

## Physical activity and checkpoint inhibition: association with toxicity and survival

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## The short questionnaire to assess health enhancing physical activity (SQUASH)

Think about an average week in the past months. Please indicate **how many days per week** you performed the following activities, how much time **on average** you were engaged in this, and (if applicable) how strenuous this activity was for you?

| <b>COMMUTING ACTIVITIES</b><br>(round trip)   | Days per week             | Average time per day  | Effort (circle please)  |
|---|---------------------------|---|---|
| Walking to/from work or school  | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Slow/moderate/fast  |
| Bicycling to/from work or school  | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Slow/moderate/fast  |
| Not applicable  | <input type="text"/>      |   |   |
| <b>ACTIVITY AT WORK AND SCHOOL</b>  |                           |   | Average time per week   |
| Light work<br>(sitting/standing with some walking, e.g., a desk job)  |                           |   | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes |
| Intense work<br>(walking job, regularly lifting heavy objects at work)  |                           |   | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes |
| <b>HOUSEHOLD ACTIVITIES</b>   |                           | Days per week   | Average time per day  |
| Light household work<br>(standing work such as cooking, washing dishes, ironing, child care, and walking work such as vacuuming, doing groceries) | <input type="text"/> days |   | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes |
| Intense household work<br>(scrubbing floor, carpet beating, walking with heavy shopping bags)   | <input type="text"/> days |   | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes |
| <b>LEISURE TIME ACTIVITIES</b>  |                           | Days per week   | Average time per day  |
| Walking   | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Slow/moderate/fast  |
| Bicycling   | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Slow/moderate/fast  |
| Gardening   | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Light/moderate/intense  |
| Odd jobs  | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Light/moderate/intense  |
| Sports (Please write down yourself)<br><i>e.g., tennis, fitness, skating, swimming, dancing</i>   |                           |   |   |
| 1.....  | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Light/moderate/intense  |
| 2.....  | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Light/moderate/intense  |
| 3.....  | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Light/moderate/intense  |
| 4.....  | <input type="text"/> days | <input type="text"/> hour <input type="text"/> <input type="text"/> minutes | Light/moderate/intense  |

**Supplementary Table 1: Frequencies of types of severe immune-related adverse events per ICI regimen.**

| Type of gr≥3 irAE        | ipilimumab+nivolumab (N=61) | anti-PD-(L)1 ± chemo/targeted therapy (N=190) |
|--------------------------|-----------------------------|---|
| colitis                  | 4 (13.8%)                   | 6 (33.3%)                                     |
| dermatitis               | 2 (6.9%)                    | 0 (0.0%)                                      |
| diabetes mellitus type 1 | 2 (6.9%)                    | 0 (0.0%)                                      |
| duodenitis               | 1 (3.4%)                    | 1 (5.6%)                                      |
| cholangitis              | 0 (0.0%)                    | 1 (5.6%)                                      |
| encephalitis             | 0 (0.0%)                    | 1 (5.6%)                                      |
| gastritis                | 3 (10.3%)                   | 0 (0.0%)                                      |
| hepatitis                | 5 (17.2%)                   | 1 (5.6%)                                      |
| hyperthyroidism          | 1 (3.4%)                    | 0 (0.0%)                                      |
| meningitis               | 2 (6.9%)                    | 0 (0.0%)                                      |
| myocarditis              | 2 (6.9%)                    | 0 (0.0%)                                      |
| myositis                 | 1 (3.4%)                    | 1 (5.6%)                                      |
| pancreatitis             | 0 (0.0%)                    | 3 (16.7%)                                     |
| pericarditis             | 0 (0.0%)                    | 1 (5.6%)                                      |
| pneumonitis              | 4 (13.8%)                   | 3 (16.7%)                                     |
| polyneuropathy           | 1 (3.4%)                    | 0 (0.0%)                                      |
| sarcoid like reaction    | 1 (3.4%)                    | 0 (0.0%)                                      |
| <b>total</b>             | <b>29 (47.5%)</b>           | <b>18 (9.5%)</b>                              |

**Supplementary Table 2: Association of physical activity at initiation of ipilimumab+nivolumab with severe immune-related adverse events (irAEs) within one year.**

| Total physical activity (MET-hours/week)                  | OR <sub>adj</sub> (95%CI) of severe irAE |
|---|--|
| Low [0 to 51]   | ref                                      |
| Intermediate (51 to 101]                                  | 0.46 (0.10-1.89)                         |
| High (101 to 371]   | 0.54 (0.97-1.06)                         |
| Moderate to vigorous leisure time and sports (hours/week) | OR <sub>adj</sub> (95%CI) of severe irAE |
| Zero [0]  | ref                                      |
| Low (0 to 6]  | 0.37 (0.08-1.56)                         |
| High (6 to 38.5]  | 0.41 (0.08-1.98)                         |

Abbreviations: OR: odds ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex and age.

**Supplementary Table 3: Fine and Gray subdistribution hazard model of the association of physical activity at immune checkpoint inhibitor initiation with severe immune-related adverse events (irAE) in patients with cancer, accounting for death as competing risk.**

| <b>Total physical activity (MET-hours/week)</b>                  | <b>HR (95%CI) of severe irAE</b> |
|--|----------------------------------|
| Low [0 to 51]  | ref                              |
| Intermediate (51 to 101]   | 0.47 (0.21-1.05)                 |
| High (101 to 371]  | 0.43 (0.21-0.90)                 |
| <b>Moderate to vigorous leisure time and sports (hours/week)</b> | <b>HR (95%CI) of severe irAE</b> |
| Zero [0]   | ref                              |
| Low (0 to 6]   | 0.30 (0.13-0.66)                 |
| High (6 to 38.5]   | 0.37 (0.18-0.78)                 |

HR, subdistribution hazard ratio; CI confidence interval; MET, Metabolic equivalent task. These analyses are adjusted for: sex, age, tumor type, setting (unresectable/metastatic vs adjuvant/curative), previous systemic therapy, and type of therapy.

