MENSTRUAL CYCLE CONTROL AND VENOUS THROMBOEMBOLISM RISK IN FEMALE ASTRONAUTS

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Demographics

Total number of humans in space	534	10.6%
Total females in space	57	
Total US astronauts in space	330	14.5%
Total US female astronauts in space	48	
Age range at US selection	26-47 yrs	
Mean age US ASCAN* finalist	32 yrs	
Mean age US female astronaut at first flight	38 yrs	
2013 selected female ASCANs*	**50%**	

**ASCAN – astronaut candidate*

Menstrual Suppression

Similar contraceptive efficacy and safety profiles to cyclic use

Fewer hormonal side effects

Aids endometriosis, menorrhagia, dysmenorrhea

Pregnancy delays selection process

Pregnancy contraindicated for most training activities

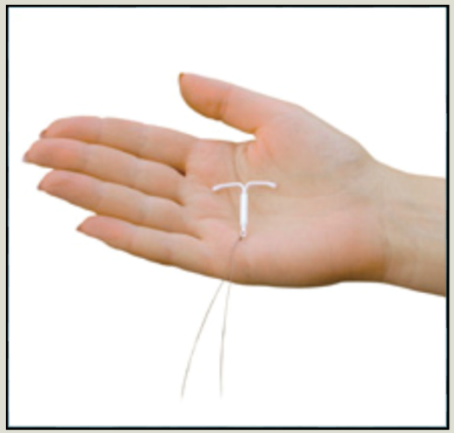
Contraindicated for spaceflight

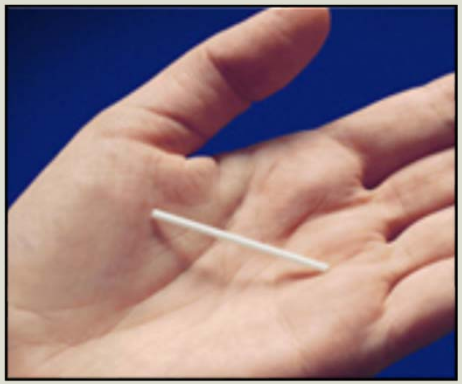
Waste management systems on board station

Microgravity environment

Personal choice

Menstrual suppression





The Contraceptive Pill

- 1950s - 21/7 cycle due to cultural and social pressures

- Combined estrogen and progesterone
- Inhibits ovulation and changes cervical mucus
- Failure rate – 1%
- Contra-indications: previous VTE, migraines, diabetes, liver disease

- Interations with other medications due to liver metabolism
- Interferance with blood lab tests
- VTE risk doubled

Intra-Uterine Devices (IUDs)

- Intra-uterine camel pebbles
- 1909 – first intra-uterine ring
- 1970s - Dalkon Shield had high rates of pelvic inflammatory disease

- Safe, effective, long acting, reversible
- Non-hormonal IUDs - copper
- Hormonal IUDs – Levonorgestrel (progestin)

- Mirena (hormonal IUD) can suppress bleeding completely
- Can be used in conjunction with oral estrogen
- Uterine perforation - rare

Hormonal Implant

- Nexplanon or Implanon – etonogesterel (progestin)
- Sub-dermal , single rod contraceptive implant
- Long acting, reversible

- Most effective contraceptive currently available
- Inhibits ovulation
- Oestradiol levels above threshold for maintaining bone mass

- Only 1 in 10 stop due to irregular bleeding

Recommendations for menstrual suppression

- Long acting reversible contraceptive (LARC)
- Mirena preferential
- Implanon – potential for irregular bleeding but due to normal BMI of astronauts, may not be a problem

- Start one year prior to flight at minimum
- Add back low dose estrogen (suggest 10 mcg) alongside LARC
- Estrogen effects on bone

Venous Thromboembolism (VTE)

