

Time-scale-dependent association between deep hypnotic exposure and intraoperative hypotension burden: a case-level, event-aligned, and within-case analysis using the VitalDB database

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Abstract

Background: Intraoperative hypotension and deep hypnotic states are both clinically important during general anesthesia. Although deeper hypnosis may plausibly contribute to arterial pressure reduction through anesthetic-related cardiovascular depression, observational relationships between hypnotic depth and arterial pressure in routine practice are shaped by anesthetic titration, hemodynamic treatment, and time-dependent clinical feedback. Using the VitalDB database, we examined the association between Bispectral Index (BIS) <40 exposure and intraoperative hypotension burden at three complementary levels: case-level, event-aligned, and within-case analyses.

Methods: This was a retrospective observational database study. We screened VitalDB cases with both BIS and invasive arterial pressure recordings. Deep hypnotic exposure was defined as the proportion of valid BIS monitoring time with BIS <40. Hypotension burden was defined as the proportion of valid mean arterial pressure (MAP) monitoring time with MAP <65 mmHg. The primary case-level outcome was substantial hypotension burden, defined as MAP <65 mmHg for at least 10% of valid monitoring time. Multivariable logistic regression was used to assess the association between BIS <40 exposure and substantial hypotension burden, adjusting for age, sex, body mass index, American Society of Anesthesiologists physical status, preoperative hypertension, and preoperative diabetes. To further explore temporal relationships, we performed event-aligned analyses around each case's first qualified hypotension onset and within-case paired-window analyses comparing an earlier stable window with the pre-hypotension window. The first qualified hypotension event was selected to avoid statistical dependence from multiple events within the same case and to prevent a small number of event-rich cases from dominating the average trajectory. We prespecified a confounding framework that distinguished baseline patient-level confounders from intraoperative management variables. The primary model adjusted for baseline variables, whereas intraoperative variables such as blood loss, fluid administration, transfusion, and vasopressor use were examined in extended sensitivity models because they may represent surgical complexity, evolving patient status, or treatment responses to hypotension.

Results: Among 2103 prescreened case identifiers, 1428 had complete BIS and arterial pressure tracks. After signal quality control, 1394 cases were included in the final case-level analysis, of which 1380 had complete covariates for adjusted models. Substantial hypotension burden occurred in 390 of 1394 cases. At the case level, cases with substantial hypotension burden had a lower BIS <40 time proportion than cases with lower hypotension burden (32.22% [interquartile range, 10.77-61.19] vs 47.74% [22.61-68.88]; $P<0.001$). The BIS <40 time proportion was weakly and inversely correlated with the MAP <65 time proportion (Spearman $\rho=-0.187$; $P<0.001$). In adjusted logistic regression, each 10% increase in BIS <40 time was associated with lower odds of substantial hypotension burden (adjusted odds ratio, 0.885; 95% confidence interval, 0.846-0.926; $P<0.001$). The direction of association was unchanged when a stricter hypotension definition (MAP <65 mmHg for $\geq 20\%$ of valid monitoring time) or adjusted linear regression with continuous hypotension burden was used.

In contrast, time-series analyses identified local peri-event changes. In the event-aligned analysis, mean MAP decreased from 78.7 mmHg during the pre-event window (-15 to -5 min) to 65.7 mmHg around hypotension onset (-1 to +1 min; $P<0.001$) and subsequently recovered to 74.6 mmHg during the post-event window (+5 to +10 min; $P<0.001$). Mean BIS decreased modestly from 44.8 before the event to 42.2 near onset ($P<0.001$), but did not increase significantly after MAP recovery (41.9; $P=0.153$). The probability of BIS <40 increased from 35.0% before the event to 41.5% near onset ($P<0.001$) and remained similar after the event (42.7%; $P=0.211$). In the strict within-case paired-window analysis, mean MAP decreased from 83.1 mmHg in the stable window to 75.2 mmHg in the pre-hypotension window (mean difference, -7.85 mmHg; $P<0.001$), mean BIS decreased from 43.9 to 41.8 (mean difference, -2.03; $P<0.001$), and the BIS <40 time proportion increased from 37.5% to 44.4% (mean difference, 6.83 percentage points; $P<0.001$).

Conclusions: At the case level, greater cumulative BIS <40 exposure was not associated with greater intraoperative MAP <65 hypotension burden; instead, a weak inverse association was observed. However, event-aligned and within-case analyses showed a modest decrease in BIS and a higher probability of BIS <40 around specific hypotension events. These findings suggest that the relationship between hypnotic depth and arterial pressure is time-scale dependent: cumulative case-level metrics may obscure short-term peri-event BIS-MAP coupling. The inverse case-level association should not be interpreted as evidence that deep hypnosis protects against hypotension, but rather as a reflection of time-dependent physiology, clinical management, and aggregation effects. These findings should be interpreted as associations rather than causal effects because BIS values, arterial pressure, and intraoperative treatments are dynamically co-managed during anesthesia.

Clinical trial number: Not applicable.

Introduction

Intraoperative hypotension is common during general anesthesia and has been associated with postoperative myocardial injury, acute kidney injury, and other adverse clinical outcomes. A mean arterial pressure (MAP) threshold of 65 mmHg is widely used to define clinically relevant hypotension, because previous studies have shown that MAP below this level, particularly when sustained, is associated with increased risk of organ injury after noncardiac surgery [1]. At the same time, processed electroencephalographic indices such as the Bispectral Index (BIS) are widely used to assess hypnotic depth and to support anesthetic dose titration.

Low BIS values, including $BIS < 40$ or $BIS < 45$, are commonly interpreted as markers of a deeper hypnotic state. Deep anesthesia has attracted clinical attention because excessively deep hypnosis may reflect anesthetic overdosage, limited physiologic reserve, or increased patient sensitivity to anesthetic drugs [2]. From a simple physiologic perspective, deeper anesthesia could contribute to arterial pressure reduction through anesthetic-related cardiovascular depression. In the operating room, however, the relationship between hypnotic depth and blood pressure is not unidirectional. Anesthesiologists continuously adjust anesthetic agents, vasoactive medications, fluid therapy, and other interventions in response to hemodynamic changes. Observed associations between BIS and MAP may therefore reflect not only drug effects, but also clinical titration, treatment responses, and time-dependent feedback.

Previous studies of low BIS, hypotension, and the so-called double-low state suggest that the temporal concurrence of low BIS and hypotension may have clinical relevance [3, 4]. However, cumulative case-level metrics, such as the total proportion of a surgical case spent with $BIS < 40$ or $MAP < 65$ mmHg, cannot distinguish whether low BIS occurred before, during, or after hypotension. This distinction is important because cumulative exposure measures and short-term physiologic trajectories may represent different aspects of intraoperative management.

