Mediation analysis of the MI-NAV study: statistical analysis plan

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This document is a mediation analysis statistical analysis plan for the MI-NAV study. Detailed information on the MI-NAV study, including primary analyses can be found in the study protocol:

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The MI-NAV study[1] is a randomised controlled trial evaluating the effectiveness of two treatment packages (motivational interviewing plus usual case management or stratified vocational advice intervention plus usual case management) compared to usual case management alone, on return to work among people on sick leave due to musculoskeletal disorders. This statistical analysis plan describes the planned mediation analysis of the MI-NAV study. If either treatment package is found to be effective, the causal mediation analysis will help explain how the treatment works. Conversely, if either treatment package is not found to be effective, the causal mediation analysis will help identify where the hypothesised mechanisms broke down.

Primary mediation objective

The primary objective was to estimate the extent to which the proposed mediators (workability and return to work expectancy) mediate the effect of the two treatment packages compared to usual case management alone, on return to work among people on sick leave due to musculoskeletal disorders. We will first consider the mediators together and estimate the joint mediation effect. Second, we will consider the mediators independently and estimate single mediation effects.

Secondary mediation objective

The secondary objective was to estimate the extent to which the joint and single mediation effects vary by risk stratification subgroup (low/medium risk vs high risk).

Interventions

Motivational interviewing plus usual case management (MI)

The participants in the MI arm, in addition to usual case management, were offered two motivational interviewing conversations provided by trained Norwegian Labour and Welfare Administration caseworkers. The first conversation was conducted as soon as possible after random allocation, and the second two weeks later.

Stratified vocational advice intervention plus usual case management (SVAI)

The participants in the SVAI arm, in addition to usual case management, were offered 1–2 telephone calls for the low/medium risk group or 3–4 telephone calls and/or face-to-face

meetings for the high-risk group with a trained physiotherapist. The first contact was ideally conducted within a week after allocation and the treatment stopped by week 26 of the sick leave period or if the participant had returned to work for more than four weeks in the same working hours as they had before going on sick leave.

Usual Case management (Control)

Usual case management was provided by Norwegian Labour and Welfare Administration caseworkers and ideally followed this timeline: within the first four weeks of sick leave, a return to work plan was made by the employer and worker; within seven weeks, a dialogue meeting between the employee, employer and other relevant stakeholders such as general practitioner, was arranged by the employer; within week 26 of the sick leave period, the Norwegian Labour and Welfare Administration arranged a second dialogue meeting between the employee, the employer and in some cases the general practitioner who issued the sick leave.

Primary outcome

The primary outcome is sickness absence days, measured as the number of sickness absence days from baseline assessment date until the six-month follow-up. Sickness absence days will be calculated from information provided by different national registries including information on sick leave payments, sick leave certificates, work assessment allowance, disability pensions and employment percentage.

Mediators

Workability, assessed by one item from the Finnish Work Ability Index (WAI)[2] recording "Current workability compared with the lifetime best" on a 0–10 numerical rating scale. The WAI is a valid and reliable assessment of workability.[2] Workability was assessed three-months after randomisation.

Return to work expectancy, assessed by one question from the Örebro Musculoskeletal Pain Screening Questionnaire short form (ÖMPSQ-SF)[3] ("In your estimation, what are the chances you will be working your normal duties in three months") on a 0–10 numerical rating scale. The ÖMPSQ-SF has been validated against the original ÖMPSQ 24-item version which is

considered reliable.[4] Return to work expectancy was assessed three-months after randomisation.

Moderator

The 10-item Keele STarT MSK tool[5] and the 10-item ÖMPSQ-SF[3] have been used in combination to stratify the participants into one of two risk groups before group allocation: low/medium risk or high risk of long-term sick leave. Participants were stratified to the high-risk subgroup if they had ≥9 points (out of 12) on the Keele STarT MSK tool and ≥ 60 points (out of 100) on the ÖMPSQ-SF at baseline.[6]

Confounders

In each model, we assumed no confounding of the treatment–mediator and treatment–outcome relationships due to random allocation of treatment. We identified potential confounders of the mediator-outcome relationship by selecting measured pre-treatment covariates that are hypothesised to be a cause of the mediator, the outcome, or both.[7] The minimum sufficient adjustment set includes age, sex, education level, sick leave in the previous year, musculoskeletal health, risk of work disability, physical activity and employer follow-up all assessed at baseline.