**Supplementary Table 4: Association of physical activity at immune checkpoint inhibitor initiation with overall survival in patients with metastatic or unresectable tumors.**

| <b>Total physical activity (MET-hours/week)</b>                  | <b>HR<sub>adj</sub> (95%CI) of death</b> |
|--|--|
| Low [0 to 51]  | ref                                      |
| Intermediate (51 to 101]   | 0.55 (0.29-1.04)                         |
| High (101 to 371]  | 0.39 (0.19-0.81)                         |
| <b>Moderate to vigorous leisure time and sports (hours/week)</b> | <b>HR<sub>adj</sub> (95%CI) of death</b> |
| Zero [0]   | ref                                      |
| Low (0 to 6]   | 0.79 (0.44-1.42)                         |
| High (6 to 38.5]   | 0.27 (0.12-0.62)                         |

Abbreviations: HR: hazard ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex, age, previous systemic therapy, and type of therapy.

**Supplementary Table 5: Association of physical activity at immune checkpoint inhibitor initiation with overall survival in patients with melanoma.**

| <b>Total physical activity (MET-hours/week)</b>                  | <b>HR<sub>adj</sub> (95%CI) of death</b> |
|--|--|
| Low [0 to 51]  | ref                                      |
| Intermediate (51 to 101]   | 0.79 (0.31-2.03)                         |
| High (101 to 371]  | 0.56 (0.21-1.50)                         |
| <b>Moderate to vigorous leisure time and sports (hours/week)</b> | <b>HR<sub>adj</sub> (95%CI) of death</b> |
| Zero [0]   | ref                                      |
| Low (0 to 6]   | 0.17 (0.06-0.51)                         |
| High (6 to 38.5]   | 0.20 (0.07-0.57)                         |

Abbreviations: HR: hazard ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex, age, setting (unresectable/metastatic vs adjuvant/curative), previous systemic therapy, type of therapy, and LDH levels.

**Supplementary Table 6: Association of physical activity at immune checkpoint inhibitor initiation with overall survival in patients with nonmelanoma tumors.**

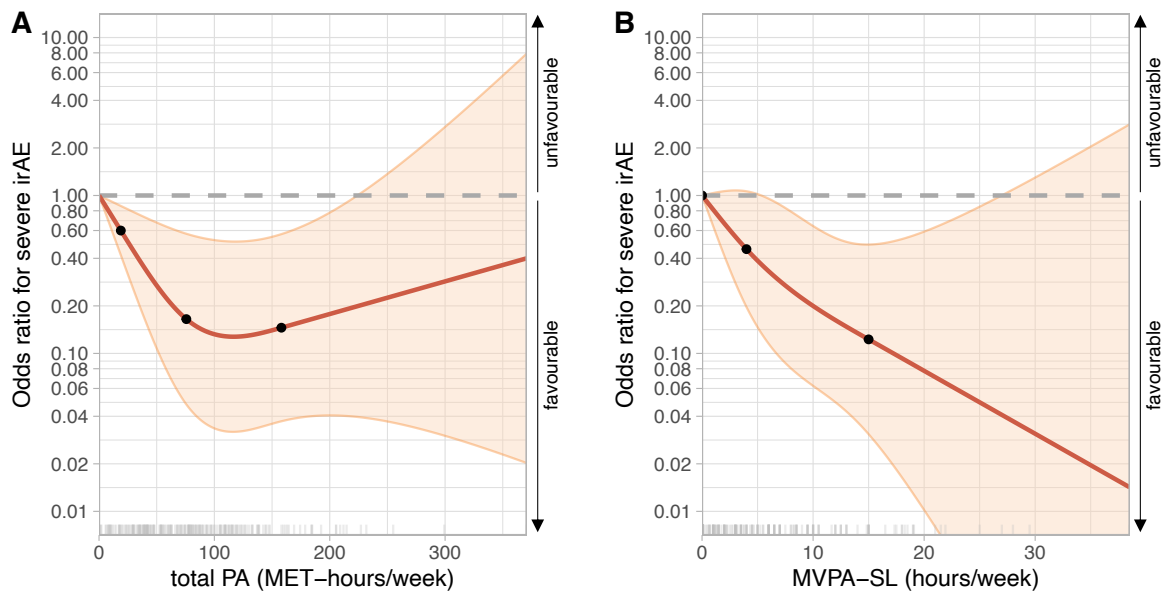
| <b>Total physical activity (MET-hours/week)</b>                  | <b>HR<sub>adj</sub> (95%CI) of death</b> |
|--|--|
| Low [0 to 51]  | ref                                      |
| Intermediate (51 to 101]   | 0.48 (0.22-1.05)                         |
| High (101 to 371]  | 0.47 (0.21-1.06)                         |
| <b>Moderate to vigorous leisure time and sports (hours/week)</b> | <b>HR<sub>adj</sub> (95%CI) of death</b> |
| Zero [0]   | ref                                      |
| Low (0 to 6]   | 1.25 (0.62-2.52)                         |
| High (6 to 38.5]   | 0.52 (0.21-1.29)                         |

Abbreviations: HR: hazard ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex, age, setting (unresectable/metastatic vs adjuvant/curative), previous systemic therapy, and type of therapy.