VitalDB is a publicly available, high-fidelity intraoperative biosignal database that includes high-resolution vital sign recordings and perioperative clinical information from surgical patients [5]. Its temporal resolution allows both calculation of case-level cumulative exposures and examination of peri-event physiologic changes around hypotension onset [6, 7]. Because hypnotic depth, arterial pressure, and hemodynamic treatment are dynamically co-managed during anesthesia, case-level associations between $BIS < 40$ exposure and hypotension burden may be strongly influenced by clinical management and time-dependent confounding. In the present study, we used VitalDB data to evaluate the relationship between $BIS < 40$ exposure and $MAP < 65$ hypotension burden. We first performed conventional case-level analyses and then complemented them with event-aligned and within-case paired-window analyses to determine whether case-level associations were consistent with short-term BIS-MAP dynamics.

Methods

Data source and ethical considerations

This was a retrospective observational database study using the publicly available and de-identified VitalDB intraoperative biosignal database [5]. The study involved secondary analysis of public data and did not involve direct patient contact. Study design and reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement [8, 9]. The case information table and monitoring track list were obtained through the VitalDB application programming interface in June 2026. For each screened case, the availability of BIS and invasive arterial pressure tracks was assessed from the VitalDB track list, and track data were downloaded according to track identifiers. The analytic cohort was constructed sequentially according to track completeness, signal quality, and covariate completeness. The RECORD reporting checklist is provided in Supplementary Table 3.

Study cohort and case selection

The source population consisted of all surgical cases in the VitalDB database ($N = 6388$). According to prespecified eligibility criteria, the analysis was restricted to noncardiac surgical cases performed under general anesthesia with operation duration longer than 2 h. This strategy was intended to identify cases with sufficient BIS and arterial pressure monitoring time and relatively comparable hemodynamic management. Excluding cardiac surgery also reduced the influence of cardiopulmonary bypass, specialized circulatory management, and cardiac surgery-specific hemodynamic interventions on the BIS-MAP relationship. This prescreening step yielded 2103 target case identifiers.

We then queried the VitalDB track list for each case and retained cases with complete BIS and invasive arterial pressure tracks. Target tracks included BIS/BIS, Solar8000/ART_SBP, Solar8000/ART_MBP, and Solar8000/ART_DBP. Inclusion in the final analysis further

required prespecified signal quality criteria, including sufficient valid monitoring duration, sufficient valid observations, and physiologically plausible BIS and arterial pressure distributions. Cases with complete covariates were included in adjusted regression models.

Signal processing and case-level exposure definitions

For each case, BIS and arterial pressure signals were summarized at the case level. Before analysis, implausible values were excluded. BIS values were retained if they were between 1 and 100; MAP values between 20 and 250 mmHg; systolic arterial pressure between 30 and 300 mmHg; and diastolic arterial pressure between 10 and 200 mmHg. For each track, we calculated the mean, minimum, fifth percentile, median, 95th percentile, maximum, number of valid observations, and valid monitoring duration.

Deep hypnotic exposure was defined as the proportion of valid BIS monitoring time with BIS < 40. Hypotension burden was defined as the proportion of valid MAP monitoring time with MAP < 65 mmHg. We also calculated a systolic hypotension burden, defined as the proportion of valid systolic arterial pressure monitoring time with systolic arterial pressure < 90 mmHg.

Quality control

Before signal quality control, eligible cases were required to have all four target tracks: BIS/BIS, Solar8000/ART_SBP, Solar8000/ART_MBP, and Solar8000/ART_DBP. To exclude records with insufficient monitoring, signal loss, or physiologically implausible arterial pressure measurements, prespecified case-level quality control criteria were applied. First, raw values outside plausible physiologic ranges were removed as described above. Second, cases were required to have at least 30 min of valid monitoring duration for MAP, BIS, systolic pressure, and diastolic pressure; at least 100 valid observations for both MAP and BIS; a MAP median of at least 45 mmHg; a MAP 95th percentile of at least 60 mmHg; a systolic pressure median of at least 70 mmHg; and a systolic pressure 95th percentile of at least 90 mmHg. Cases failing any of these criteria were considered at risk for inadequate monitoring, arterial pressure signal loss, or severe artifact and were excluded from the primary analysis.

Among the 2103 prescreened case identifiers, 1428 had complete BIS and invasive arterial pressure target tracks. After signal quality control, 1394 cases remained in the final case-level analysis. Among these, 1380 cases had complete covariate data and were included in adjusted regression models. The complete cohort flow is shown in Supplementary Table 2.

Covariates

Patient- and case-level covariates were obtained from the VitalDB case information table and merged with the case-level BIS and arterial pressure summaries by case identifier. The main adjusted model included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, preoperative hypertension, and preoperative diabetes. Emergency surgery and anesthesia type were not included in adjusted models because these variables had no variation in the quality-controlled cohort.

In addition to the primary adjusted model, we performed an extended adjustment analysis to assess whether intraoperative management factors influenced the case-level association. The extended model further included operation duration, estimated blood loss, intraoperative crystalloid volume, colloid volume, red blood cell transfusion, fresh frozen plasma transfusion, ephedrine dose, and phenylephrine dose. Because these intraoperative variables may simultaneously reflect patient status, clinical management, and treatment responses to hypotension, the extended model was considered a sensitivity analysis rather than the primary causal model.

Confounding framework and model specification

Because BIS values and arterial pressure are dynamically monitored and actively managed during general anesthesia, the observed association between BIS < 40 exposure and hypotension burden was not treated as a simple causal effect. Before model fitting, we prespecified a conceptual framework to distinguish baseline patient-level confounders, surgical complexity variables, and intraoperative management variables (Fig. 1).

The primary adjustment set included variables that were available before or early during surgery and were unlikely to be consequences of intraoperative hypotension: age, sex, body mass index, ASA physical status, preoperative hypertension, and preoperative diabetes.

These variables were selected according to clinical plausibility because they may influence both anesthetic sensitivity and hemodynamic vulnerability.

Intraoperative variables, including operation duration, estimated blood loss, crystalloid and colloid administration, red blood cell transfusion, fresh frozen plasma transfusion, ephedrine use, and phenylephrine use, were not included in the primary model because they may represent surgical complexity, evolving patient status, or treatment responses to hypotension. These variables may therefore lie on the causal pathway or act as time-dependent management variables rather than simple baseline confounders. We included them only in extended sensitivity models to evaluate whether the case-level association was robust to additional adjustment for measured intraoperative and management-related factors.

This modeling strategy was intended to describe the association between cumulative BIS < 40 exposure and hypotension burden while avoiding overinterpretation of the results as causal. Residual confounding from unmeasured anesthetic dose, anesthetic concentration, vasopressor timing, fluid responsiveness, blood loss timing, surgical stimulation, and other time-varying clinical decisions remains possible.

Case-level statistical analysis

Continuous variables are reported as median [interquartile range], and categorical variables as number (percentage). Baseline characteristics were compared according to the presence or absence of substantial hypotension burden, defined as MAP < 65 mmHg for at least 10% of valid monitoring time. Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the chi-square test or Fisher exact test, as appropriate.

