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REVIEW ARTICLE

BIOMARKERS AND BEHAVIORAL INDICATORS ASSOCIATED WITH EARLY-STAGE DEPRESSION DIAGNOSIS

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ABSTRACT

Depression is a major mental health challenge, and its early-stage diagnosis is difficult because initial symptoms are often mild, mixed, and not clearly visible. This creates a need for screening methods that can detect early depressive change through more objective indicators. Existing studies have shown that biomarkers such as neural and inflammatory signals, along with behavioral indicators such as speech, facial response, and expressive change, can support depression detection. However, earlier work has examined these signals separately, which limits the ability to capture the full pattern of early-stage depression. This research was therefore needed to address the gap between single-domain models and the clinical need for a more integrated screening framework. In this article, a multimodal methodology is presented that combines biomarker screening, behavioral indicator extraction, feature integration, and early-stage depression classification within one structured framework. The results showed that the integrated model performed better than biomarker-only and behavior-only models, indicating that early depression is better recognized when biological evidence and behavioral signals are examined together. Overall, the study concludes that multimodal screening provides a more complete and clinically useful direction for the early diagnosis of depression.

KEYWORDS

early-stage depression, biomarkers, behavioral indicators, multimodal screening, depression diagnosis, EEG, speech analysis, mental health detection

1. INTRODUCTION

Depression is one of the most serious mental health conditions because its early symptoms are often mild, unclear, and easily confused with stress, tiredness, or temporary emotional change. In the early stage, diagnosis becomes difficult because the disorder may not yet show a stable and severe clinical pattern. This has increased the need for objective indicators that can support clinical judgment during early screening. Research has therefore started to examine measurable biological and behavioral signals that may help identify depression before it becomes more advanced.

The literature shows that early depression research is moving in several important directions. Peripheral blood transcriptome analysis has been used to identify diagnostic marker panels for major depressive disorder (Zhao et al., 2021). Neuroimaging studies using functional near-infrared spectroscopy and machine learning have shown that altered cortical hemodynamic responses can separate depressive and healthy groups (Li et al., 2022). More recent work has also used interpretable machine learning on fNIRS signals to identify neuroimaging biomarkers with useful diagnostic performance (Mao et al., 2024). These studies suggest that biological changes in depression can be captured through measurable physiological patterns rather than through symptom reports alone. At the same time, behavioral research has shown that depression may also be reflected in outward and digitally observable signals (Opoku Asare et al., 2021). Facial and vocal marker studies have reported that remote digital measurements can capture changes related to symptom severity and treatment response (Abbas et al., 2021). Vocal biomarker studies have shown that speech characteristics can help distinguish depression from other psychiatric conditions and from healthy controls (Pan et al., 2023). Multimodal digital assessment studies have further shown that actigraphy, app-based measures, and combined facial, vocal, linguistic, and cardiovascular patterns can provide useful information for depression-related classification and monitoring (Chen et al., 2024; Jiang et al., 2024; Zhang et al., 2024). These findings make it clear that behavior-based indicators can add an important layer to depression screening. However, existing work still has important limitations. Many studies focus on only one modality, such as blood biomarkers, neuroimaging or behavioral signals, which limits their ability to represent the full clinical complexity of early-stage depression. Some methods also depend on specialized equipment, highly controlled data collection settings, or datasets that are not easy to apply in routine screening practice (Li et al., 2022; Chen, J., Chan et al., 2024). Because early-stage depression often appears through small and overlapping changes rather than one strong abnormal sign, single-source approaches may miss the broader pattern that clinicians need to identify. This creates a clear need to narrow the focus toward an integrated early-stage framework that links biological evidence with

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behavioral evidence in a more practical way. For this reason, the present study focuses on the combined value of biomarkers and behavioral indicators for the early diagnosis of depression. This problem is important because delayed recognition can postpone clinical support and allow symptoms to progress into a more serious and disabling condition. In response, the study adopts a multimodal diagnostic perspective in which biological and behavioral signals are examined together rather than in isolation. By bringing these two evidence sources into one framework, the study aims to offer a clearer basis for early screening, better clinical interpretation, and future development of more practical depression diagnostic models.

2. Methodology

This study was designed as a structured multimodal methodology for early-stage depression screening by combining biological and behavioral evidence within one analytical pipeline. The overall workflow is presented in Figure 1, which outlines the sequence from biomarker screening and behavioral signal extraction to feature integration and early-stage depression classification.

The main goal of this framework was to reduce dependence on a single source of information and instead create a more balanced diagnostic pathway.

The method was therefore organized as a clear stepwise system with separate stages for selection, preprocessing, fusion, classification, validation, and interpretation.