**Supplementary Table 7: Association of physical activity at immune checkpoint inhibitor initiation with overall survival in cancer patients with ECOG performance status 0 or 1.**

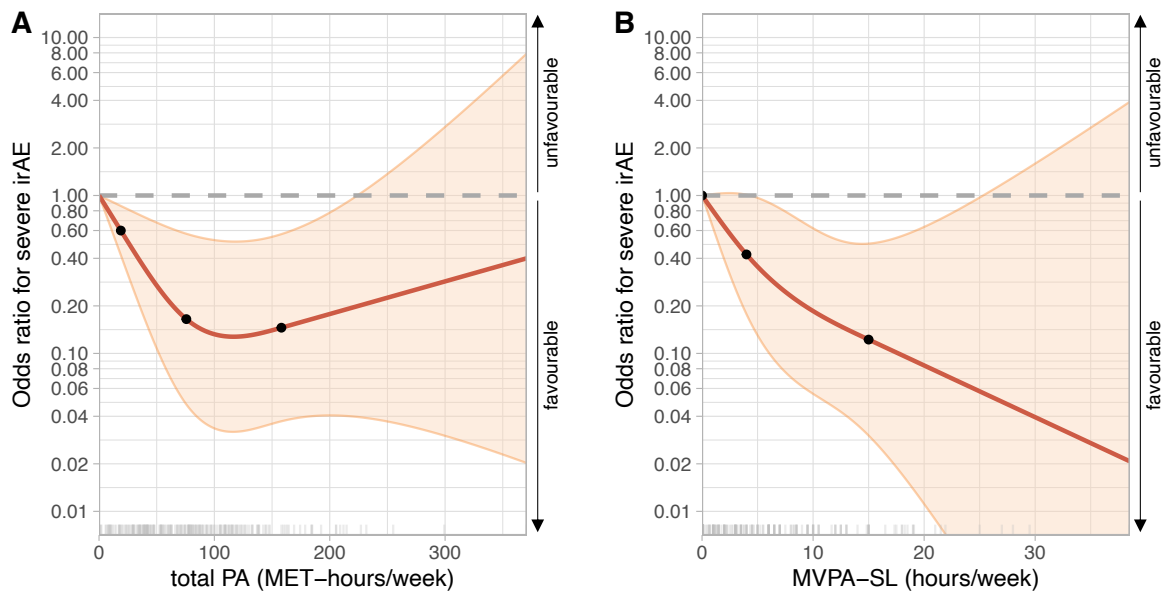
| <b>Total physical activity (MET-hours/week)</b>                  | <b>HR<sub>adj</sub> (95%CI) of death</b> |
|--|--|
| Low [0 to 51]  | ref                                      |
| Intermediate (51 to 101]   | 0.74 (0.39-1.38)                         |
| High (101 to 371]  | 0.61 (0.32-1.15)                         |
| <b>Moderate to vigorous leisure time and sports (hours/week)</b> | <b>HR<sub>adj</sub> (95%CI) of death</b> |
| Zero [0]   | ref                                      |
| Low (0 to 6]   | 0.64 (0.34-1.19)                         |
| High (6 to 38.5]   | 0.45 (0.23-0.92)                         |

Abbreviations: HR: hazard ratio; CI: confidence interval; MET: Metabolic Equivalent Task. These analyses are adjusted for sex, age, tumor type, setting (unresectable/metastatic vs adjuvant/curable), and type of therapy.

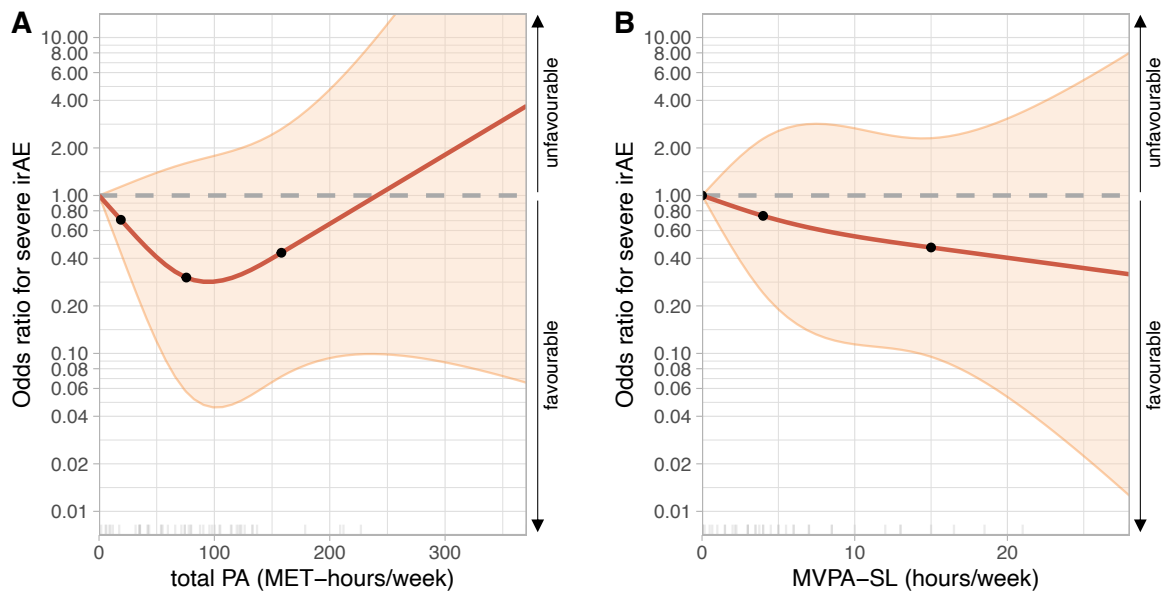


**Supplementary Figure 1: Association between physical activity at immune checkpoint inhibitor initiation and severe immune-related adverse events (irAE) within one year in patients with cancer. a** Metabolic Equivalent Task (MET) hours per week. **b** Time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL). These curves represent odds ratio (OR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, tumor type, treatment setting, previous systemic therapy, and type of therapy.