The main exposure was the BIS < 40 time proportion. The primary case-level outcome was substantial hypotension burden. Spearman correlation analysis was used to assess the relationship between the BIS < 40 time proportion and the MAP < 65 time proportion. BIS < 40 exposure was also categorized into four groups: 0%, > 0% to 10%, 10% to 30%, and ≥ 30% of valid BIS monitoring time. The MAP < 65 time proportion was compared across exposure groups using the Kruskal-Wallis test and pairwise Wilcoxon tests with Benjamini-Hochberg correction.

Multivariable logistic regression was used to assess the association between BIS < 40 exposure and substantial hypotension burden. BIS < 40 exposure was scaled per 10% increase in valid monitoring time. Adjusted models included age, sex, BMI, ASA physical status, preoperative hypertension, and preoperative diabetes. Robustness analyses used a stricter outcome definition, MAP < 65 mmHg for at least 20% of valid monitoring time. In addition, adjusted linear regression was performed with the MAP < 65 time proportion as a continuous outcome. Results are reported as odds ratios or regression coefficients with 95% confidence intervals and P values.

Event-aligned analysis around hypotension onset

To evaluate short-term temporal relationships between MAP and BIS, we performed event-aligned analyses around each case's first qualified hypotension onset. Raw MAP and BIS signals were binned into 30-s intervals, and the median value within each bin was used. A qualified hypotension event was defined as the first transition from a nonhypotensive state to MAP < 65 mmHg that persisted for at least 60 s, with sufficient MAP and BIS data in the 15 min before and after the event. The onset of this event was defined as T0.

For each included event, MAP and BIS trajectories were aligned to T0. The mean and interquartile range were calculated at each relative time point. We also calculated the event-aligned probability of BIS < 40. Quantitative comparisons were prespecified across three windows: the pre-event window (-15 to -5 min), the peri-T0 window (-1 to +1 min), and the post-event window (+5 to +10 min). Paired Wilcoxon tests were used to compare MAP, BIS, and the probability of BIS < 40 across windows.

Within-case paired-window analysis

To further evaluate whether BIS changed before hypotension within the same patient, we performed a within-case paired-window analysis. For each event-aligned case, an earlier stable control window (T0 -15 to -10 min) was compared with a pre-hypotension window (T0 -5 to -0.5 min). To ensure a relatively stable comparator, the strict analysis retained only cases in which the stable window had a MAP < 65 time proportion of ≤ 10%. For each window, mean MAP, mean BIS, MAP < 65 time proportion, and BIS < 40 time proportion were calculated. Within-case comparisons used paired Wilcoxon tests.

Bootstrap resampling validation

To assess the internal robustness of the case-level association, we performed bootstrap resampling validation. Specifically, 1000 resamples with replacement were generated for both the main adjusted logistic model and the extended adjusted logistic model. Each resample was refitted, and the odds ratio for substantial hypotension burden per 10% increase in BIS < 40 time was extracted. The bootstrap median odds ratio, 2.5th to 97.5th percentile interval, and the proportion of bootstrap estimates with odds ratios below 1 were calculated to evaluate the stability of the association direction.

Results

Cohort characteristics

Among 6388 surgical cases in the VitalDB database, 2103 target case identifiers were obtained after applying the prespecified criteria of noncardiac surgery, general anesthesia, and operation duration longer than 2 h. Of these, 1428 cases had complete BIS and invasive arterial pressure target tracks. After signal quality control, 1394 cases were included in the final case-level analysis, and 1380 cases had complete covariates for adjusted models. The event-aligned analysis included 1050 cases with a qualified first hypotension event and sufficient peri-event BIS and MAP data. The strict within-case paired-window analysis included 729 cases. The complete cohort flow is provided in Supplementary Table 2.

Substantial hypotension burden, defined as MAP <65 mmHg for at least 10% of valid monitoring time, occurred in 390 cases; the remaining 1004 cases had lower hypotension burden. Compared with cases with lower hypotension burden, cases with substantial hypotension burden were slightly older (median age, 62 [51-70.75] vs 59 [49-68] yr; $P=0.013$), had a higher proportion of ASA physical status III (22.7% vs 10.2%; $P<0.001$), and more often had preoperative hypertension (41.8% vs 30.4%; $P<0.001$). Notably, the BIS <40 time proportion was lower in cases with substantial hypotension burden than in cases with lower hypotension burden (32.22% [10.77-61.19] vs 47.74% [22.61-68.88]; $P<0.001$). Baseline characteristics according to hypotension burden are summarized in Table 1.

Case-level association between BIS <40 exposure and hypotension burden

The complete-case dataset for adjusted models included 1380 cases. The BIS <40 time proportion was weakly but significantly inversely correlated with the MAP <65 time proportion (Spearman $\rho=-0.187$; $P<0.001$; Table 2 and Figure 3). When BIS <40 exposure was grouped by time proportion, the median MAP <65 time proportion decreased as the BIS <40 exposure category increased, suggesting that greater cumulative deep hypnotic exposure was not associated with greater case-level hypotension burden (Figure 2 and Supplementary Table 1).

In adjusted logistic regression, each 10% increase in BIS <40 time was associated with lower odds of substantial hypotension burden (adjusted odds ratio, 0.885; 95% confidence interval, 0.846-0.926; $P<0.001$; Table 2 and Figure 4). When a stricter hypotension burden threshold was used (MAP <65 mmHg for at least 20% of valid monitoring time), the direction of association remained consistent (adjusted odds ratio, 0.865; 95% confidence interval, 0.809-0.923; $P<0.001$; Table 2). In adjusted linear regression using MAP <65 time proportion as a continuous outcome, each 10% increase in BIS <40 time was associated with a 0.58 percentage-point lower MAP <65 time proportion ($\beta=-0.584$; 95% confidence interval, -0.796 to -0.371; $P<0.001$; Table 2).

In the extended sensitivity model, which further included operation duration, estimated blood loss, intraoperative fluid and blood product administration, and vasoactive medication use, the inverse case-level association remained directionally consistent (Supplementary Table 4). The extended logistic regression included 1199 complete cases; each 10% increase in BIS <40 time was associated with lower odds of substantial hypotension burden (adjusted odds ratio, 0.883; 95% confidence interval, 0.836-0.933; $P<0.001$). In the extended linear regression, each 10% increase in BIS <40 time was associated with a 0.51 percentage-point lower MAP <65 time proportion ($\beta=-0.505$; 95% confidence interval, -0.716 to -0.294; $P<0.001$). Because these intraoperative variables may partly represent surgical complexity, treatment responses, or time-dependent management processes, this model was interpreted as a robustness analysis rather than as the primary causal model.

Event-aligned analysis around hypotension onset

To examine whether the case-level association reflected short-term BIS-MAP dynamics around hypotension, we performed event-aligned analyses around the first qualified hypotension onset in each case. Event-aligned trajectories showed that MAP fell clearly near T0 and then gradually recovered. Mean MAP decreased from 78.7 mmHg during the pre-event window (-15 to -5 min) to 65.7 mmHg during the peri-T0 window (-1 to +1 min; $P<0.001$), and then recovered to 74.6 mmHg during the post-event window (+5 to +10 min; $P<0.001$ compared with the peri-T0 window). These event-aligned MAP changes are shown in Figure 5 and summarized in Table 3.

