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Care delivery modality and downstream opioid exposure in musculoskeletal care: a real-world analysis of opioid-naive patients

Ana P. Pereira
Sword Health, 169 Madison Ave STE 15501
Beatriz Domingues
Sword Health, 169 Madison Ave STE 15501
Akshat Pradhan
Sword Health, 169 Madison Ave STE 15501
Anabela C. Areias
Sword Health, 169 Madison Ave STE 15501
Dora Janela
Sword Health, 169 Madison Ave STE 15501
Xin Tong
University of Virginia
Virgílio Bento
Sword Health, 169 Madison Ave STE 15501
Luke Belz
Sword Health, 169 Madison Ave STE 15501
Steve P. Cohen
Northwestern University Feinberg School of Medicine
Carolina Moreira
Sword Health, 169 Madison Ave STE 15501
Fernando Dias Correia
Sword Health, 169 Madison Ave STE 15501
Fabíola Costa
f.costa@swordhealth.com

Sword Health, 169 Madison Ave STE 15501

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Abstract

Whether the mode of delivery of first-line conservative musculoskeletal (MSK) care influences downstream opioid use remains unclear. We conducted an observational retrospective cohort study using a U.S. administrative claims database to evaluate opioid prescribing among opioid-naive individuals with new-onset MSK conditions initiating AI-enabled, digitally delivered care versus in-person physical therapy (N = 30,900).

Using inverse probability weighting and complementary analytic approaches, we assessed opioid initiation and prescribing patterns over 12 months under both conventional and more stringent definitions of opioid exposure. Under the stringent definition, opioid initiation was lower among individuals receiving digitally delivered care (1.8% vs 3.2%; adjusted OR 0.54, 95% CI 0.49; 0.59; $p < 0.001$), with fewer prescriptions per 100 patients (5.7 vs 11.4). Compared with conventional definitions, differences in prescribing intensity and profile were attenuated.

These findings suggest that care delivery pathways may influence opioid prescribing and support scalable, digitally delivered care models in opioid stewardship.

INTRODUCTION

Musculoskeletal (MSK) conditions are the leading cause of disability worldwide[1–4], affecting an estimated 1.71 billion individuals[5], and being a major driver of healthcare utilization and expenditures[1,6]. Clinical guidelines recommend nonpharmacologic conservative care as first-line treatment[7–9]. However, adherence to these recommendations remains poor; U.S. national ambulatory data indicate that opioids are often prescribed ahead of physical therapy for MSK conditions in clinical practice[10]. Opioids were prescribed in 21.5% of visits involving new MSK pain conditions considered as likely to become chronic, representing more than twice the rate at which physical therapy was recommended (10.0%)[10]. Early opioid exposure has been associated with adverse outcomes, with limited evidence supporting sustained benefit for chronic MSK pain[11–16]. Notably, in a large U.S. claims analysis of 88,985 opioid-naive adults with new MSK diagnoses, early physical therapy significantly mitigated opioid risk, reducing both odds of subsequent opioid initiation and prescribing intensity[17].

Access to in-person physical therapy remains limited due to geographic, logistical, and cost-related barriers, often delaying initiation of guideline-concordant care[18–20]. Such delays may prompt escalation to pharmacologic management[17,21–23].

Digitally delivered MSK care programs have been developed to improve access, timeliness, and continuity of conservative treatment[24–27]. These models aim to reduce barriers to care initiation and support sustained engagement through structured exercise, education, and behavioral interventions[25,28–30]. They often include clinician oversight and may incorporate AI-enabled approaches to personalize treatment and guide care progression[25,28,31]. Prior work has demonstrated that these

interventions achieve improvements comparable to in-person physical therapy[28,32–34], and large U.S. claims analyses have linked them to lower downstream healthcare utilization, including surgical escalation[35,36].

However, whether differences in the delivery mode of conservative MSK care influence downstream opioid exposure remains largely unknown, particularly in real-world settings and with analytic approaches designed to address confounding.

In this study, we applied a multi-method observational causal inference framework to examine downstream opioid exposure, including initiation, dose, and prescribing burden, among opioid-naive individuals with new-onset MSK pain who initiated conservative care either remotely (hereafter referred to as an AI-enabled care program) or in-person. We hypothesized that the initiation of an AI-enabled digital care program would be associated with similar or lower rates of opioid initiation to in-person physical therapy. Understanding whether the mode of delivery of conservative MSK care influences opioid prescribing patterns has important implications for care design, access and scalability of care, and opioid stewardship.

RESULTS

Study Cohort

From an initial population of over 1 million individuals identified in an administrative claims database, 30,900 opioid-naive patients (defined as having no opioid prescriptions in the 12 months prior) met eligibility criteria, including initiation of a conservative MSK care pathway and continuous medical and pharmacy claims for at least 12 months before and after the index event (Supplementary Fig. 1). Of these, 15,405 individuals initiated AI-enabled MSK care (intervention group, IG) and 15,495 initiated in-person physical therapy (comparator group, CG).

Covariate Balance and Confounding Control

To address confounding inherent to observational comparisons, we applied inverse probability weighting (IPW) using propensity scores estimated from demographic (sex, age), socioeconomic (social deprivation index – SDI), geographic, clinical (MSK condition, concurrent MSK, comorbidities as measured by the Elixhauser index, presence of mental health or substance use diagnosis), and healthcare utilization (namely total all-cause costs of care (TCOC), as a proxy of overall health status[37]) (Fig. 1; Supplementary Table 1). Post-weighting, all covariate standardized mean differences (SMDs) were well balanced overall (below 0.10), indicating substantial improvement in cohort comparability relative to the unweighted population (Supplementary Figs. 2 and 3; exact SMD reported in Table 1; unweighted population characteristics in Supplementary Table 2). While the nominal sample size remained unchanged (N = 30,900), the effective sample size (ESS) after weighting was 19,395,

suggesting moderate weight variability with 62.8% of the original sample effectively contributing to the analysis.