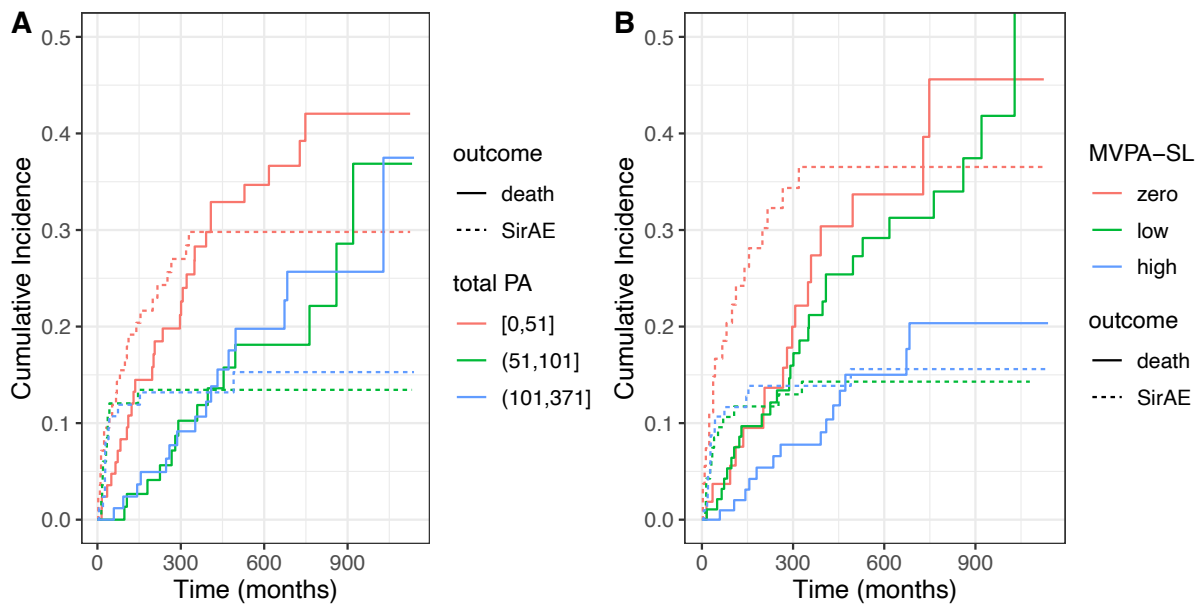




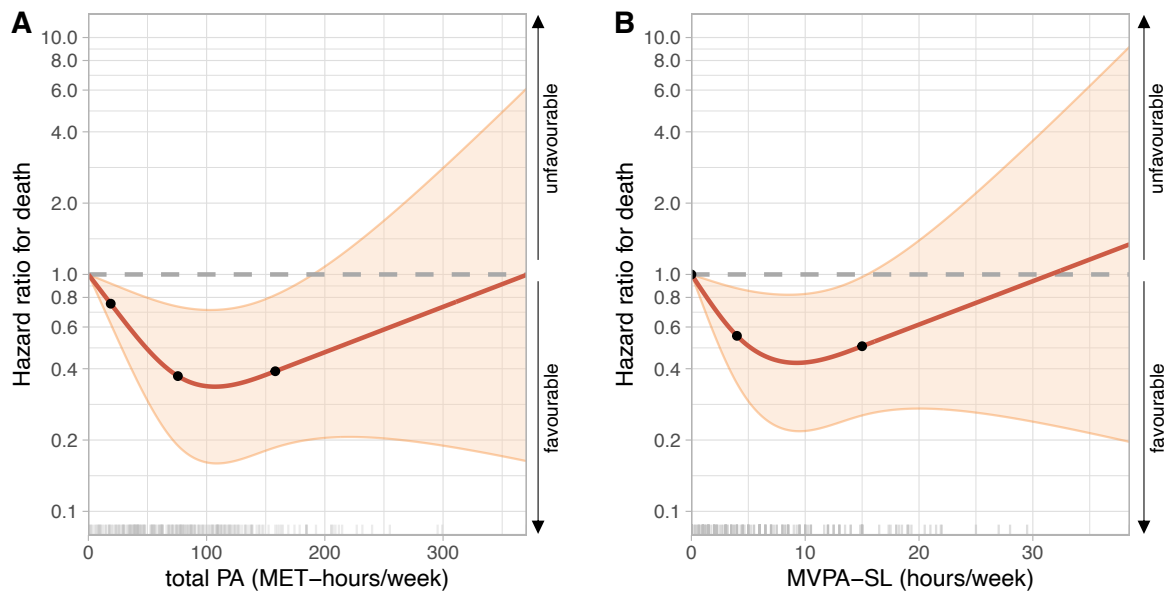
**Supplementary Figure 2: Association between physical activity at immune checkpoint inhibitor initiation and severe immune-related adverse events (irAE) in patients with cancer with additional adjustment for ECOG performance status. a** Metabolic Equivalent Task (MET) hours per week. **b** Time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL). These curves represent odds ratio (OR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, ECOG performance status, tumor type, treatment setting, previous systemic therapy, and type of therapy.