Rationale for choice of mediators

Workability and return to work expectancy have been selected as the mediators for our mediation analysis. Workability, defined as an interaction between the person, the task and the working environment,[8] has been shown to strongly relate to continuing work, avoiding sickness absence, or returning to work after sick leave.[9] Patient return to work expectations have been shown to play an important role in return to work outcomes.[10] In patients with musculoskeletal injuries, return to work expectancy has been shown to mediate the relationship between psychological factors associated with injury and return to work outcomes.[11–13] Both the MI and SVAI treatment arms incorporate cognitive and behavioural components aimed at reducing sickness absence days and increasing both workability and return to work expectations as a key treatment targets.[1,14–16]

Data collection

To ensure a temporal sequence between the treatment, mediator, and outcome, data was collected over three sequential time points: 1) baseline, prior to randomisation (primary outcome, mediators, confounders, moderator); 2) three months after randomisation (mediators); and 3) six months after randomisation (outcome).

Effects of interest

For each treatment package and each mediator:

1. We will estimate the effect and corresponding uncertainty estimates for the treatment–mediator relationship, the treatment-outcome relationship and the mediator-outcome relationship.

2. We will estimate the natural indirect and direct effects of treatment on the outcome considering the mediators simultaneously (joint mediated effect), and independently (single mediated effect).

3. We will estimate the proportion mediated which is the fraction of the treatment-outcome relationship that is explained by the indirect effect.

4. We will estimate the extent to which the natural indirect and direct effects are moderated by risk subgroup.

Causal models and assumptions

We specified two joint mediator models and four independent single mediator models (Table 1). The causal models are represented in the directed acyclic graph (Figure 1). In each model, we assumed that the treatment-mediator and treatment-outcome relationships would be unconfounded because of random allocation of treatment. We assumed that the mediator-outcome relationship is unconfounded following adjustment for the sufficient set of potential observed confounders. We also assumed that the two mediators were independent of one another. Because the causal effect of the mediator on the outcome could depend on the treatment status, we will include treatment-mediator interaction terms into the models.

Statistical analysis

We will use a regression-based inference approach for causal mediation analysis.[17,18] Analyses will be performed in R (version 3.6.3; R Foundation for Statistical Computing) using the *CMAverse* package.[18]

We will estimate effects for the treatment–mediator and mediator–outcome relationship with two regression models: the mediator model and the outcome model. We will specify the mediator model as a linear regression of the mediator at three months after randomisation (dependent variable) on treatment allocation and baseline values of the mediator (equation 1). The outcome model will be specified as a linear regression of the outcome at six months after randomisation (dependent variable) on the mediator at baseline and three months after randomisation, treatment allocation, possible confounders of the mediator-outcome relationship, and a treatment allocation x mediator interaction term to increase model flexibility (equation 2).[19]

Equation 1	$m = \beta_0 + \beta_1 x + \beta_2 m^* + \varepsilon$
Equation 2	$y = \theta_0 + \theta_1 x + \theta_2 m + \theta_3 xm + \theta_4 m^* + \theta_5 c' + \varepsilon$

* value at baseline

' vectors of covariates

Using the mediator and outcome regression models, we will simulate potential values of the mediator for each participant under each level of the treatment; then simulate potential outcome values for each participant under all combinations of the treatment and simulated mediator values. From these observed and simulated potential values of the mediator and outcome, we will estimate the indirect, direct and total treatment effects. We will estimate standard errors and the corresponding 95% confidence intervals of these causal effects through bootstrapping. We will use the *cmest* function from the *CMAverse* package to estimate the causal mediation effects.

Moderated-mediated effects

We will estimate if the indirect and direct effects vary between participant risk stratification subgroup (low/medium risk vs high risk).

Missing data

We will assess the proportion and patterns of missing mediator and outcome data. We will conduct all analyses on complete cases if the proportion of missing data is less than 5% for any of the mediators or outcome. If missing data exceeds 5% we will use multiple imputations by chain equations to impute 10 datasets using the 'mice' package.[20]

Sensitivity analyses

We will conduct sensitivity analyses using the mediational E-value[21] approach to determine the robustness of the estimated indirect and direct effects to bias introduced by unmeasured pre-treatment confounding. The mediational E-value describes the strength of the confounder-outcome relationship and the approximate strength of the confounder-mediator relationship that, together, would be required to reduce the direct or indirect effect to 0. We will use the *cmsens* function from the *CMAverse* package to conduct sensitivity analysis for unmeasured confounding via the E-value approach.

Model	Treatment	Mediator at 3 months (M1)	Mediator at 3 months (M2)	Outcome at 6 months
Multiple mediator models				
1.1	MI	Workability	Return to work expectancy	Sickness absence days
1.2	SVAI	Workability	Return to work expectancy	Sickness absence days
Single mediator models				
2.1	MI	Workability	-	Sickness absence days
2.2	SVAI	Return to work expectancy	-	Sickness absence days
2.3	MI	Return to work expectancy	-	Sickness absence days
2.4	SVAI	Workability	-	Sickness absence days

Table 1. Overview of mediator models.