Table 1
Baseline characteristics of the intervention group (AI care program) and the comparison group (in-person physical therapy) in the weighted cohort.

	Weighted Cohort		
	Intervention Group (ESS = 8,989.6)	**Comparator Group (ESS = 10,586.1)**	**SMD**
Demographic characteristics			
Sex, %:			
Female	57.0	55.3	0.034
Male	43.0	44.7	-0.034
Age categories (years), %:			
18–40	22.0	26.9	-0.113
41–64	65.9	61.7	0.087
65+	12.1	11.3	0.024
Geographic U.S. Region, %:			
Midwest	53.5	58.4	-0.103
Northeast	14.4	10.8	0.110
South	22.4	21.0	0.033
West	9.8	10.0	-0.007
Social Deprivation Index, %:			
0–20	35.2	36.0	-0.016
21–40	26.6	26.9	-0.008
41–60	17.4	17.1	0.006
61–80	13.0	12.7	0.010
81–100	7.8	7.3	0.019
Clinical data			
MSK symptomatic anatomical site, %:			
Spine	42.0	40.6	0.027
Lower Limb	34.5	38.2	-0.076
Upper Limb	23.5	21.2	0.056

	Weighted Cohort		
	Intervention Group (ESS = 8,989.6)	**Comparator Group (ESS = 10,586.1)**	**SMD**
Demographic characteristics			
Concurrent MSK conditions, %:			
0	82.1	81.7	0.010
1+	17.9	18.3	-0.010
Mental health conditions, %:			
No	92.3	91.6	0.029
Yes	7.7	8.4	-0.029
Substance use disorders, %:			
No	99.2	99.1	0.010
Yes	0.8	0.9	-0.010
Elixhauser Comorbidity Index, mean (SD)	-0.26 (2.7)	-0.25 (2.6)	-0.004
Elixhauser Comorbidity Index, %:			
< 0	15.6	16.4	-0.023
0	78.0	76.9	-0.029
1–4	3.2	3.3	-0.010
≥ 5	3.2	3.4	-0.011
TCOC, mean (SD) ($)	2,610.4 (11,127.3)	2,822.9 (9,311.9)	-0.023

Abbreviations: MSK, musculoskeletal; SMD, Standardized Mean Differences; TCOC, total all-cause costs of care.

Briefly, the weighted cohort was predominantly female, and middle-aged, with a majority of participants residing in the US Midwest and South regions (detailed information in Table 1). Clinical presentations were well-balanced across both groups, with spine-related conditions being the most prevalent (42.0% in the IG vs 40.6% in the CG, SMD = 0.027), followed by lower-limb (34.5% vs 38.2%, SMD = -0.076) and upper-limb conditions (23.5% vs 21.2%, SMD = 0.056).

Comorbidity burden was low and comparable between groups (Elixhauser index ≤ 0: 93.6% IG, 93.3% CG; SMD = -0.004). Baseline total all-cause cost of care (TCOC) was also balanced, with groups showing

statistical similarity after weighting (IG: $2,610.4, SD 11,127.3; CG: $2,822.9, SD 9,311.9; SMD = -0.023).

Primary Outcome: Opioid Initiation

Under the conventional definition of opioid exposure (≥ 1 prescription), opioid use over 12 months occurred in 3.7% (95% CI 3.1; 4.5) of the IG and 7.4% (95% CI 6.1; 8.8) of the CG, corresponding to an absolute difference of 3.7 (95% CI 2.9; 4.3) percentage points (pp) ($p < 0.001$), following an IPW and multivariable analysis (Supplementary Table 3). Divergence between groups emerged early and widened progressively over the follow-up period (Fig. 2a). The observed adjusted odds ratio (aOR) was 0.49 (95% CI 0.46; 0.52, $p < 0.001$; unadjusted OR 0.49, 95% CI 0.45; 0.54, $p < 0.001$). E-value analysis (3.52; lower bound 3.24) suggested that a relatively strong unmeasured confounder would be required to explain the observed association.

Using a more stringent definition of opioid initiation (≥ 2 prescriptions or ≥ 1 prescription with higher-tablet counts), rates were 1.8% (95% CI 1.3; 2.3) in the IG and 3.2% (95% CI 2.4; 4.3) in the CG (absolute difference: 1.5 pp, 95% CI 1.0; 1.9, $p < 0.001$), with differences also emerging early after the index (Fig. 2b). An aOR of 0.54 (95% CI 0.49; 0.59; $p < 0.001$) was estimated alongside an E-value of 3.13 (lower bound 2.80; unadjusted OR 0.56, 95% CI 0.49; 0.63, $p < 0.001$). Unweighted outcome comparisons are presented in Supplementary Tables 4 and 5.