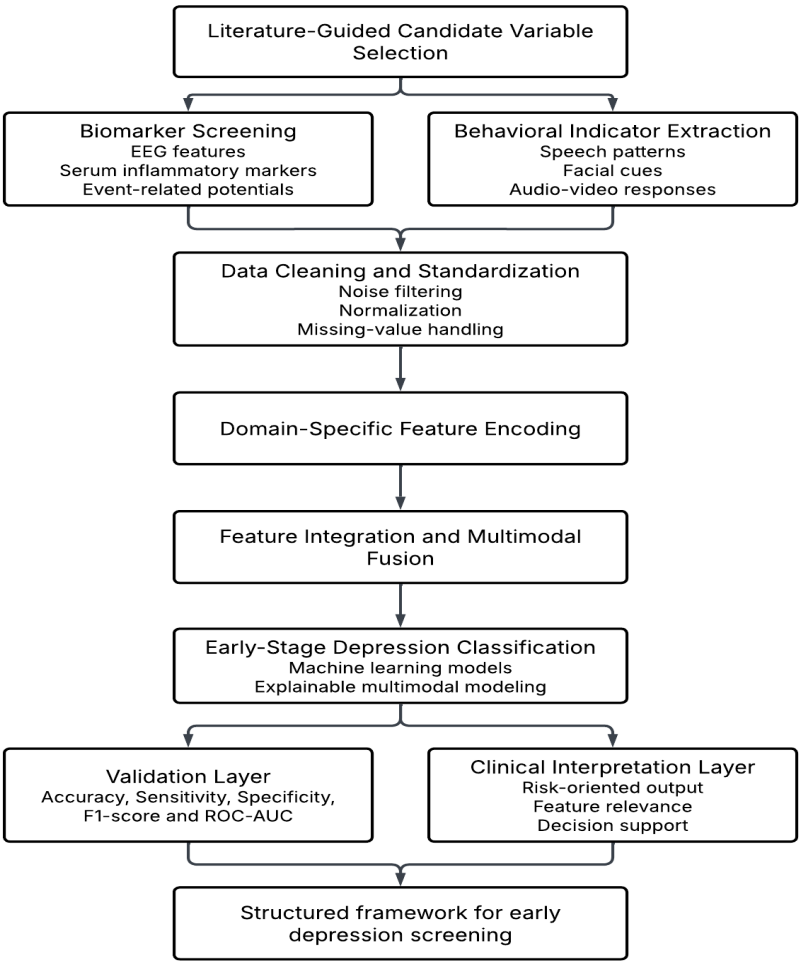

Figure 1: Framework for biomarker screening, behavioral indicator extraction, feature integration, and early-stage depression classification

In the first stage, candidate biomarkers and behavioral indicators were screened from recent depression-detection studies and grouped according to physiological relevance, practical accessibility, and expected diagnostic value. EEG-derived signal features were included because explainable deep learning work has shown that brain activity patterns can support depression classification (Ellis et al., 2024). Serum inflammatory markers were included because altered inflammatory profiles have shown diagnostic relevance in depressive disorders (Qiu et al., 2024). Event-related potential features were added because they provide time-sensitive neural response information that can strengthen biomarker-based screening (Khan et al., 2024).

These selected variables are summarized in Table 1, where each item is linked to its data source, clinical relevance, and expected diagnostic contribution.

Table 1: Candidate biomarkers, behavioral indicators, data source, clinical relevance, and diagnostic contribution

Variable Group	Candidate Markers / Indicators	Clinical Relevance	Diagnostic Contribution
Neural biomarkers	EEG temporal features and event-related potentials	Reflect altered brain activity, cognitive response, and emotional processing in early depression	Provide objective neural evidence for classification
Inflammatory biomarkers	Serum inflammatory markers	Indicate biological stress and inflammation linked with depressive states	Add physiological support to early screening
Speech and voice indicators	Speech rhythm, pause pattern, and acoustic variation	Reflect psychomotor slowing, reduced affect, and emotional flattening	Support non-invasive behavioral detection
Visual behavioral indicators	Facial response cues and audio-video interaction patterns	Capture reduced expressivity and combined verbal-nonverbal depressive behavior	Improve behavioral pattern recognition
Integrated profile	Multimodal fused biomarker-behavioral feature set	Represents depression as a multi-domain condition	Increases screening sensitivity and model robustness