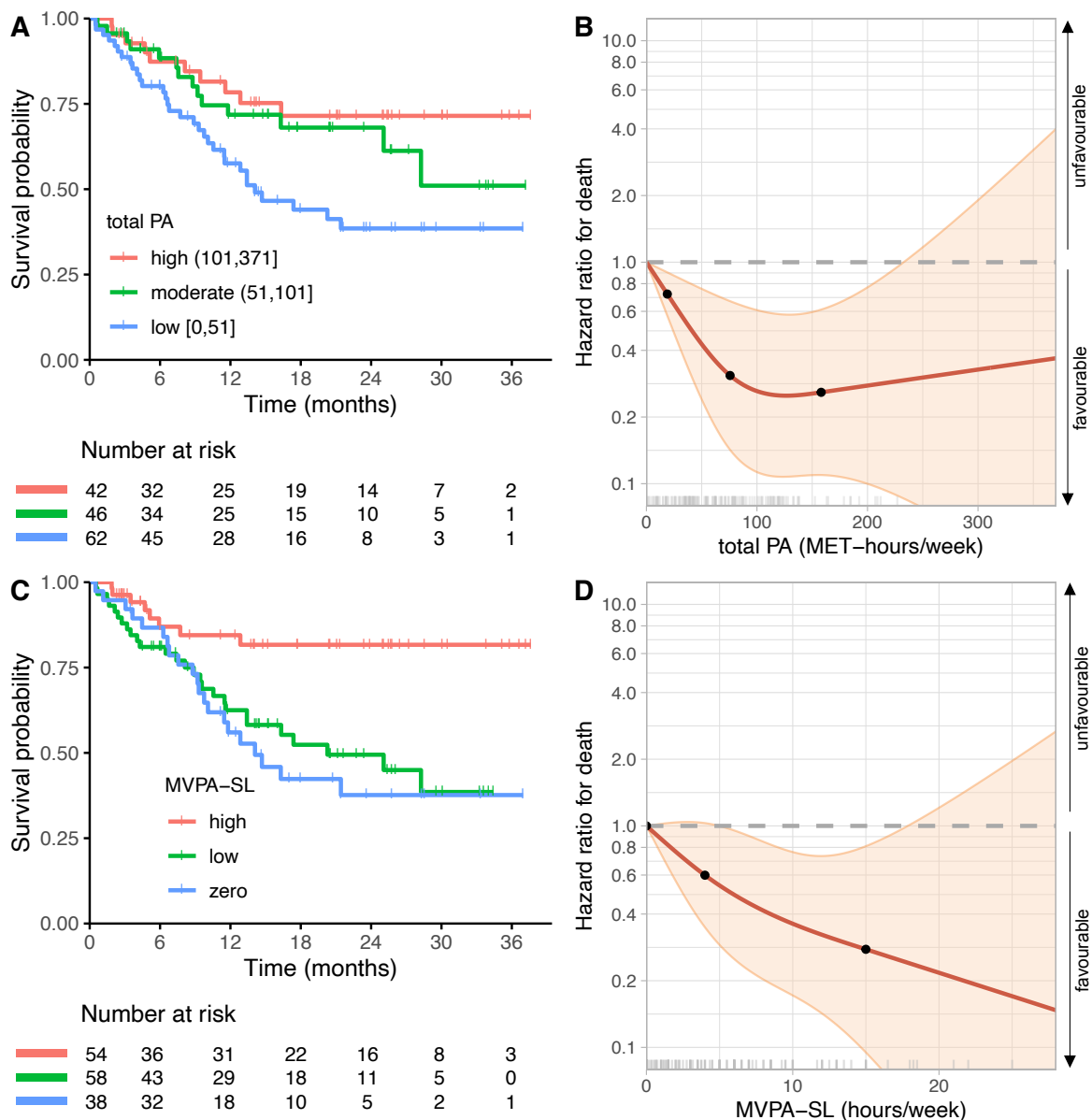
**Supplementary Figure 3: Association between physical activity at immune checkpoint inhibitor initiation and severe immune-related adverse events (irAE) in patients with cancer treated with ipilimumab+nivolumab. a** Metabolic Equivalent Task (MET) hours per week. **b** Time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL). These curves represent odds ratio (OR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, tumor type, treatment setting and previous systemic therapy.