These results were consistent across demographic, socioeconomic, and clinical subgroups including pain site and mental health (Supplementary Table 6). The effect of the care delivery mode on opioid initiation was larger for the IG compared with in-person care among males (aOR 0.42, 95% CI 0.37; 0.49, $p < 0.001$), individuals with lower limb conditions (aOR 0.42, 95% CI 0.36; 0.48, $p < 0.001$) and those in areas of high social deprivation (SDI 61–80) (aOR 0.43, 95% CI 0.34; 0.54), $p < 0.001$, Fig. 2c, Supplementary Table 4). We also observed regional heterogeneity, with lower likelihood of opioid initiation in the West (aOR 0.43, 95%CI 0.32; 0.57, $p < 0.001$), while the association was not statistically significant in the Northeast ($p = 0.594$) (Fig. 2c, Supplementary Table 6).

Opioid Prescribing Burden

Across both the conventional and conservative opioid exposure definitions, a lower proportion of individuals with multiple opioid prescription fills during follow-up was consistently observed in the IG compared to the CG (conventional: 0.9% (95% CI 0.6; 1.3) vs 2.3% (95% CI 1.7; 3.2), absolute difference 1.4 pp (95% CI 0.9; 1.8; $p < 0.001$); conservative: 0.9% (95% CI 0.6; 1.3) vs 2.0% (95% CI 1.5; 2.8), absolute difference 1.1 pp, (95% CI 0.7; 1.5; $p < 0.001$)).

Similarly, the rate of opioid prescriptions per 100 patients was lower among individuals in the IG than in the in-person care group, representing an absolute difference for the conventional definition of 8.7 prescriptions (95% CI 4.1; 13.3, $p = 0.001$; IG: 8.0 (95% CI 4.9; 12.9) vs CG: 16.7 (95% CI 10.3; 27.1)) (Supplementary Table 3), and 5.7 prescriptions (95% CI 1.8; 9.6, $p = 0.006$; IG: 5.7 (95% CI 3.1; 10.6) *vs*

CG: 11.4 (95% CI 6.2; 21.2)) for the conservative. Unweighted outcomes are available in Supplementary Tables 4 and 5.

Sensitivity Analyses

To assess whether residual confounding or model specification could explain the observed associations, we conducted several sensitivity analyses.

Propensity Score Matching

Using the more stringent definition of opioid exposure, 1:1 propensity score matching produced a matched cohort of 8,488 individuals (4,244 per group; Fig. 1) with well-balanced baseline characteristics (Supplementary Tables 1 and 15 and Supplementary Fig. 4), yielding results consistent with the primary weighted analysis.

Opioid initiation occurred in 2.2% (95% CI 1.8; 2.7) of patients initiating AI-enabled MSK care vs 5.0% (95% CI 4.4; 5.7) of those initiating in-person physical therapy, representing an absolute difference of 2.8 pp (95% CI 2.0; 3.6) ($p < 0.001$) (Supplementary Table 16). The likelihood of opioid initiation was lower among patients in IG relative to those in the CG (OR 0.43, 95% CI 0.34; 0.55, $p < 0.001$; E-value of 4.10, lower CI: 3.05).

The proportion of individuals with multiple opioid prescription fills during follow-up was lower in the IG than in the CG (absolute difference 1.8 pp, 95% CI 1.2; 2.4; $p < 0.001$), as well as the total prescription burden (prescriptions per 100 patients, absolute difference of 7.1, 95% CI 4.7; 9.4) (Supplementary Table 16). Although non-significant, this trend extended to the magnitude of overall opioid exposure, as the mean daily MMEs dispensed in the IG was 37.9 (95% CI 34.2; 41.6), *vs* 43.3 (95% CI 40.1; 46.5) in the CG (difference: 5.4, 95% CI 0.1; 10.8; $p = 0.054$) (Supplementary Table 17). Similarly, prescribing intensity and profile were directionally consistent with the primary weighted results among patients who received opioid prescriptions (Supplementary Table 17).

Falsification Analysis

Prescribing patterns of metformin and simvastatin, medications unrelated to MSK care, showed no between-group differences under either weighting or matching approaches (Supplementary Table 18), supporting the specificity of the observed associations and reducing the likelihood that findings were driven by residual confounding related to healthcare utilization or treatment-seeking behavior.

DISCUSSION

In this large, real-world cohort of opioid- and surgery-naive adults with MSK conditions, initiation of first-line conservative care through different delivery pathways was associated with differences in

downstream opioid exposure. Individuals initiating an AI-enabled, digitally delivered care pathway consistently exhibited lower opioid use across multiple dimensions, including initiation, prescribing burden, intensity, and profile compared with those initiating in-person physical therapy. When applying more stringent criteria to define opioid exposure (requiring repeated prescriptions or higher dispensing volume), differences in opioid initiation and prescribing burden remained directionally consistent, while differences in prescribing intensity and profile were attenuated and no longer statistically significant. This pattern suggests that the observed associations are not driven solely by low-intensity or incidental opioid use, while highlighting that differences in higher-risk prescribing may be more sensitive to outcome definition. While causal effects cannot be established, findings were consistent across demographic, socioeconomic, and clinical subgroups and were robust to multiple analytic approaches (weighting, matching, alternative opioid initiation definition, and falsification analyses), designed to address confounding. As with all observational analyses, the possibility of residual bias cannot be excluded.

Most opioid epidemiology studies use relatively inclusive definitions such as any filled prescription or any opioid exposure during follow-up, particularly when evaluating initiation[17,41,42]. Rates of opioid initiation observed among individuals starting in-person physical therapy in this study were within the range of prior U.S. reports in opioid-naive patients with MSK conditions[21,41], and substantially lower than rates reported in broader MSK populations receiving mixed or pharmacologically-oriented care pathways[43,44]. For example, in a large claims-based study of nearly 2.5 million opioid-naive patients with newly diagnosed low back pain or lower extremity pain, up to 32% received an opioid prescription within the first year[43]. Prior work has also shown that initiating care with a physical therapist, rather than a physician, is associated with a 20–50% lower likelihood of opioid prescribing,[42,45,46]. Together, these findings reinforce evidence that prioritizing conservative, nonpharmacologic care as first-line treatment is associated with reduced opioid exposure.

