Velocity: A Review. IEEE Sensors Journal. 2021 1;21(2):1139-51. doi:10.1109/JSEN.2020.3018880.

27. Berret B, Darlot C, Jean F, Pozzo T, Papaxanthis C, Gauthier JP. The Inactivation Principle: Mathematical Solutions Minimizing the Absolute Work and Biological Implications for the Planning of Arm Movements. PLOS Computational Biology. 2008 oct 24;4(10):e1000194. doi:10.1371/journal.pcbi.1000194.

28. Gaveau J, Papaxanthis C. The Temporal Structure of Vertical Arm Movements. PLOS ONE. 2011 jul 12;6(7):e22045. doi:10.1371/journal.pone.0022045.

29. Mancini M, Salarian A, Carlson-Kuhta P, Zampieri C, King L, Chiari L, et al. ISway: a sensitive, valid and reliable measure of postural control. Journal of NeuroEngineering and Rehabilitation. 2012 aug 22;9(1):59. doi:10.1186/1743-0003-9-59.

30. Højsgaard S, Halekoh U, Yan J, Ekstrøm CT. geepack: Generalized Estimating Equation Package; 2025. Available from: `https://cran.r-project.org/web/packages/geepack/index.html`.

31. Lenth RV, Piaskowski J, Banfai B, Bolker B, Buerkner P, Giné-Vázquez I, et al.. emmeans: Estimated Marginal Means, aka Least-Squares Means; 2025. Available from: `https://cran.r-project.org/web/packages/emmeans/index.html`.

32. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2025. Available from: `https://www.R-project.org/`.