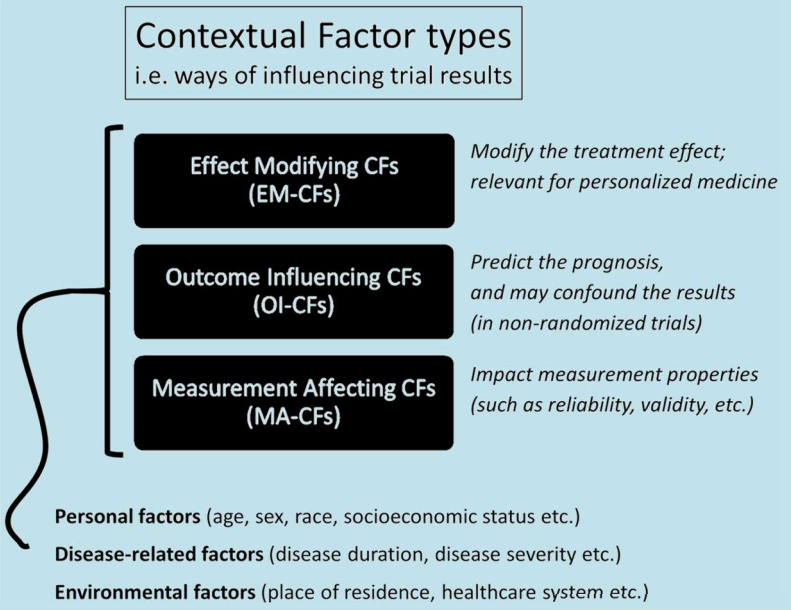
Cheat sheet

OMERACT Outcome Measures in Rheumatology
Contextual Factors Working Group

What are contextual factors?

The three contextual factor *types* describe three different ways that contextual factors can influence the results of a trial (*see figure*) [1]. To limit which specific factors can be considered contextual factors, the factors must be either personal, disease-related, or environmental.
The contextual factor *types* are ***not*** mutually exclusive, e.g., a specific factor, such as sex, may be an EM-CF, OI-CF, and MA-CF (*see evidence example for axial spondyloarthritis on the next page*).



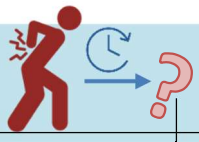
Scenarios

EM-CFs

Older patients seem to have less effect from drug *X*, compared to younger patients.

Maybe drug *X* is only relevant for younger patients.

*(evidence from randomized controlled trials could demonstrate that **age** modifies the treatment effect of drug X, i.e., is an **'effect modifier'**, and, hence, EM-CF)*

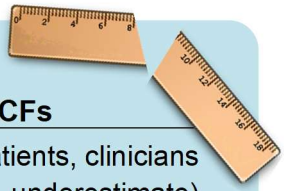


OI-CFs

Patients with disease *Y* and low socio-economic status seem to do worse over time than patients with higher socio-economic status.

Researchers need to consider the influence of socio-economic status ('**confounder**') on the results of non-randomized studies.

*(evidence from longitudinal observational studies could demonstrate that **socio-economic status** predicts the prognosis, i.e., is an OI-CF)*



MA-CFs

In overweight patients, clinicians count fewer (i.e., underestimate) swollen joints on their assessment, than what is seen with ultrasound.

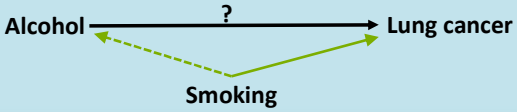
Researchers should be aware of these measurement affecting issues when counting swollen joints.

*(evidence from studies of measurement instruments [psychometric/clinimetric studies] could demonstrate that being **overweight** influences the validity of joint count, i.e., is a MA-CF)*

Statistical terms related to EM-CFs and OI-CFs

Effect modifiers: Variables that describe patient subgroups for which the treatment effect differs [2] and which are usually baseline characteristics. E.g., if the effect of a treatment is different between younger and older patients, then *age* is an effect modifier (***red arrow***). Effect modifiers are important for ***personalized medicine***, where patients receive the treatment that is most likely to help them, based on their characteristics (effect modifiers). Researchers can use certain statistical tests (so-called 'test of interaction') to identify effect modifiers.

Confounders: Variables that might confuse the association that is seen in a study. E.g., there seems to be an association between alcohol intake and the occurrence of lung cancer. But this does not mean alcohol causes lung cancer. The link is really between smoking and lung cancer - but because people who drink alcohol are more likely to smoke and therefore get lung cancer, it *looks* like there is an association between alcohol and lung cancer, if we do not take smoking into account. So smoking confuses ('confounds') the association between alcohol and lung cancer (***green arrows***). Confounders is a well-known issue in observational studies. In randomized controlled trials, the randomization usually ensures that confounders are equally distributed between the intervention and control groups (e.g., same number of smokers in each group) and hence, the observed treatment effect is usually *not* influenced by confounders.



Evidence example: Patients with axial spondyloarthritis (AxSpA) – Sex differences

A specific factor (such as age, sex, disease duration, etc.) may in some cases fit within *more than one* CF type. Here, we provide an example where **sex** is an EM-CF, OI-CF, and MA-CF.