The present study extends this body of evidence by suggesting that differences in opioid exposure may also be observed across modes of conservative care delivery. Under the conventional definition of opioid exposure, differences between care delivery modes extended beyond initiation to multiple prescribing dimensions, including dose, potency, and drug schedule, with magnitudes comparable to those reported in system-level opioid stewardship interventions[47–50]. Patients in the IG were less likely to receive higher daily doses (i.e., ≥ 50 & ≥90 MMEs/day), higher-potency opioids and Schedule II medications. These findings are clinically relevant, as opioid-related harms increase in a dose-dependent manner[38,51], and higher-potency opioids and Schedule II medications are associated with greater risk of dependence and opioid use disorder[39,40].

To focus on a more stringent opioid initiation metric, to address potential noise from incidental, short-course prescriptions, a more conservative approach was also pursued requiring at least two prescriptions or one prescription with a larger tablet count. The findings were consistent regarding lower opioid initiation and prescription burden among IG vs CG. Subgroup analyses provided additional insight

into the generalizability and context-dependence of these findings. Associations were observed across demographic, socioeconomic, and clinical strata, including among individuals residing in areas of higher social deprivation, suggesting that the observed differences are not limited to more advantaged populations, a particularly relevant insight given known disparities in access to conservative MSK care and opioid prescribing patterns[52,53]. At the same time, variation in outcome estimates across regions, including absence of effect in the Northeast, suggests that local practice patterns, access to care, or unmeasured contextual factors may influence the relationship between care delivery pathways and opioid use. Similarly, stronger associations observed in certain clinical subgroups, such as lower limb conditions, may reflect differences in care pathways, symptom trajectories, or treatment responsiveness. These findings should be interpreted as exploratory and hypothesis-generating, and warrant further investigation in studies specifically designed to assess heterogeneity of treatment effects.

Differences in prescribing intensity and profile were not statistically significant overall under these more stringent criteria. However, the presence of subgroup-specific differences suggests that the broader trends may be primarily driven by these specific populations. Given the smaller sample size inherent in the stricter definition, these results warrant cautious interpretation and further study using expanded datasets for the identified subgroups.

Several mechanisms may plausibly underlie the observed associations. Differences in access to care represent a key factor: barriers to in-person physical therapy, including travel, scheduling, and insurance constraints, may delay or limit engagement with conservative care[54], which digitally delivered care pathways may facilitate[18–20,25,28]. Previously, we have shown that when controlling for equal treatment dosage, similar pain and function outcomes were observed across both in-person and remote physical therapy[33,34]. Herein, greater median total sessions per patient were observed on the remote physical therapy than on the in-person group (although session duration was not controlled for). Greater continuity of care may increase the likelihood that nonpharmacologic treatment is pursued before escalation to pharmacologic management. Additionally, differences in care context may influence prescribing opportunities, including access to clinicians able to initiate or renew opioid prescriptions. These mechanisms were not directly evaluated and should be considered hypothesis-generating. Future research using prospective or quasi-experimental designs will be important to better disentangle the relative contributions of access, adherence, care context, and other pathway-specific factors.

This study has several strengths. First, it leverages a large, real-world claims dataset, enabling evaluation of care delivery pathways and opioid prescribing patterns in routine clinical practice across a diverse population of opioid-naive individuals with MSK conditions. Second, the study design incorporated an active comparator, initiation of in-person physical therapy, reducing confounding related to healthcare-seeking behavior compared with untreated or usual-care comparisons. Third, the evaluation of opioid prescribing across several clinically relevant domains, including initiation (under conventional and conservative definitions), exposure metrics, and prescribing intensity and profiles, provides a more comprehensive assessment of opioid-related risk than single-outcome analyses. Finally, we applied multiple complementary analytic approaches, including IPW, propensity score matching, alternative

opioid initiation definition, falsification analyses using negative control medications, and quantitative bias analysis using E-values, to interrogate the robustness of the findings to measured and unmeasured confounding. The consistency of results across these approaches, as well as across multiple dimensions of opioid exposure, strengthens confidence in the observed associations.

This study also has important limitations. As with all retrospective observational analyses, causal inference cannot be established. Although we used multiple analytic strategies to control for several key variables, residual confounding cannot be excluded, including unmeasured factors such as pain severity, functional status, social support network, patient preferences, digital literacy, or clinician prescribing tendencies that may influence both care pathway selection and opioid use. Second, treatment assignment was not randomized, and selection into digitally delivered versus in-person care pathways may reflect differences in care access, motivation, or healthcare engagement that are not fully captured in claims data. Third, measures of care engagement and adherence may not be directly comparable across delivery modalities, limiting insights into potential mechanisms underlying the observed differences. Fourth, claims data do not capture patient-reported outcomes, and do not confirm medication consumption, only dispensing. Fifth, variation in regional estimates suggests that unmeasured contextual factors, including local practice patterns or access to care, may influence the observed associations. Finally, the findings may not generalize to populations outside the insured U.S. setting or to other models of digitally delivered or in-person care.