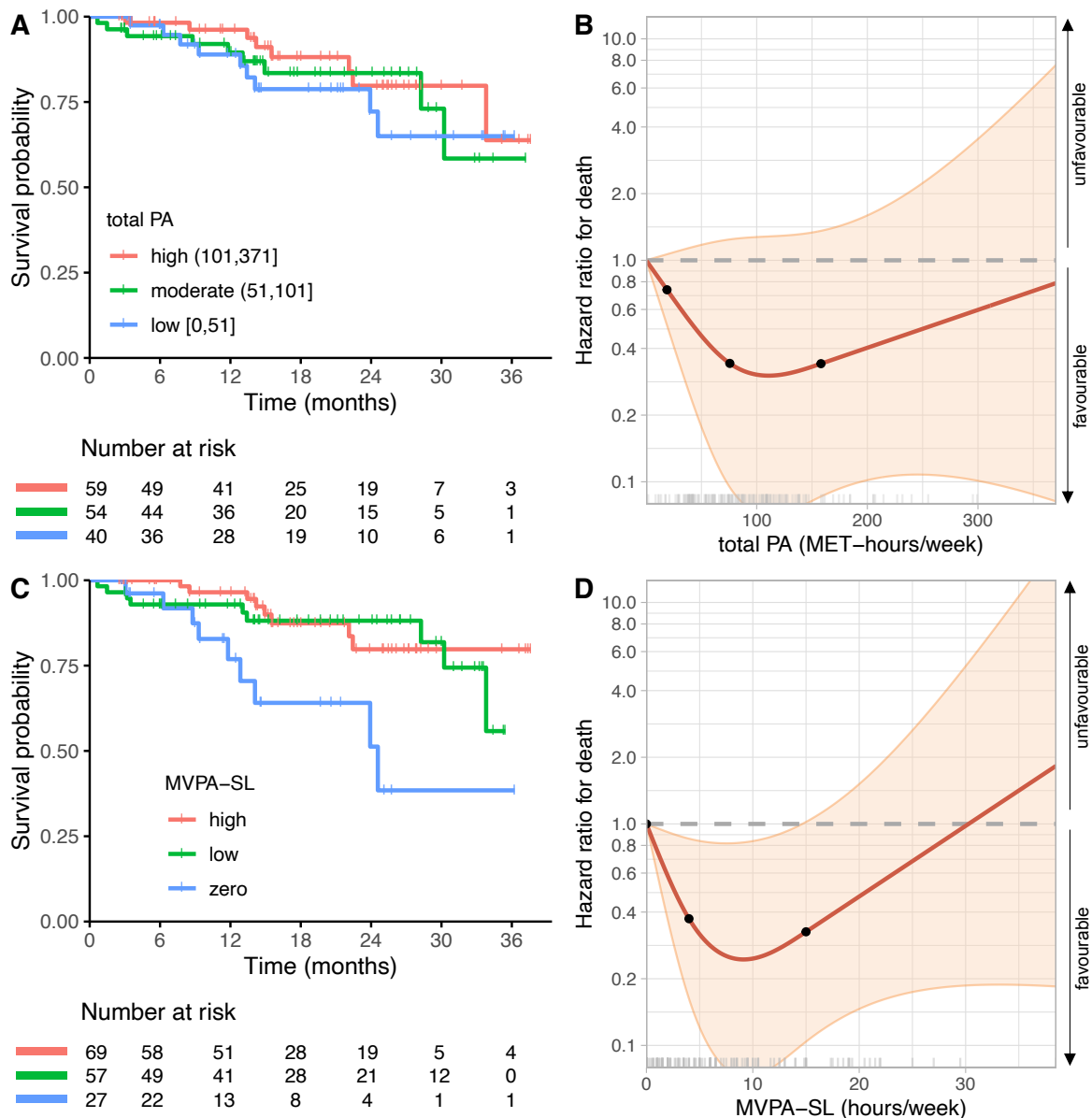
**Supplementary Figure 4: Cumulative incidence functions of severe immune-related adverse events (SirAE) and death according to physical activity at immune checkpoint inhibitor initiation. a** Metabolic Equivalent Time (MET) hours per week; **b** time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL).



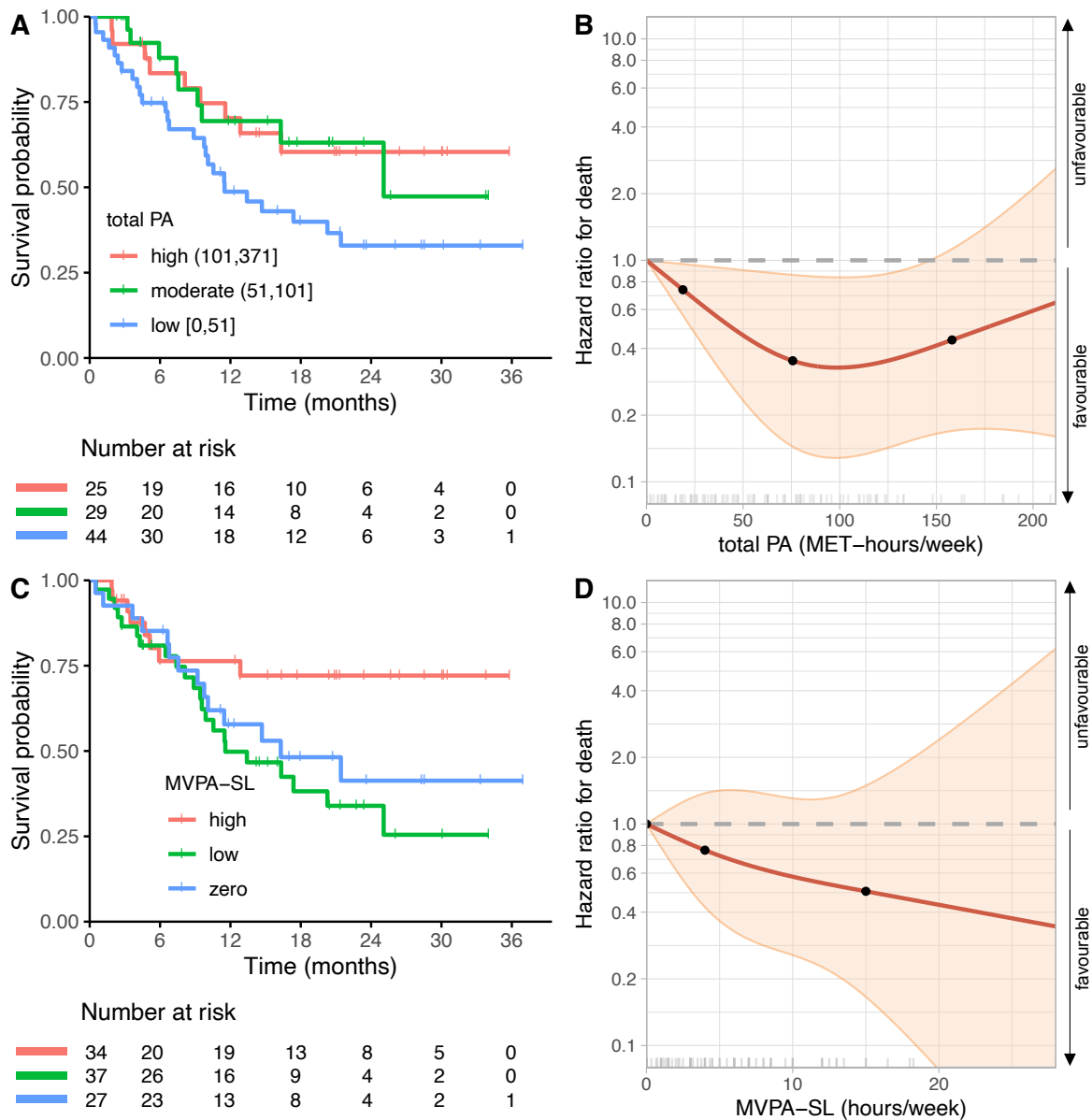
**Supplementary Figure 5: Association between physical activity at immune checkpoint inhibitor initiation and overall survival. a** Metabolic Equivalent Task (MET) hours per week. **b** Time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL). These curves represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, tumor type, treatment setting previous systemic therapy, and type of therapy.