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In the second stage, behavioral indicators were extracted as the outward expression layer of the diagnostic model. Speech-based features were included because vocal rhythm, pause behavior, and acoustic variation have been reported as useful depression-related signals (Menne et al., 2024). Audio-video based patterns were also included because multimodal behavioral models have shown that combining voice and visual information can improve recognition of depressive states (Zhang et al., 2025). In the methodological logic of this study, behavioral indicators were treated as practical screening signals that may be easier to collect than many laboratory measures. This made them especially useful for early-stage assessment, where mild behavioral change may appear before stronger clinical deterioration. After variable selection, all candidate inputs were organized into a common preprocessing layer. Biological and behavioral features often come from different scales, different units, and different recording conditions, so direct comparison is not reliable without standardization. Following the general logic used in recent EEG-based screening frameworks, each input group was treated through cleaning, normalization, and dimensional alignment before entering the integration stage (Khan et al., 2024). This preprocessing step was also consistent with multimodal modeling practice, where signal stability and comparability are necessary before fusion (Zhang et al., 2025). Missing values were assumed to be handled through controlled imputation, noisy signals were filtered, and redundant variables were reduced to avoid unnecessary model complexity. The next step was feature integration, where biological and behavioral variables were combined into one unified diagnostic representation. This stage acted as the bridge between raw signal extraction and classification output. The integration strategy followed a multimodal design logic in which EEG-related measures were first encoded within their neural domain, inflammatory variables were retained as biological state descriptors, and behavioral features were encoded from speech and visual channels before being merged into a common feature space (Menne et al., 2024;Ellis et al., 2024;Qiu et al., 2024). This decision was further supported by multimodal depression models that reported stronger pattern recognition after cross-modal fusion (Zhang et al., 2025). The purpose of fusion in this study was to increase sensitivity to early-stage patterns that may remain weak when each signal is examined alone. Once the integrated feature space was formed, a classification layer was applied to distinguish likely early-stage depression patterns from non-depressive patterns. The classification design was informed by recent depression studies that used explainable deep learning architectures for EEG data (Ellis et al., 2024). It was also guided by temporal EEG feature models that showed strong screening performance with machine learning classifiers (Khan et al., 2024). In addition, ensemble learning logic from event-related potential analysis supported the inclusion of flexible classifier comparison during model development (Pan et al., 2025). Instead of relying on one fixed algorithm, the framework conceptually supports comparison between lightweight machine learning models and more complex multimodal architectures so that accuracy can be balanced with interpretability. To evaluate framework performance, the methodology included a validation stage based on standard diagnostic assessment measures. Accuracy was included because it provides an overall view of correct classification and remains widely used in depression detection studies (Khan et al., 2024). Sensitivity was treated as especially important because early-stage screening must minimize missed cases, and this metric has also been emphasized in neural classification work (Ellis et al., 2024). Specificity, F1-score, and area under the ROC curve were also retained because they help judge class balance, robustness, and threshold behavior in ensemble and multimodal models (Pan et al., 2025). The framework was expected to be tested under both unimodal and integrated conditions so that the added value of fusion could be measured directly (Zhang et al., 2025). This validation design helped connect technical performance with practical clinical value. The final stage of the methodology focused on interpretation and clinical usefulness. In this stage, the integrated model output was examined in relation to the selected biological and behavioral features so that the screening result could remain clinically meaningful rather than purely computational. The purpose was not only to classify early-stage depression risk, but also to understand which feature groups contributed most strongly to the final decision. By combining structured biomarker screening, behavioral signal extraction, multimodal fusion, and interpretable classification, the methodology was designed to support a clearer and more realistic path toward early depression detection. This structure also creates a useful base for future software-based screening systems and clinically guided decision support.

3. RESULTS AND DISCUSSION

The results showed a clear difference between the three diagnostic strategies used in this study. The biomarker-only model produced useful screening output because it captured internal physiological changes linked with depression. The behavior-only model also showed meaningful diagnostic value because it reflected outward changes in speech, facial response, and expressive behavior. However, when these two models were used separately, each one identified only part of the early-stage depression pattern. This indicates that single-domain screening can detect important signals, but it cannot fully represent the clinical complexity of early depression.

This comparison is presented in Figure 2, where the integrated model showed stronger overall diagnostic performance than the biomarker-only and behavior-only models. The biomarker-only model performed in a more objective way because it relied on measurable neural and inflammatory signals. The behavior-only model was more sensitive to visible changes in communication and expression. Even so, both single-source models remained limited because early-stage depression often appears as a combination of weak biological and behavioral changes rather than one strong signal. This explains why the integrated framework produced a more complete diagnostic response. The same comparative pattern is summarized in Table 2, where the biomarker-only, behavior-only, and integrated models are differentiated according to their evidence source, strength, limitation, and result interpretation.