Taken together, these findings suggest that the mode of delivery of first-line conservative MSK care may influence downstream opioid prescribing trajectories. Although causal inference remains limited by the observational design, the consistency of findings across analytic approaches and outcome definitions supports the hypothesis that care delivery pathways represent a potentially modifiable component of opioid stewardship. As scalable, access-expanding approaches, AI-enabled digitally delivered care models may support health systems and payers align with approaches to reduce opioid exposure while helping to address structural barriers to guideline-concordant care.

METHODS

Study Design

We conducted a retrospective, observational study designed to emulate a target trial. The study compared initiation of digitally delivered versus in-person conservative MSK care among opioid- and surgery-naive adults with new-onset MSK conditions, evaluating associations with downstream opioid exposure. To address potential confounding, we applied complementary approaches: propensity score–based inverse probability weighting (IPW), matched-cohort analyses, falsification testing using negative control medications, and quantitative bias analysis using E-values.

This study used administrative medical and pharmacy claims data from individuals with access to an AI-enabled MSK care program offered as a benefit through employer-sponsored commercial insurance

plans in the U.S. The study compared opioid-related outcomes between individuals initiating digitally delivered MSK care (intervention group - IG) and those initiating in-person physical therapy (comparator group - CG). Data were obtained from a large, HIPAA-compliant, deidentified U.S. claims database (PurpleLab), spanning April 2022 to August 2025.

The study was conducted in accordance with the Declaration of Helsinki and followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines (Supplementary Table 19). Because the dataset was fully deidentified the study did not meet the regulatory definition of human subjects research[55–57] and was exempt from institutional review board oversight and informed consent requirements.

Sample size

Given the retrospective, observational design, no formal prospective sample size calculation was performed. The study size was determined by the number of eligible individuals in the available claims data, and the resulting cohort yielded outcome event counts for multivariable modeling and sensitivity analyses.

Study population

Eligible individuals were adults (≥ 18 years) residing in the U.S. with an MSK-related index event between April 2023 and August 2024. The index date was defined as the initiation of conservative care, corresponding to enrollment in the AI-enabled digitally delivered MSK care program for the IG or an initial in-person physical therapy evaluation for the CG, as determined through claims.

Target MSK conditions were identified using International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes recorded in claims data (Supplementary Table 20). These included common conditions indicated for physical therapy, such as joint and soft tissue disorders (e.g., tendinopathies and arthropathies) affecting the low back, neck, shoulder, knee, hip, ankle, elbow, and wrist/hand. Individuals were required to have continuous medical and pharmacy claims coverage for at least 12 months before and 12 months after the index date. To restrict the cohort to opioid-naive cases, individuals were excluded if they had any opioid prescription or MSK-related surgery during the pre-index period (12 months). Additionally, we excluded patients with prior care for the index pain site, unless that care occurred only within the 3 months immediately preceding the index date. To ensure initial episodes of care, the 3-month waiver period could not include physical therapy. Additional exclusion criteria included medical claims indicating active cancer treatment, cognitive impairment (e.g., dementia), pregnancy or perinatal status, or diagnoses related to trauma, poisoning, or burns at any time during the study period (Supplementary Table 21). Individuals with extreme healthcare utilization, defined as total annual medical expenditures exceeding US $500,000, were also excluded to limit the influence of outliers.

Intervention Group

The intervention consisted of an AI-enabled, digitally delivered MSK care program combining software-based support with clinician oversight. The program delivered a multimodal intervention including exercise therapy, education, and cognitive behavioral components, as previously described [33,34,58,59].

Participants voluntarily enrolled through digital platforms and, following enrollment, completed a structured intake assessment, reviewed by a licensed doctor of physical therapy. Based on this evaluation, an individualized, guideline-concordant treatment plan was prescribed and longitudinally monitored by the clinician.

Exercise therapy was delivered through an FDA-listed medical device software platform, which guided patients through prescribed exercises and provided real-time feedback using motion tracking technologies, including computer vision–based algorithms. Patients accessed the program through a mobile application that delivered exercise instructions, educational content, behavioral support modules and secured two-way messaging with the treating clinician through an integrated in-app communication channel.

The platform incorporated AI–enabled components to support both patient engagement and clinical management. Patient-facing features included real-time feedback on exercise performance, and bidirectional communication with an AI agent. Clinician-facing tools included a web-based portal that enabled remote monitoring of patient progress and provided algorithm-driven recommendations and alerts to flag patients that require more immediate attention.

Active Comparator Group

The comparator group comprised individuals who initiated in-person physical therapy during the study period, defined by a physical therapy evaluation claim (Current Procedural Terminology (CPT) codes 97161, 97162, 97163, or 97164) identified in the Restructured BETOS Classification System[60]. The index date corresponded to a physical therapy evaluation associated with a MSK diagnosis recorded as the primary reason for care.

In-person physical therapy represents standard conservative management for MSK conditions and typically involves face-to-face evaluation and treatment by a licensed physical therapist.

Data sources and privacy

Medical and pharmacy claims data were obtained from the PurpleLab platform, a large U.S. healthcare claims aggregation database (Supplementary Note 1). Medical claims included diagnosis codes (ICD-10), procedure codes (CPT and HCPCS), service dates, and place of service. Pharmacy claims included

records of dispensed medications, including National Drug Codes (NDCs), dispensing dates, quantity supplied, and days of supply. Claims data also included deidentified patient demographics, such as sex, age, and geographic region.

Additional demographic (i.e., area-level socioeconomic indicators derived from ZIP code–linked Social Deprivation Index (SDI)) and clinical information was obtained from program records and used to supplement claims-based variables where available. These data were collected under prior institutional review board approval with electronic informed consent.