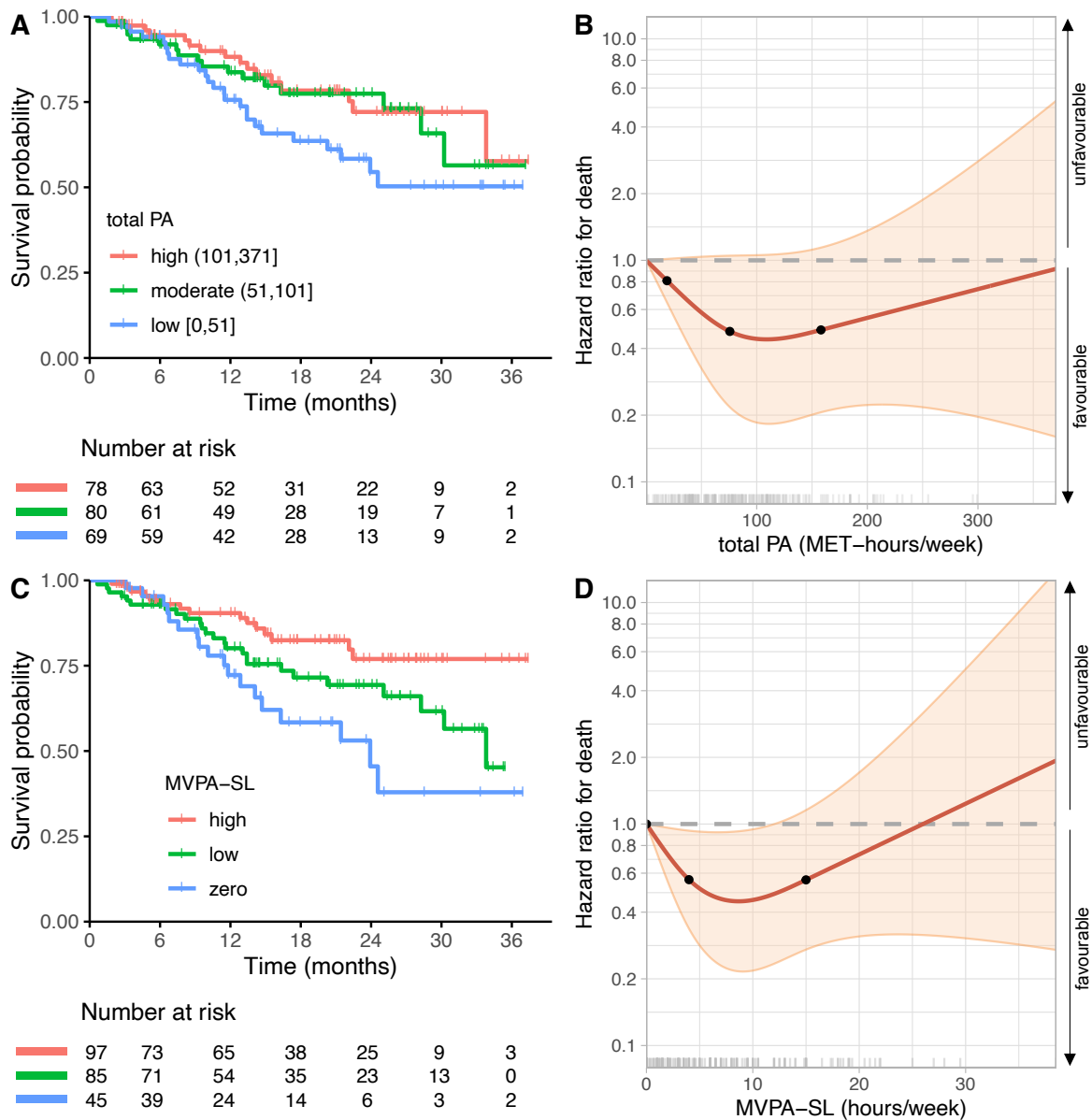
**Supplementary Figure 6: Association between physical activity at immune checkpoint inhibitor initiation and overall survival in patients with metastatic or unresectable disease.** Kaplan Meier curves (**a,c**) and restricted cubic spline models (**b,d**) of survival of patients with irresectable tumors treated with immune checkpoint inhibitors stratified by physical activity levels. **a,b** Total physical activity (Metabolic Equivalent Task (MET) hours per week). **c,d** Time spent on moderate-to-vigorous-intensity activities during sports and leisure time (MVPA-SL). Restricted cubic spline models (**b,d**) represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, tumor type, previous systemic therapy, and type of therapy.