In contrast, the magnitude of BIS change was smaller. Mean BIS decreased from 44.8 during the pre-event window to 42.2 near T0 ($P<0.001$), but did not increase significantly during the post-event window (41.9; $P=0.153$ compared with the peri-T0 window). Similarly, the probability of BIS <40 increased from 35.0% before the event to 41.5% near T0 ($P<0.001$) and remained similar during the post-event window (42.7%; $P=0.211$ compared with the peri-T0 window). These event-aligned findings indicate that hypotension onset was accompanied by a modest decrease in BIS and an increased probability of BIS <40 , but that MAP recovery was not accompanied by a corresponding increase in BIS. The corresponding BIS trajectory and BIS <40 probability are shown in Figure 5 and summarized in Table 3.

Within-case paired-window analysis

The strict within-case paired-window analysis retained 729 events after restricting the comparator window to cases with little hypotension during the stable control period. Within each patient, we compared the stable control window (T0 -15 to -10 min) with the pre-hypotension window (T0 -5 to -0.5 min). Mean MAP decreased from 83.1 mmHg in the stable window to 75.2 mmHg in the pre-hypotension window (mean difference, -7.85 mmHg; $P<0.001$). Mean BIS also decreased, from 43.9 to 41.8 (mean difference, -2.03; $P<0.001$). The MAP <65 time proportion increased from 0.92% to 3.91% ($P<0.001$), and the BIS <40 time proportion increased from 37.5% to 44.4% (mean difference, 6.83 percentage points; $P<0.001$). These within-case results support the event-aligned analysis, showing that the period immediately preceding hypotension had lower MAP, slightly lower BIS, and a higher BIS <40 time proportion than an earlier stable period within the same case. These within-case comparisons are summarized in Table 3 and illustrated in Supplementary Figure 1.

Bootstrap resampling validation

Bootstrap internal validation showed that the main case-level association was stable across repeated resampling. In 1000 bootstrap resamples of the main adjusted logistic model, the bootstrap median odds ratio for each 10% increase in BIS <40 time was 0.885, with a 95% bootstrap interval of 0.844 to 0.928. All bootstrap estimates had odds ratios below 1, suggesting that the inverse direction of the case-level association was internally stable. Bootstrap results are provided in Supplementary Table 5.

Discussion

This study was restricted according to anesthesia type, operation type, and operation duration; therefore, the findings primarily apply to longer noncardiac surgical cases performed under general anesthesia. This selection strategy provided sufficiently long and relatively comparable intraoperative BIS and invasive arterial pressure recordings and reduced the influence of cardiac surgery-specific circulatory management on the BIS-MAP relationship. However, it also limits generalizability to short procedures, cardiac surgery, and cases not performed under general anesthesia.

In this retrospective analysis of the VitalDB database, the relationship between BIS <40 exposure and MAP <65 hypotension burden depended strongly on the time scale of analysis. At the case level, greater cumulative BIS <40 exposure was not associated with greater cumulative hypotension burden. Instead, the BIS <40 time proportion was weakly and inversely associated with MAP <65 burden in correlation analysis, grouped exposure comparisons, adjusted logistic regression, analyses using a stricter hypotension threshold, and adjusted linear regression. In contrast, event-aligned and within-case analyses showed that specific hypotension events were accompanied by a modest decrease in BIS and an increased probability of BIS <40 . These findings indicate that case-level summary measures and short-term peri-event analyses capture different aspects of the BIS-MAP relationship.

The inverse case-level association observed in this study should be interpreted in the context of substantial confounding by clinical management. A patient with unstable hemodynamics may prompt the anesthesiologist to reduce hypnotic depth, administer vasopressors, provide fluid therapy, or modify other aspects of anesthetic management. Conversely, a hemodynamically stable patient may tolerate longer periods of low BIS values without developing substantial hypotension. Therefore, the finding that greater cumulative BIS <40 exposure was associated with a lower case-level hypotension burden should not be interpreted as evidence that deeper

anesthesia protects against hypotension. More plausibly, it reflects a combination of patient vulnerability, anesthetic titration, hemodynamic treatment, surgical stimulation, and aggregation of time-varying processes into case-level summary measures.

Although extended adjustment for intraoperative variables did not materially change the direction of the association, these variables were available only as cumulative case-level measures. They could not capture the timing of vasopressor administration, anesthetic dose changes, blood loss, fluid responsiveness, or changes in surgical stimulation. Thus, the extended model only partially addresses measured intraoperative confounding and cannot replace formal time-varying causal modeling.

Time-series analyses provide a more granular view. In the event-aligned analysis, MAP decreased clearly near hypotension onset and then recovered. BIS also decreased modestly near T0, and the probability of BIS < 40 increased. However, BIS did not rise significantly after MAP recovered. This temporal dissociation suggests that post-event MAP recovery may reflect hemodynamic treatment, fluid administration, changes in surgical stimulation, or spontaneous physiologic recovery, rather than simple lightening of anesthesia. The within-case paired-window analysis further showed that, within the same patient, the pre-hypotension window had lower BIS and a higher BIS < 40 time proportion than an earlier stable window. Taken together, these results suggest short-term local BIS-MAP coupling around specific hypotension events, even though cumulative case-level BIS < 40 exposure did not translate into greater cumulative hypotension burden.

These findings are consistent with previous work emphasizing the clinical importance of concurrent low BIS and hypotension, often referred to as the double-low state [3, 4]. Importantly, the present study further suggests that cumulative exposure metrics and event-level synchrony metrics are not interchangeable. A patient may have a high cumulative BIS < 40 time proportion during hemodynamically stable periods and experience hypotension only during lighter or dynamically changing phases of anesthesia. Conversely, local BIS decreases may occur before or during some hypotension events without producing a positive case-level dose-response relationship. The present findings therefore argue against any simple unidirectional interpretation: higher cumulative BIS < 40 exposure should not be considered protective, and case-level BIS < 40 burden should not be treated as a direct determinant of hypotension burden.

Clinically, neither BIS < 40 exposure nor hypotension burden should be interpreted in isolation. Hypotension is influenced by baseline physiologic vulnerability, anesthetic titration, vasoactive medication use, fluid therapy, surgical stimulation, intravascular volume status, and comorbidity. In the adjusted models in this study, ASA physical status was strongly associated with substantial hypotension burden, supporting the importance of baseline physiologic vulnerability. The relationship between hypnotic depth and arterial pressure is therefore more likely to depend on patient risk profile and dynamic intraoperative management than on cumulative BIS < 40 exposure alone.