Data from all sources were linked using anonymized unique identifiers and deidentified in accordance with HIPAA. Standardized preprocessing procedures were applied to ensure consistency in coding and variable definitions across datasets (Supplementary Note 2).

Outcomes

Outcomes during the 12-month follow-up were assessed under two definitions for opioid exposure: conventional, defined as the dispensing of at least one opioid prescription; conservative, defined as the dispensing of two or more prescriptions, or a single prescription of 20 or more tablets[61]. The latter was selected to provide a more stringent metric for opioid initiation by minimizing potential misclassification of sporadic or incidental opioid use (e.g., associated with a surgical procedure[61]).

The primary outcome was defined as incident opioid initiation. Opioid use was identified from pharmacy claims using NDCs and from medical claims using opioid-related procedure codes (Supplementary Table 22).

Secondary outcomes included opioid burden and prescribing patterns (including intensity and profiles). Opioid burden was measured by the rate of multiple (2+) prescriptions and the number of prescriptions per 100 patients. Prescribed intensity was quantified as the average daily dose in morphine milligram equivalents (MMEs/day). MMEs were calculated for each dispensed prescription using standard conversion factors[38,62,63] based on opioid type, strength, and quantity dispensed (Supplementary Table 23). Prescribing intensity was further evaluated using clinically relevant thresholds of ≥ 50 and ≥ 90 MMEs/day[38,39]. Opioid profiles were assessed by potency relative to morphine and drug schedule classification according to the U.S. Drug Enforcement Administration (DEA), where lower schedule numbers indicate higher abuse potential[39,40] (Supplementary Table 24).

Chronic opioid therapy (defined as ≥ 90 consecutive days of opioid use[64,65]) was also evaluated but not included as an outcome given its very low incidence (< 1% among opioid users in both groups), limiting the feasibility of adjusted analyses in this cohort.

Engagement was evaluated over the 12-month post-index period for patients receiving either AI-enabled or in-person physical therapy, based on physical therapy visit claims in the CG and claims and logged

participation in the IG.

Statistical analysis

Data were tested for normality using the Shapiro-Wilk test. Parametric or non-parametric statistical analyses were subsequently selected based on the distribution of the data, as detailed below. Baseline characteristics of the unweighted cohorts were summarized descriptively.

Inverse Probability Weighting

To address potential confounding and baseline imbalances between groups, we applied an IPW approach. Propensity scores, defined as the probability of initiating digitally delivered versus in-person care conditional on baseline covariates, were estimated using multivariable logistic regression incorporating demographic, socioeconomic, and clinical characteristics (Supplementary Table 1)[66]. To improve estimator stability and reduce the influence of extreme weights, propensity scores were truncated at the 1st and 99th percentiles. Covariate balance after weighting was assessed using standardized mean differences (SMDs), with values < 0.10 generally considered indicative of good balance; after weighting, covariates were well balanced overall, with only minimal residual imbalances (Supplementary Fig. 2).

Outcome models were estimated in the weighted cohort and additionally adjusted for baseline covariates, yielding doubly robust estimates. Covariates included sex, age category, geographic region, index MSK condition, SDI, Weighted Elixhauser comorbidity group, number of MSK conditions, baseline mental health and substance use diagnoses, and baseline total all-costs of care (TCOC). Robust variance estimators were used to account for weighting.

Weighted outcome analyses were conducted using survey-weighted regression models to estimate adjusted odds ratios (aORs), proportions, and means. Model families were chosen based on outcome distributions: quasibinomial (logit link) for binary outcomes, quasipoisson (log link) for count outcomes, and Gamma (log link) for right-skewed continuous outcomes (e.g., MME/day). All 95% CIs and p-values were derived using robust sandwich variance estimators to account for weighting.

Subgroup analyses were performed to assess the consistency of findings across prespecified strata, including sex, age categories, geographic region, SDI, MSK anatomical site, and the presence of mental health or substance use diagnoses; given the consistent trends observed across both opioid exposure definitions, only results from the more stringent definition are reported. Within each subgroup, outcome models were estimated using the same weighting and covariate adjustment strategy as in the primary analysis. Outcomes evaluated in subgroup analyses included opioid initiation, average daily opioid dose (MMEs/day), prescribing above clinically relevant MMEs thresholds (≥ 50 and ≥ 90 MMEs/day), opioid potency, and DEA schedule classification.

All analyses were conducted using R (version 4.2.2; R Foundation for Statistical Computing), particularly *ipw, survey* and *emmeans* packages for propensity score weighting and robust variance estimation. To account for multiple comparisons, p-values were adjusted using the Benjamini–Hochberg false discovery rate method across outcomes (opioid initiation (including subgroup analysis), prescriptions per 100 individuals, ≥ 2 prescriptions, MMEs/day, ≥ 50 and ≥ 90 MMEs/day, potency categories, and DEA schedule categories). Other subgroup analyses were considered exploratory and were not adjusted for multiple comparisons. Statistical significance was defined as a two-sided α of 0.05.

Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the findings.

First, a propensity score–matched cohort was constructed using a 1:1 nearest-neighbor matching format based on the same baseline covariates included in the primary weighting model (Supplementary Table 1). Propensity scores were estimated using a generalized linear model. Matching was constrained on baseline TCOC to improve comparability between groups. Covariate balance after matching was assessed using SMDs, with values of < 0.10 considered acceptable (Supplementary Fig. 4). Opioid-related outcomes were re-estimated in the matched cohort to evaluate consistency with the primary analysis using the most stringent opioid criteria.