**Supplementary Figure 7: Association between physical activity at immune checkpoint inhibitor initiation and overall survival in patients with melanoma.** Kaplan Meier curves (**a,c**) and restricted cubic spline models (**b,d**) of survival of patients with melanoma treated with immune checkpoint inhibitors stratified by physical activity levels. **a,b** Metabolic Equivalent Task (MET) hours per week. **c,d** Time spent on moderate-to-vigorous-intensity activities during sports and leisure time (MVPA-SL). Restricted cubic spline models (**b,d**) represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, treatment setting, previous systemic therapy, type of therapy, and lactate dehydrogenase (LDH).

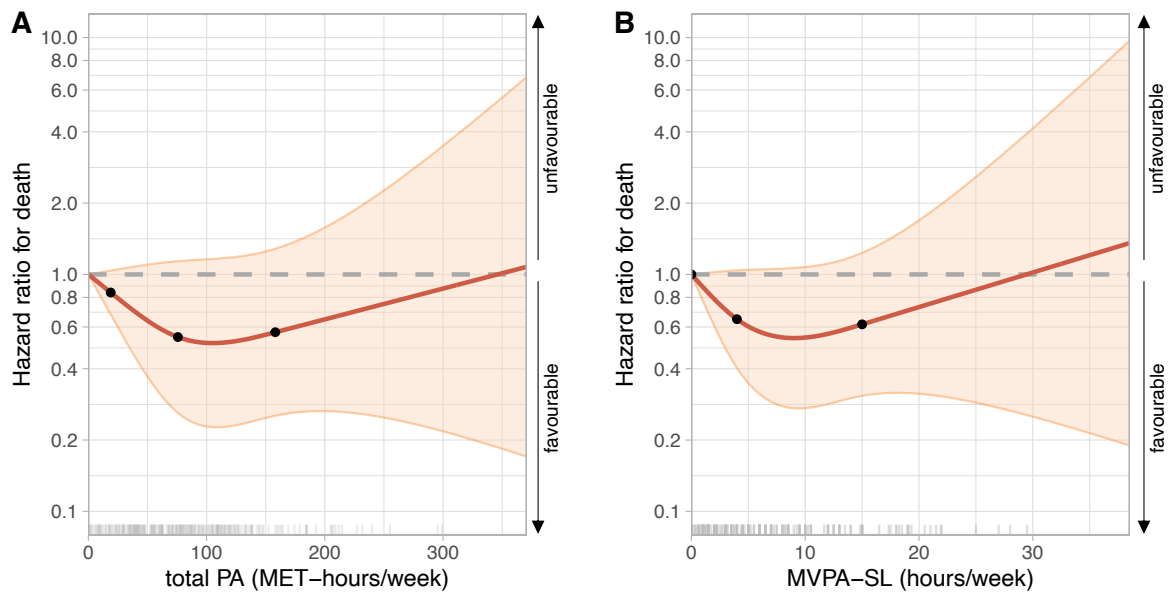


**Supplementary Figure 8: Association between physical activity at immune checkpoint inhibitor initiation and overall survival in patients with nonmelanoma tumors.** Kaplan Meier curves (**a,c**) and restricted cubic spline models (**b,d**) of survival of patients with melanoma treated with immune checkpoint inhibitors stratified by physical activity levels. **a,b** Metabolic Equivalent Task (MET) hours per week. **c,d** Time spent on moderate-to-vigorous-intensity activities during sports and leisure time (MVPA-SL). Restricted cubic spline models (**b,d**) represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, treatment setting, previous systemic therapy, and type of therapy.



**Supplementary Figure 9: Association between physical activity at immune checkpoint inhibitor initiation and overall survival in patients with cancer with ECOG performance status 0 or 1.** Kaplan Meier curves (**a,c**) and restricted cubic spline models (**b,d**) of survival of patients with ECOG performance status 0 or 1 treated with immune checkpoint inhibitors stratified by physical activity levels. **a,b** Time spent on moderate-to-vigorous-intensity activities during sports and leisure time (MVPA-SL). **c,d** Metabolic Equivalent Task (MET) hours per week. Restricted cubic spline models (**b,d**) represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, treatment setting, previous systemic therapy, and type of therapy.





**Supplementary Figure 10: Association between physical activity at immune checkpoint inhibitor initiation and overall survival (OS) in patients with cancer with additional adjustment for ECOG performance status. a** Metabolic Equivalent Task (MET) hours per week. **b** Time spent on moderate-to-vigorous-intensity physical activity during sports and leisure time (MVPA-SL). These curves represent hazard ratio (HR) with 95% confidence interval (CI) with 0 as reference and are adjusted for sex, age, ECOG performance status, tumor type, treatment setting, previous systemic therapy and type of therapy.