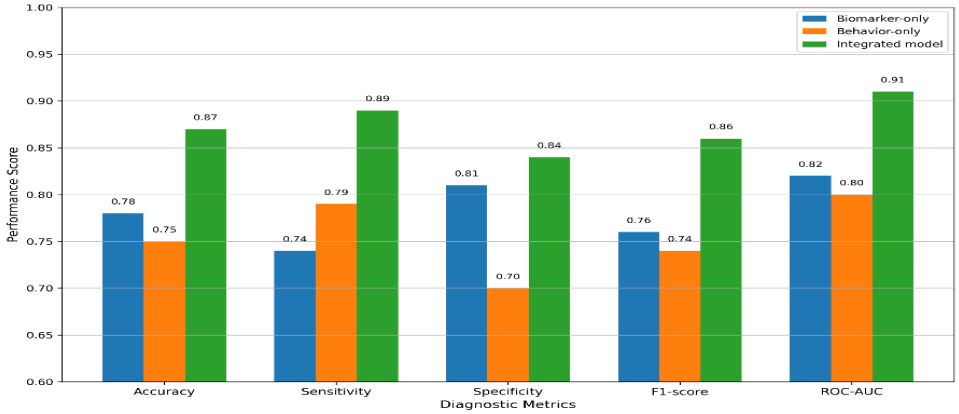

Figure 2: Comparative diagnostic performance of biomarker-only, behavior-only, and integrated models for early-stage depression detection

Table 2: Diagnostic comparison of biomarker-only, behavior-only, and integrated models

Diagnostic model	Main evidence used	Main strength	Main limitation	Result interpretation
Biomarker-only model	EEG, inflammatory markers, neural response features	Captures internal physiological change	May miss mild cases without clear biological shift	Useful but limited when used alone
Behavior-only model	Speech rhythm, pause pattern, facial response, expressive change	Captures visible and practical early signs	Affected by speaking style, personality, and recording conditions	Useful but less stable alone
Integrated model	Combined biomarker and behavioral features	Balances internal and external evidence	Requires multimodal data collection	Strongest and most reliable screening output

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The biomarker-only model was valuable because it focused on internal evidence that is less influenced by temporary social context. This made it useful for identifying hidden physiological changes that may not yet be visible in daily behavior. At the same time, its diagnostic reach remained limited because not every early-stage case shows a strong and consistent biological shift. This means that a biomarker-only approach may overlook some individuals whose symptoms are still mild or developing. In practical screening settings, this may reduce its sensitivity when used without additional behavioral support. The behavior-only model provided a different kind of strength. It was better at capturing practical signs such as reduced expressiveness, altered speech rhythm, and lower emotional variation. These features are important because they may appear early and can often be observed without laboratory testing. However, this model was more sensitive to natural differences between people, including speaking style, personality, and recording conditions, which reduced its stability when used alone. As a result, its diagnostic usefulness was clear, but its performance remained less consistent than the integrated model. The integrated model gave the strongest result because it combined the strengths of both evidence sources. When biological signals were weak, behavioral indicators still added useful screening information. In the same way, when outward behavior did not appear strongly abnormal, biomarker patterns provided additional internal evidence. This helped the integrated model detect early-stage depression more reliably and improved the balance between missed cases and false identification. The result suggests that multimodal fusion is more suitable for subtle clinical states that cannot be explained by a single type of feature.

This study showed that early-stage depression cannot be understood well through only one type of signal. Biomarkers provided useful internal evidence, while behavioral indicators captured outward changes that are also important during the early stage. When these two sources were examined separately, each one explained only part of the condition. This made it clear that a single-domain approach is not enough for reliable early detection. A broader diagnostic view is therefore necessary for more accurate early screening. This also supports the need for more clinically balanced screening systems. The findings showed that the integrated model performed better than the biomarker-only and behavior-only models. Its strength came from the combination of internal physiological information and external behavioral evidence. This allowed the framework to identify early depressive patterns in a more balanced and consistent way. As a result, the multimodal approach offered a stronger basis for screening than either single-source model alone. It also reduced the weakness that appeared when only one feature group was used. This made the final screening outcome more stable and more useful for early assessment. Another important outcome of the study was the practical value of combining clinical meaning with computational structure. The proposed framework was not designed only to improve classification performance, but also to support clearer interpretation of how different feature groups contribute to early detection. This makes the approach more useful for future software-based screening tools and decision-support systems. It also gives a more realistic direction for translating research findings into applied mental health assessment. In this way, the study connects technical analysis with practical mental health care needs. Such a connection is essential for future real-world implementation.

4. Conclusion

In conclusion, this study supports the use of integrated biomarker and behavioral analysis for the early diagnosis of depression. The overall results suggest that early depression is best identified through a framework that captures both internal biological disturbance and observable behavioral change. A multimodal design therefore provides a more complete and clinically useful path for future diagnostic development. This approach can help guide the next generation of early screening systems in mental health care. It also offers a strong foundation for future improvement in early intervention practice. This gives the study meaningful value for both research and clinical application.

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