Second, E-values were calculated to assess the potential impact of unmeasured confounding on the observed treatment effects, following the approach described by VanderWeele and Ding[67,68]. E-values are reported for both the point estimate and the confidence interval limit closest to the null.

Finally, negative control analyses were performed by comparing prescribing rates of medications unrelated to MSK care (metformin and simvastatin; Supplementary Table 25) between groups, to assess potential residual differences in healthcare utilization.

Declarations

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

The codes that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contribution Statement

All authors made a significant contribution to the work reported as follows:

F. Costa conceptualized the study. A.P.P., B.D., and A.P. curated the data, while A.P.P., B.D., A.C.A., and X.T. conducted the formal analysis. A.P.P., B.D., A.C.A., and F. Costa contributed to the interpretation of the data. V.B. provided the necessary resources for the research. A.P.P, B.D., A.C.A., and F. Costa drafted the original manuscript, and all authors participated in reviewing and editing the final version. All authors have read and approved the published version of the manuscript.

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Competing Interests

The authors declare the following competing interests: A.P.P., B.D., A.P., A.C.A., D.J., V.B., L.B., C.M., F.D.C., and F. Costa are employees of Sword Health, the sponsor of this study. V.B. and F.D.C. also holds equity in Sword Health, and V.B. is the CEO of the same company. S.P.C. is an independent scientific and clinical consultant who received an adviser honorarium from Sword Health. XT, an independent scientific consultant, received a scientific advisor honorarium from Sword Health.

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Figures

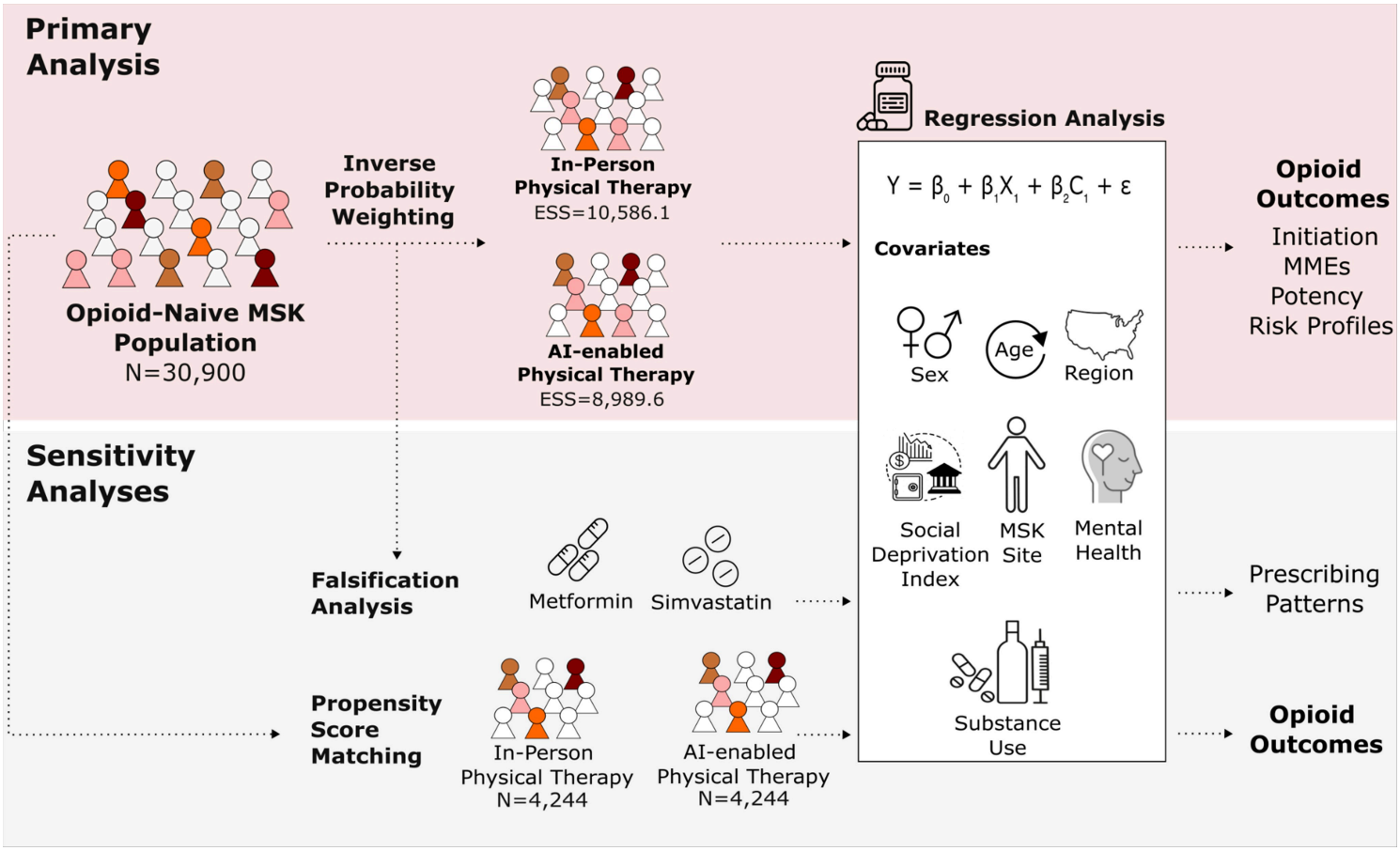


Figure 1

Study design and analytical framework. A cohort of 30,900 opioid-naive patients with MSK conditions who initiated either in-person or AI-enabled physical therapy was identified from a large claims database. Inverse probability weighting (IPW) with covariate-adjusted outcome models was employed to compare opioid outcomes, including initiation, Morphine Milligram Equivalents (MMEs), analgesic potency relative to morphine, and risk profiles, between groups, over 12 months following treatment initiation. ESS corresponds to the Effective Sample Size after applying IPW. To assess the robustness of the primary findings, sensitivity analyses included Propensity Score Matching (N = 4,244 per group) and a falsification analysis using negative control outcomes (metformin and simvastatin). All models were adjusted via multiple regression for covariates, including sex, age, region, Social Deprivation Index (SDI), MSK site, mental health status, and substance use diagnosis.