Notably, the inverse case-level association persisted after additional adjustment for operation duration, estimated blood loss, fluid and blood product administration, and intraoperative vasoactive medication use. This suggests that the case-level finding was not fully explained by simple differences in recorded intraoperative management variables. Nevertheless, these variables were still cumulative case-level measures and could not capture the timing of anesthetic titration, vasopressor administration, bleeding, fluid responsiveness, or changes in surgical stimulation. The extended model can therefore only partly address intraoperative confounding and cannot substitute for formal modeling of time-varying confounders.

At present, external validation is limited by the lack of another database with comparable BIS and high-frequency invasive arterial pressure recordings. Bootstrap internal validation showed that the direction of the main case-level association was stable across repeated resampling. However, bootstrap validation cannot replace true external validation, and extrapolation of these findings to other institutions, monitoring systems, and anesthesia practice environments should be cautious.

This study has several limitations. First, the observational design precludes causal inference. Second, the most important limitation is the inability to fully account for time-varying confounding. Anesthetic dose changes, vasopressor timing, fluid administration, blood loss, and surgical stimulation may occur before, during, or after hypotensive episodes, but these processes were not available as synchronized high-resolution covariates in the present analysis. Although event-aligned and within-case analyses improved temporal resolution, they could not fully control for these dynamic interventions. Third, despite adjustment for multiple baseline covariates, residual confounding related to surgical type, anesthetic management, medications, and clinical response remains possible. Fourth, the analysis relied on routine monitoring data; although signal quality control was applied, residual artifacts may remain. Fifth, because the initial case list was generated using prespecified screening criteria, the results may not generalize to all VitalDB cases or to other institutions, monitoring systems, and anesthesia practices. Finally, because no external database with comparable BIS and high-

frequency arterial pressure data was available, the findings should be interpreted as hypothesis-generating and physiologically informative rather than definitive.

Future studies should integrate higher-resolution data on anesthetic dosing, vasoactive medication timing, fluid administration, blood loss, and surgical events to better separate direct physiologic coupling from clinical feedback regulation. More advanced time-varying causal models, marginal structural models, or self-controlled designs based on matched perioperative windows may help clarify whether changes in hypnotic depth occur before, during, or after hemodynamic deterioration.

Conclusions

In this VitalDB database analysis, cumulative case-level BIS < 40 exposure was not associated with increased cumulative MAP < 65 hypotension burden. Instead, case-level analyses showed a weak inverse association between BIS < 40 exposure and hypotension burden. However, event-aligned and within-case analyses demonstrated a modest decrease in BIS and an increased probability of BIS < 40 around specific hypotension events. These findings suggest that the relationship between hypnotic depth and arterial pressure is time-scale dependent. Cumulative case-level metrics may obscure short-term peri-event BIS-MAP coupling. Without further control for dynamic clinical management, neither case-level nor event-level associations should be interpreted causally.

Declarations

Data availability

The raw VitalDB data are publicly available. The case-level summary dataset, event-aligned dataset, and R analysis code generated for this study are available from the corresponding author upon reasonable request, subject to journal policy.

1. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

2. Ethical Approval

Not applicable. This study did not involve human participants or animal subjects, and therefore did not require formal ethical approval.

3. Acknowledgements

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4. Conflict of Interest

The authors declare no conflicts of interest.

5. Clinical trial number

Not applicable.

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Tables

Table 1. Baseline characteristics of the quality-controlled cohort according to hypotension burden.

Values are presented as median [interquartile range] or number (percentage). Substantial hypotension burden was defined as MAP <65 mmHg for at least 10% of valid monitoring time. Continuous variables were compared using the Wilcoxon rank-sum test; categorical variables were compared using the chi-square test or Fisher exact test, as appropriate.

Variable	Overall	Lower hypotension burden	Substantial hypotension burden	P value
N	1394	1004	390	
Age, yr	60 [50, 69]	59 [49, 68]	62 [51, 70.75]	0.013
Sex	Female: 571 (41.0%); Male: 823 (59.0%)	Female: 413 (41.1%); Male: 591 (58.9%)	Female: 158 (40.5%); Male: 232 (59.5%)	0.880
BMI, kg/m2	22.8 [20.6, 25.0]	22.9 [20.7, 25.0]	22.7 [20.1, 25.0]	0.232
ASA physical status	I: 341 (24.7%); II: 850 (61.6%); III: 189 (13.7%)	I: 291 (29.3%); II: 600 (60.5%); III: 101 (10.2%)	I: 50 (12.9%); II: 250 (64.4%); III: 88 (22.7%)	<0.001
Preoperative hypertension	No: 926 (66.4%); Yes: 468 (33.6%)	No: 699 (69.6%); Yes: 305 (30.4%)	No: 227 (58.2%); Yes: 163 (41.8%)	<0.001
Preoperative diabetes	No: 1218 (87.4%); Yes: 176 (12.6%)	No: 888 (88.4%); Yes: 116 (11.6%)	No: 330 (84.6%); Yes: 60 (15.4%)	0.065
BIS <40 time, %	42.74 [17.98, 66.70]	47.74 [22.61, 68.88]	32.22 [10.77, 61.19]	<0.001
MAP <65 time, %	5.02 [1.56, 11.42]	2.90 [0.98, 5.67]	17.72 [13.35, 26.22]	<0.001
Mean MAP, mmHg	82.93 [77.83, 88.90]	86.02 [81.84, 90.68]	75.55 [72.54, 79.13]	<0.001

Table 2. Case-level association between BIS <40 exposure and intraoperative hypotension burden.

BIS <40 exposure was defined as the proportion of valid monitoring time with BIS <40. In adjusted regression models, exposure was scaled per 10% increase in BIS <40 time. Adjusted models included age, sex, BMI, ASA physical status, preoperative hypertension, and preoperative diabetes. Hypotension burden was defined by the MAP <65 mmHg time proportion.

Analysis	Outcome	Exposure	Effect measure	Estimate	95% CI	P value
Spearman correlation	MAP <65 time proportion	BIS <40 time proportion	Spearman rho	-0.187		<0.001
Adjusted logistic regression	MAP <65 time proportion ≥10%	BIS <40 time proportion per 10% increase	Adjusted OR	0.885	0.846 to 0.926	<0.001
Adjusted logistic regression	MAP <65 time proportion ≥20%	BIS <40 time proportion per 10% increase	Adjusted OR	0.865	0.809 to 0.923	<0.001
Adjusted linear regression	MAP <65 time proportion	BIS <40 time proportion per 10% increase	Adjusted beta	-0.584	-0.796 to -0.371	<0.001

Table 3. Event-aligned and within-case analyses around hypotension onset.

T0 was defined as the first qualified transition to MAP <65 mmHg lasting at least 60 s. Event-aligned windows were the pre-event window (-15 to -5 min), peri-T0 window (-1 to +1 min), and post-event window (+5 to +10 min). The strict within-case paired-window analysis included 729 cases and compared a stable control window (-15 to -10 min) with a pre-hypotension window (-5 to -0.5 min). For event-aligned analyses, P1 compares the pre-event and peri-T0 windows, and P2 compares the peri-T0 and post-event windows. For within-case analyses, P1 compares the stable control and pre-hypotension windows.