MI = motivational interviewing; SVAI = stratified vocational advice intervention
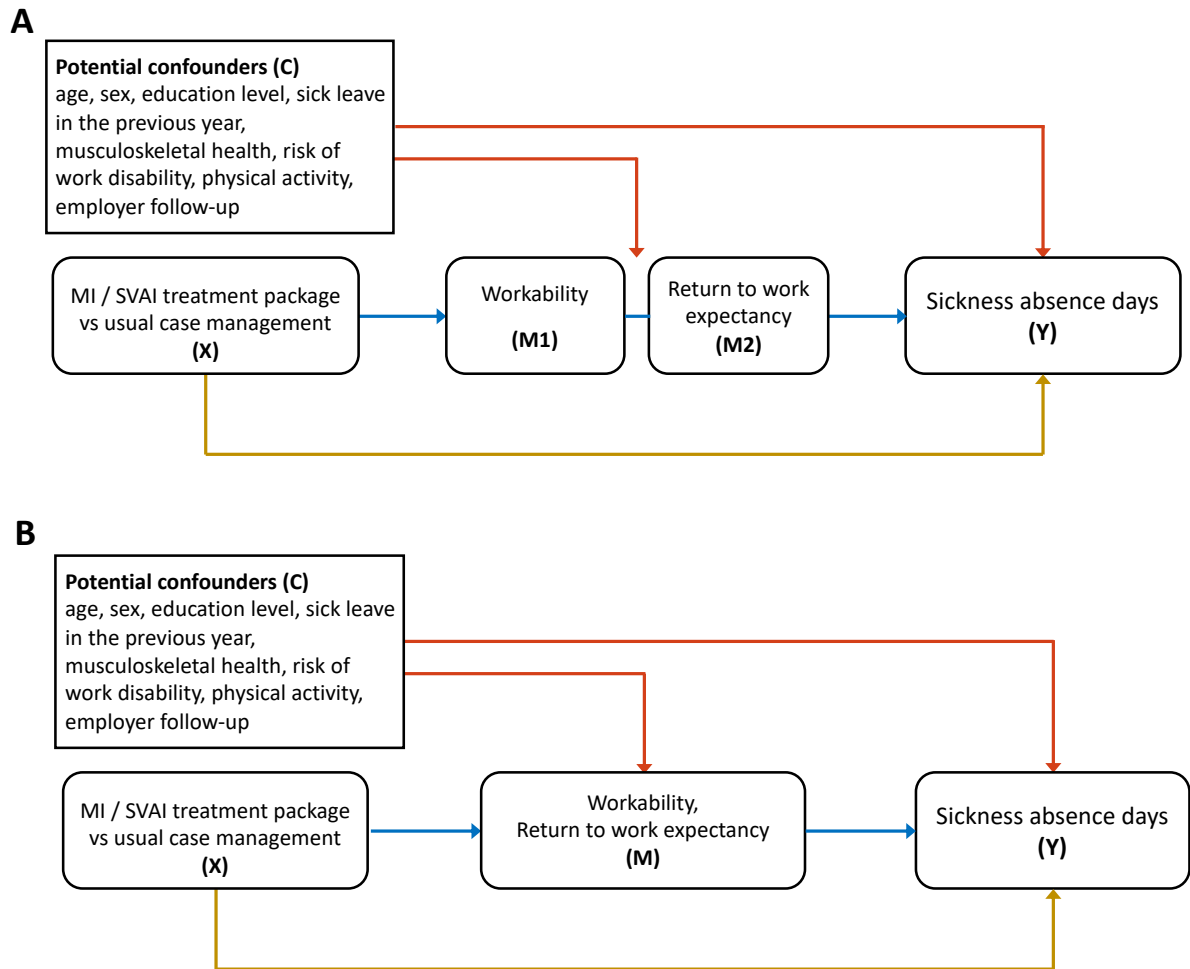
Figure 1. Directed acyclic graphic depicting the simplified causal pathways for the effect of the two treatment packages (MI and SVAI) compared to usual case management on the outcome sickness absence days, via the hypothesized mediators workability and return to work expectancy. The potential confounders are measured at baseline, the mediators are assessed at 3 months after allocation, and the outcome is measured at 6 months after allocation. Blue lines represent indirect effects. Yellow lines represent direct effects. Red lines represent possible effects that could induce confounding for indirect and direct effects. A) A multiple mediator model where the treatment (X) exerts its effect on the outcome (Y) via an indirect path through both mediators (M1) and (M2), and a direct path (X to Y). B) A single mediator model where the treatment (X) exerts its effect on the outcome (Y), via an indirect path through the mediator (M) independently, and a direct path (X to Y). The treatment–mediator (X to M) relationship is represented by the blue line from the treatment package to the mediators. The mediator–outcome (M to Y) relationship is represented by the blue line from the mediators to the outcome.