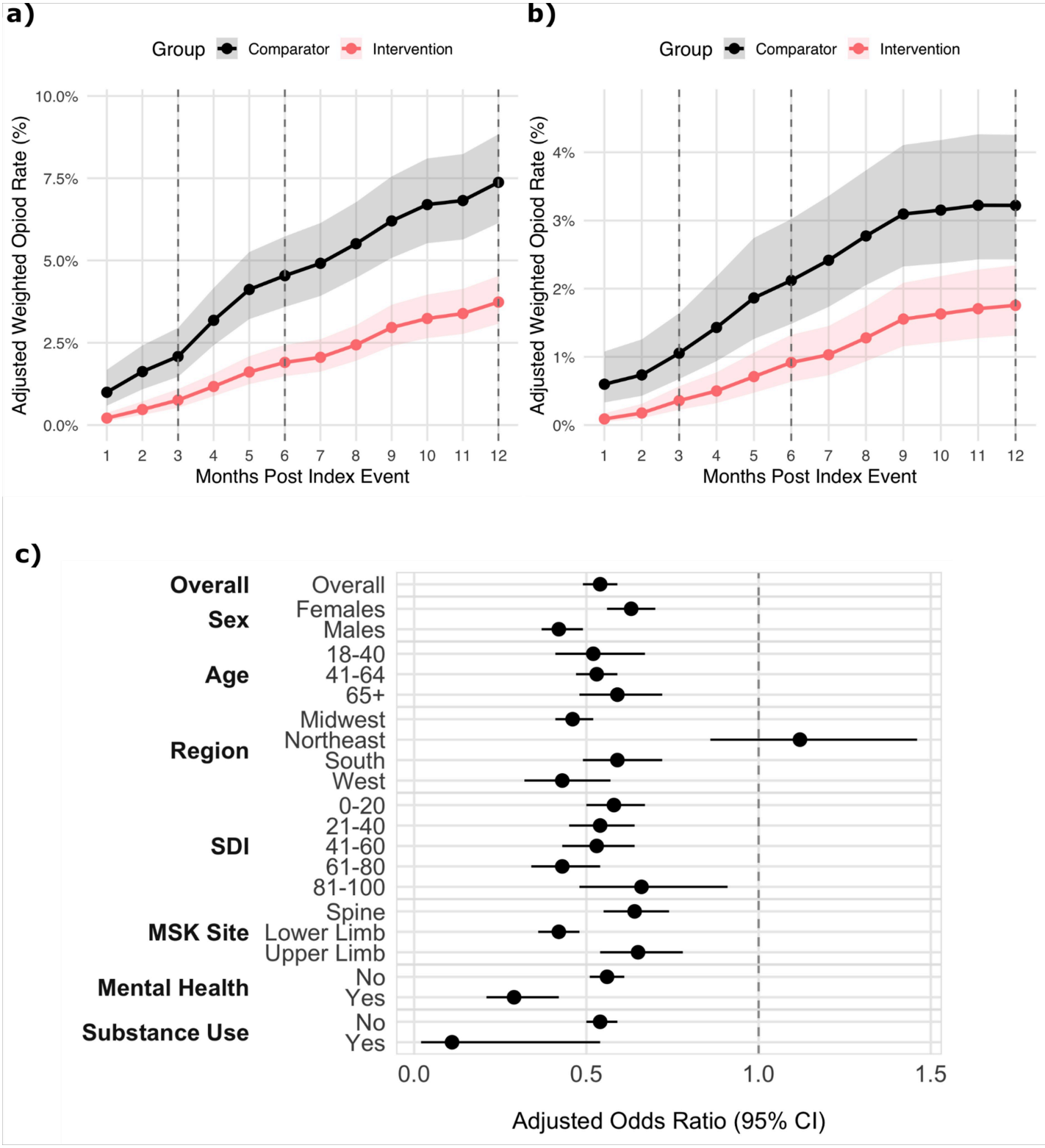


Figure 2

Opioid Initiation. Opioid initiation rates over the 12-month post-index period under the a) conventional definition of opioid exposure being at least 1 prescription and b) conservative definition of ≥2 prescriptions or ≥1 prescription with higher-tablet counts. Lines depict adjusted weighted opioid initiation rates (%). The AI-enabled intervention group (red) showed a lower rate of opioid initiation compared to the in-person comparator group (black) despite the definition used. Shaded areas represent

95% confidence intervals (CI). c) Adjusted Odds Ratios of Opioid Initiation. Forest plot showing adjusted odds ratios (aOR) and 95% confidence intervals (CI) for opioid initiation overall and across demographic and clinical subgroups. The vertical dashed line at 1.00 represents the null; aOR < 1.00 indicates a reduced likelihood of initiation in the intervention group. Abbreviations: MSK, musculoskeletal; SDI, Social Deprivation Index.

Supplementary Files

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- SupplementaryMaterial.pdf