Analysis	Metric	Window 1	Value 1	Window 2	Value 2	Window 3	Value 3	Mean difference	P1	P2	N
Event-aligned	Mean MAP, mmHg	Pre-event (-15 to -5 min)	78.70	Peri-T0 (-1 to +1 min)	65.70	Post-event (+5 to +10 min)	74.60		<0.001	<0.001	1,050
Event-aligned	Mean BIS	Pre-event (-15 to -5 min)	44.80	Peri-T0 (-1 to +1 min)	42.20	Post-event (+5 to +10 min)	41.90		<0.001	0.153	1,050
Event-aligned	BIS <40 probability, %	Pre-event (-15 to -5 min)	35.00	Peri-T0 (-1 to +1 min)	41.50	Post-event (+5 to +10 min)	42.70		<0.001	0.211	1,050
Strict within-case	Mean MAP, mmHg	Stable control (-15 to -10 min)	83.08	Pre-hypotension (-5 to -0.5 min)	75.23			-7.85	<0.001		729
Strict within-case	Mean BIS	Stable control (-15 to -10 min)	43.87	Pre-hypotension (-5 to -0.5 min)	41.84			-2.03	<0.001		729
Strict within-case	MAP <65 time, %	Stable control (-15 to -10 min)	0.92	Pre-hypotension (-5 to -0.5 min)	3.91			3.00	<0.001		729
Strict within-case	BIS <40 time, %	Stable control (-15 to -10 min)	37.54	Pre-hypotension (-5 to -0.5 min)	44.38			6.83	<0.001		729

Figures

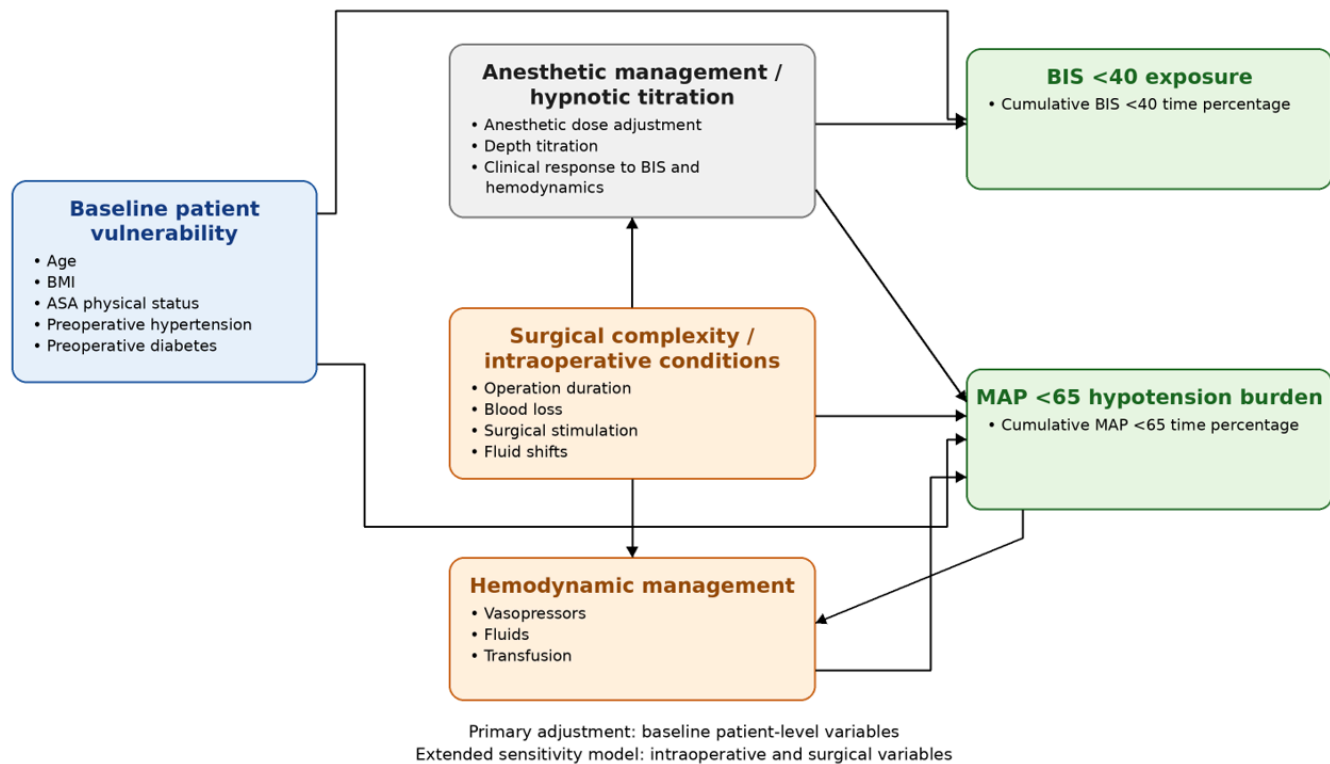


Figure 1

Conceptual framework for confounding in the association between BIS<40 exposure and intraoperative hypotension burden.

The observed association between cumulative BIS<40 exposure and MAP<65 hypotension burden may be influenced by baseline patient vulnerability, anesthetic management, surgical complexity, and hemodynamic treatment. Baseline patient-level variables were included in the primary adjustment model. Intraoperative variables, including operation duration, blood loss, fluid administration, transfusion, and vasopressor use, were evaluated in extended sensitivity models because they may reflect both surgical complexity and treatment responses to hypotension. This framework illustrates why the case-level BIS–MAP association should not be interpreted as a direct causal effect.