References

1. Øiestad BE, Aanesen F, Løchting I, et al. Study protocol for a randomized controlled trial of the effectiveness of adding motivational interviewing or stratified vocational advice intervention to usual case management on return to work for people with musculoskeletal disorders. The MI-NAV study. *BMC Musculoskelet Disord*. 2020;21(1):1-10. doi:10.1186/s12891-020-03475-z

2. Ilmarinen J. The Work Ability Index (WAI). *Occup Med*. 2006;57(2):160-160. doi:10.1093/occmed/kqm008

3. Linton SJ, Nicholas M, MacDonald S. Development of a short form of the Örebro musculoskeletal pain screening questionnaire. *Spine (Phila Pa 1976)*. 2011;36(22):1891-1895. doi:10.1097/BRS.0b013e3181f8f775

4. Johnston V. Örebro Musculoskeletal Pain Screening Questionnaire. *Aust J Physiother*. 2009;55(2):141-141. doi:10.1016/S0004-9514(09)70049-2

5. Dunn K, Campbell P, Lewis M, et al. Refinement and validation of a tool for stratifying patients with musculoskeletal pain. *Eur J Pain*. 2021;00:1-13. doi:10.1002/ejp.1821

6. Tveter AT, Øiestad BE, Rysstad TL, et al. Risk assessment for prolonged sickness absence due to musculoskeletal disorders: Protocol for a prospective cohort study. *BMC Musculoskelet Disord*. 2020;21(1):1-8. doi:10.1186/s12891-020-03354-7

7. Vanderweele TJ. Principles of confounder selection. *Eur J Epidemiol*. 2019;34:211-219. doi:10.1007/s10654-019-00494-6

8. Ilmarinen J. Work ability—a comprehensive concept for occupational health research and prevention. *Scand J Work Environ Health*. 2009;35(1):1-5. doi:10.5271/sjweh.1304

9. Lederer V, Loisel P, Rivard M, Champagne F. Exploring the Diversity of Conceptualizations of Work (Dis)ability: A Scoping Review of Published Definitions. *J Occup Rehabil*. 2014;24(2):242-267. doi:10.1007/s10926-013-9459-4

10. Main CJ, Foster N, Buchbinder R. How important are back pain beliefs and expectations for satisfactory recovery from back pain? *Best Pract Res Clin Rheumatol*. 2010;24(2):205-217. doi:10.1016/j.berh.2009.12.012

11. Carriere JS, Thibault P, Sullivan MJL. The Mediating Role of Recovery Expectancies on the Relation Between Depression and Return-to-Work. *J Occup Rehabil*. 2015;25(2):348-356. doi:10.1007/s10926-014-9543-4

12. Carriere JS, Thibault P, Milioto M, Sullivan MJL. Expectancies Mediate the Relations among Pain Catastrophizing, Fear of Movement, and Return to Work Outcomes after Whiplash Injury. *J Pain*. 2015;16(12):1280-1287. doi:10.1016/j.jpain.2015.09.001

13. Carriere JS, Thibault P, Adams H, Milioto M, Ditto B, Sullivan MJL. Expectancies mediate the relationship between perceived injustice and return to work following whiplash injury: A 1-year prospective study. *Eur J Pain*. 2017;21(7):1234-1242. doi:10.1002/ejp.1023

14. Page KM, Tchernitskaia I. Use of motivational interviewing to improve return-to-work and work-related outcomes: A review. *Aust J Rehabil Couns*. 2014;20(1):38-49. doi:10.1017/jrc.2014.5

15. Wynne-Jones G, Artus M, Bishop A, et al. Effectiveness and costs of a vocational advice service to improve work outcomes in patients with musculoskeletal pain in primary care: A cluster randomised trial (SWAP trial ISRCTN 52269669). *Pain*. 2018;159(1):128-138. doi:10.1097/j.pain.0000000000001075

16. Aanesen F, Berg R, Løchting I, et al. Motivational Interviewing and Return to Work for People with Musculoskeletal Disorders: A Systematic Mapping Review. *J Occup Rehabil*. 2021;31(1):63-71. doi:10.1007/s10926-020-09892-0

17. VanderWeele T, Vansteelandt S. Mediation Analysis with Multiple Mediators. *Epidemiol Method*. 2014;2(1). doi:10.1515/em-2012-0010

18. Shi B, Choirat C, Coull BA, VanderWeele TJ, Valeri L. CMAverse. *Epidemiology*. 2021;Publish Ah. doi:10.1097/EDE.0000000000001378

19. Vanderweele TJ. *Explanation in Causal Inference*. Oxford University Press; 2015.

20. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):1-67.

21. Smith LH, VanderWeele TJ. Mediational E-values. *Epidemiology*. 2019;30(6):835-837. doi:10.1097/EDE.0000000000001064