***The effect of treatment* on outcome (see figure below)**
In this example with AxSpA patients, we are interested in the effect of *treatment* with TNF-inhibitors on the *outcome* disease activity, assessed with BASDAI (**black arrow** in figure). However, sex influences this relationship in three ways (as an EM-CF, OI-CF, and MA-CF) and should be taken into account.

Effect modifying (EM-CFs; red arrow)
Among AxSpA patients, women generally experience less effect from treatment compared to men [3,4,5] when this is investigated in randomized trials (confirmed with a statistical test for interaction). So sex is in this case an effect modifier (and, hence, an EM-CF).

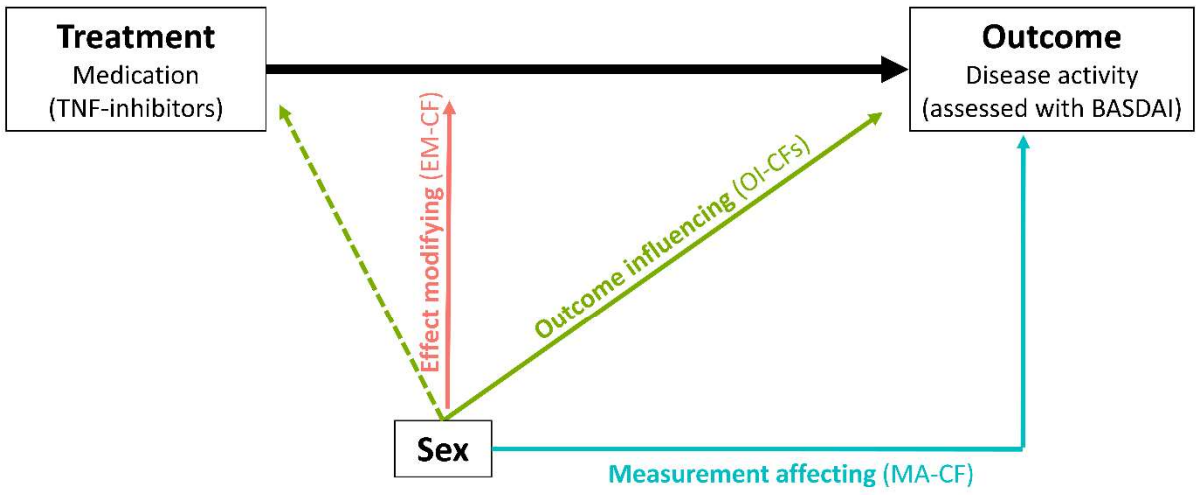
Outcome influencing (OI-CFs, green arrow)
Among AxSpA patients, women generally have a worse prognosis as measured by BASDAI [3,4]. So sex is in this case a prognostic factor (and, hence, an OI-CF) – and a potential confounder (***dashed arrow***). *Confounding* will be present if men and women are not distributed evenly across the treatments (/exposures) to be investigated. That is, if use of a medication is being compared against use of no medication, and there are more men in the medication group than in the no-medication group, then the medication may seem more effective than it truly is. This is because the difference between the groups may be partly explained by the difference in prognosis between men and women, rather than by the treatment with medication.

Measurement affecting (MA-CFs; blue arrow)
Among AxSpA patients, women seem to have higher disease activity when measured with BASDAI, but not when measured with ASDAS [6]. It has further been suggested that sex-specific thresholds for BASDAI should be used (higher threshold for women) [7]. ASDAS does not seem to require sex-specific cutoffs [8]. Sex is a MA-CF when BASDAI is being used as a measurement tool.

Recommendations
In the above, we just learned that sex influences the relationship between treatment and outcome in AxSpa. The ***green***, ***red***, and ***blue*** boxes contain recommendations for taking sex into account as an EM-CF, OI-CF, and MA-CF, respectively.

ASDAS: Ankylosing Spondylitis Disease Activity Score; AxSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; LOS: longitudinal observational studies.

Evidence for patients with AxSpA



Recommendation:	Recommendation:	Recommendation:
Measure sex in trials and report treatment effects separately for men and women in AxSpA research *(because sex is an EM-CF)*	Measure sex and adjust for sex in LOS, so sex does not confound the association between treatment and outcome in AxSpA research *(because sex is and OI-CF)*	Use outcome measures that are not influenced by sex, e.g., ASDAS instead of BASDAI, in AxSpA research *(sex is an MA-CF for BASDAI, but **not** for ASDAS)*

References: 1) Nielsen et al. Semin Arthritis Rheum. 2021;51(3):601-6. **2)** Wang et al. N Engl J Med 2007;357(21):2189-94. **3)** Stovall et al. Nat Rev Rheumatol 2022;18:665-9 (2022). **4)** Rusman et al. Curr Rheumatol Rep. 2018;20:35. **5)** van der Horst-Bruinsma et al. Ann Rheum Dis 2013;72:1221-4. **6)** Blasco-Blasco et al. J Rheumatol. 2021 Sep;48(9):1395-1404. **7)** Cohen et al. Rheumatol. 2006; 33(1):79-81. **8)** Kilic et al. Int J Rheum Dis. 2017;20(9):1201-11.