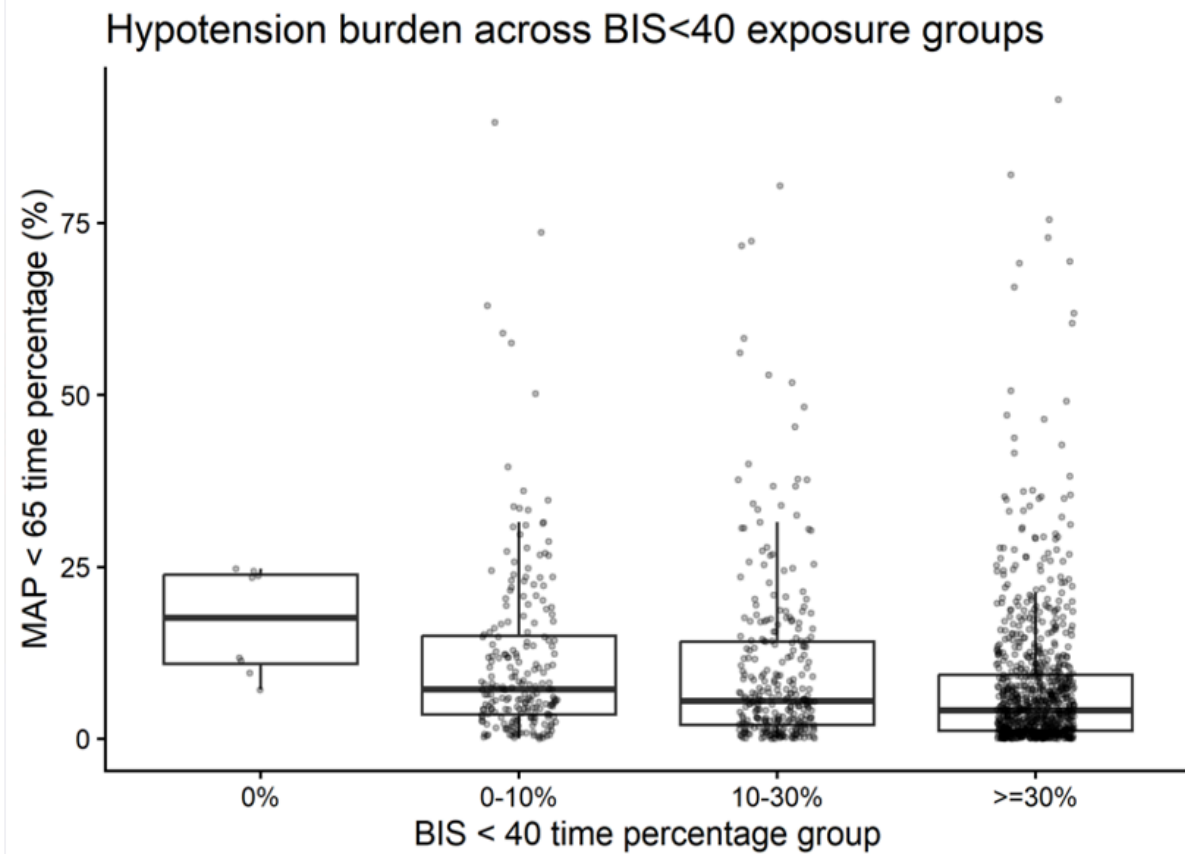


Figure 2

Hypotension burden across BIS <40 exposure groups.

Boxplots show the distribution of the MAP <65 time proportion after grouping cases by the proportion of valid monitoring time with BIS <40. Each point represents one case-level observation. At the case level, greater cumulative BIS <40 exposure was not associated with greater MAP <65 hypotension burden.

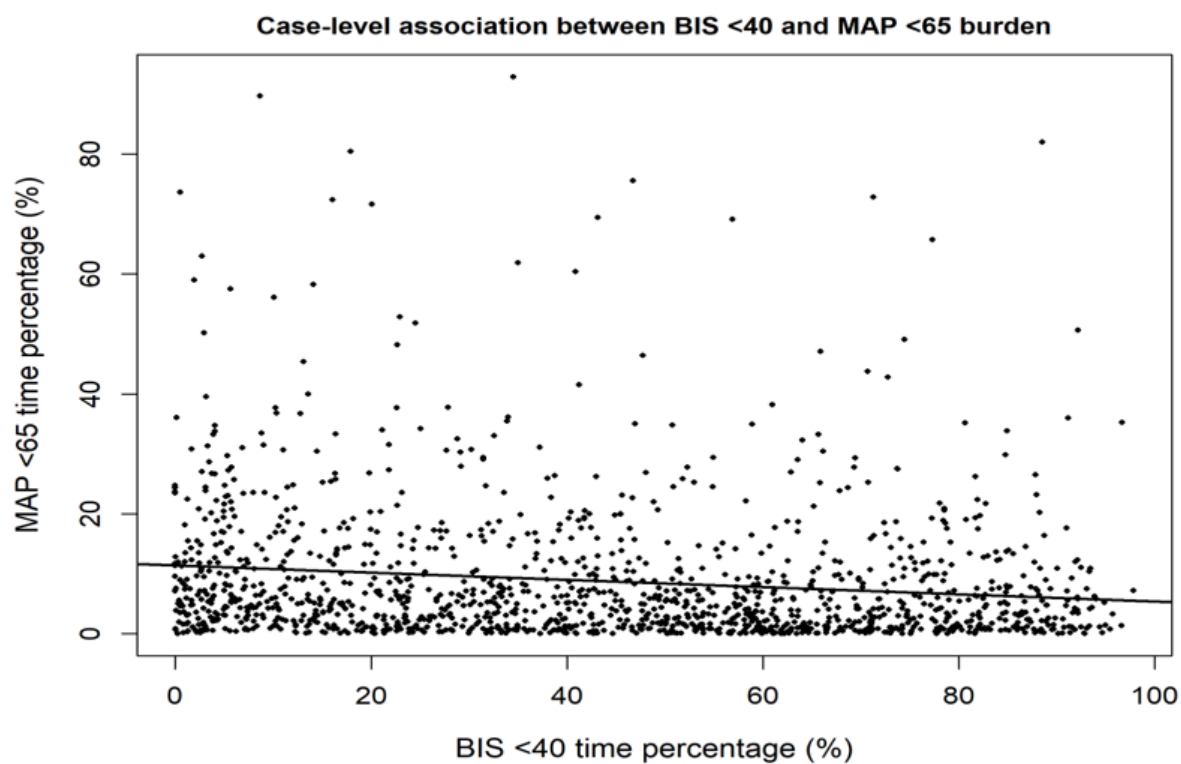


Figure 3

Case-level relationship between BIS <40 exposure and MAP <65 hypotension burden.

The scatterplot shows the relationship between the proportion of valid monitoring time with BIS <40 and the proportion of valid monitoring time with MAP <65 mmHg. The fitted line shows the overall case-level trend.

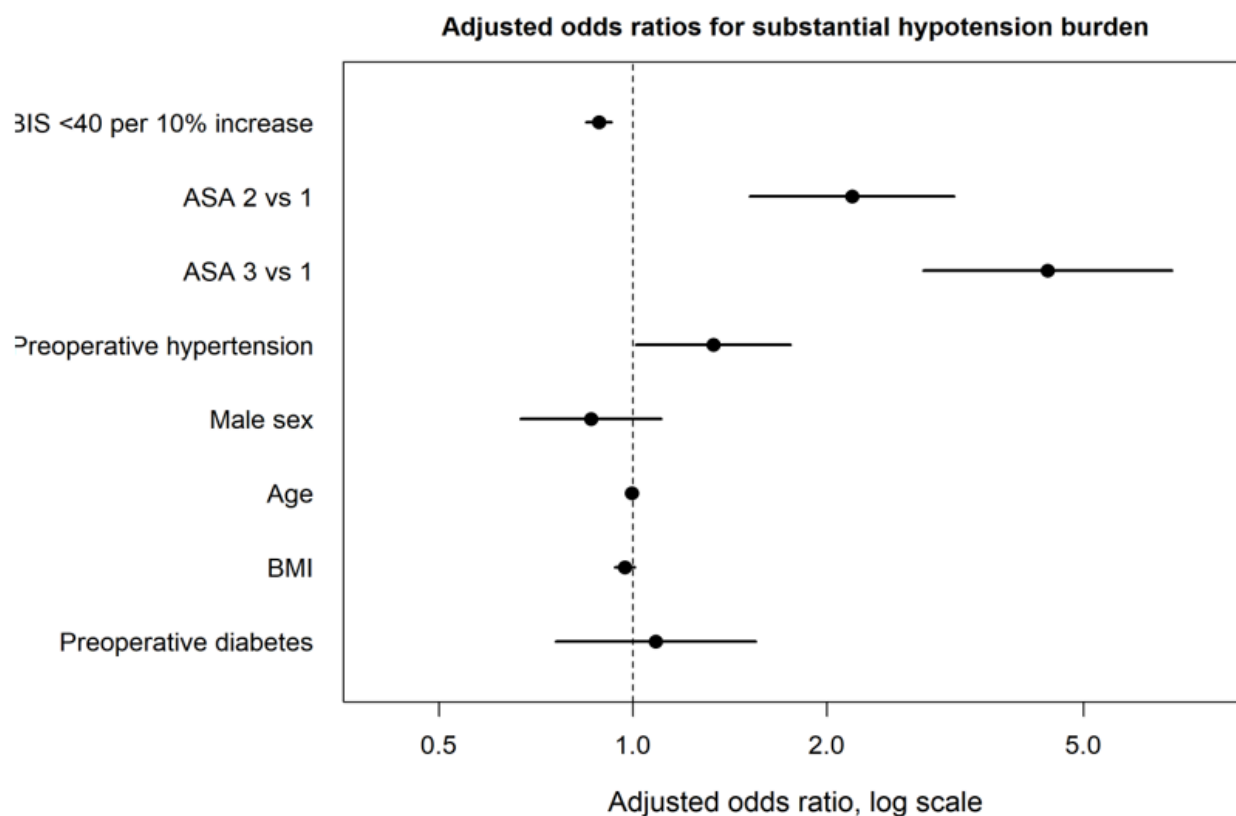


Figure 4

Adjusted associations with substantial hypotension burden.

The forest plot shows adjusted odds ratios for substantial hypotension burden, defined as MAP <65 mmHg for at least 10% of valid monitoring time. Odds ratios were derived from multivariable logistic regression adjusted for age, sex, BMI, ASA physical status, preoperative hypertension, and preoperative diabetes. BIS <40 exposure was scaled per 10% increase in valid monitoring time.

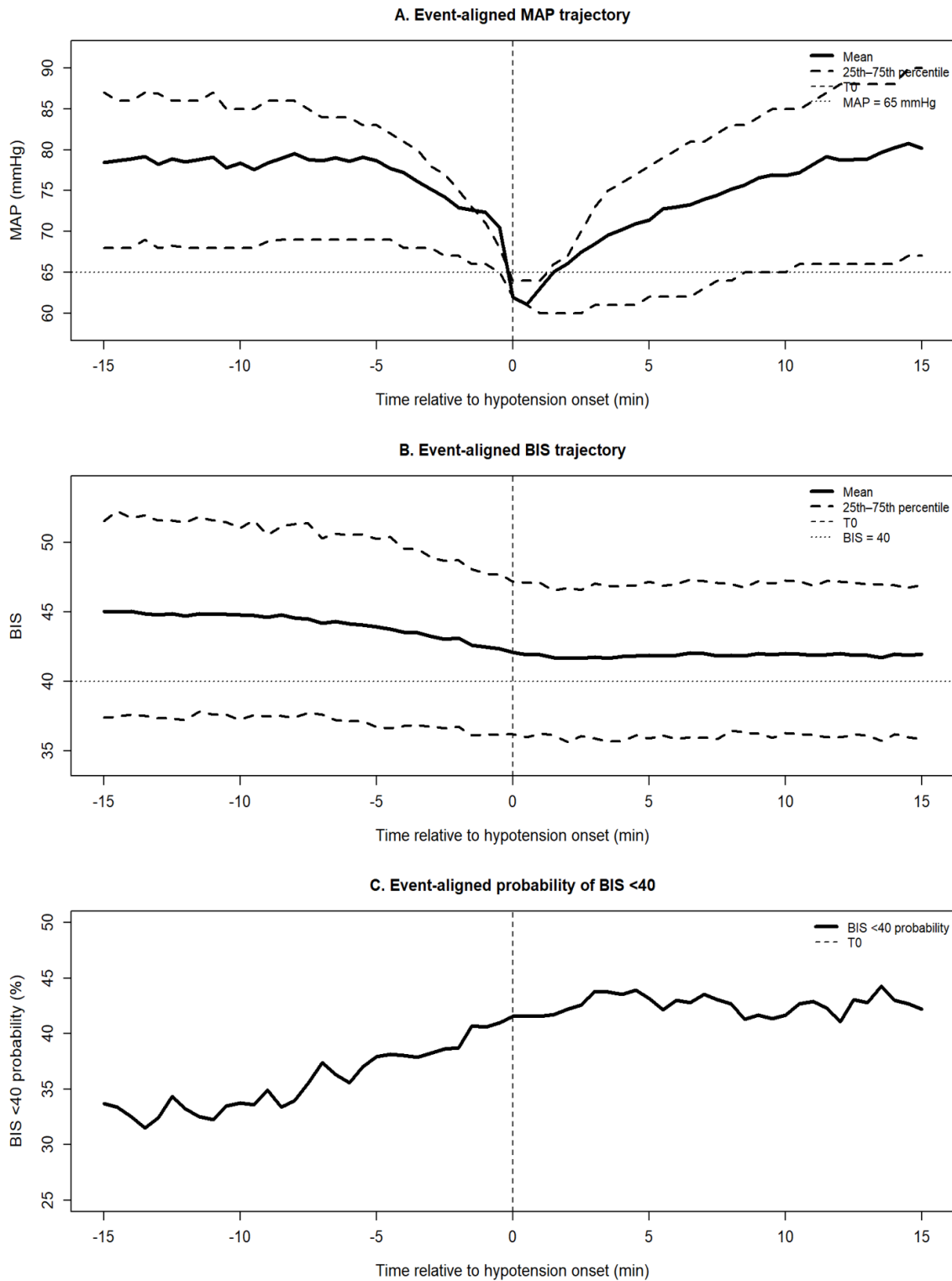


Figure 5

Event-aligned MAP and BIS trajectories around hypotension onset.

Hypotension onset T0 was defined as the first transition to MAP <65 mmHg lasting at least 60 s, with sufficient BIS and MAP data in the peri-event window. Panel A shows event-aligned MAP trajectories. Panel B shows event-aligned BIS trajectories. Panel C shows the event-aligned probability of BIS <40. Solid lines indicate mean values, and dashed lines indicate the 25th to 75th percentile range. MAP decreased clearly near T0 and recovered after the event. In contrast, BIS decreased modestly near T0, but did not increase significantly after MAP recovery.

Supplementary Files

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