"Venous Thromboembolism is a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE)"

i.e. blood clots in the venous system of the legs or lungs

Sudden Death

Lethal

Underdiagnosed

Preventable

Common

Dangerous

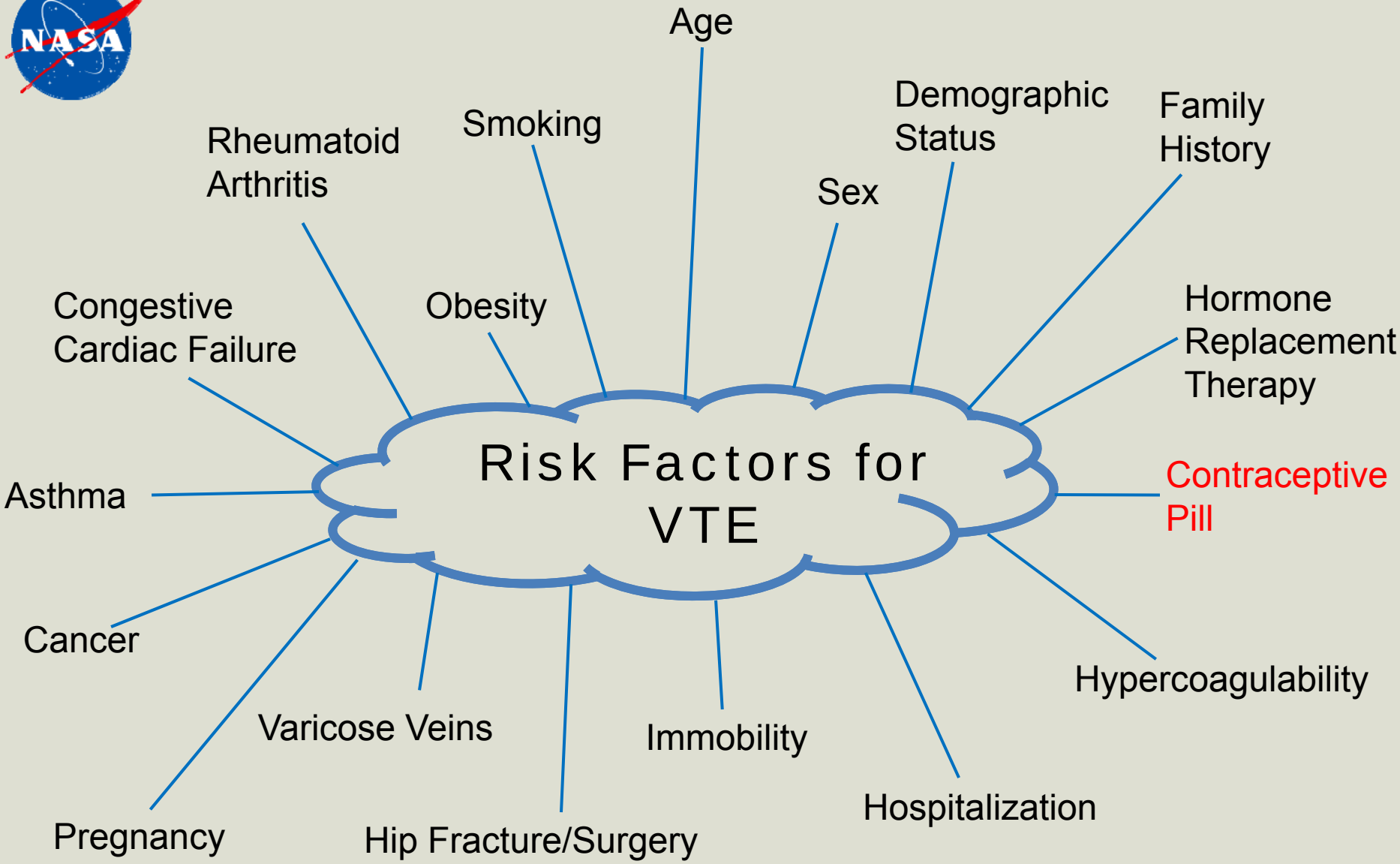
Serious

Treatable

Economic burden

Public health problem

Silent killer


Risk Factors for VTE
Age
Demographic Status
Family History
Smoking
Rheumatoid Arthritis
Sex
Congestive Cardiac Failure
Obesity
Hormone Replacement Therapy
Asthma
Contraceptive Pill
Cancer
Hypercoagulability
Varicose Veins
Immobility
Hospitalization
Pregnancy
Hip Fracture/Surgery

VTE and spaceflight

- No episodes pre-, during or post-flight documented
- Oral contraception doubles risk of VTE terrestrially
- Terrestrial risk calculators do not consider astronaut selection, pre-flight training or space flight environment
- Pre-flight Training:
  - Long haul travel
  - Diving
  - Injury risk
  - Immobility – Soyuz training

Potential In flight Risk Factors

- **Hemoglobin**: <1st centile → OR of VTE is 3.4
- **Mean Corpuscular Volume(MCV):** <1st centile → OR for VTE is 1.95 (hematinics); >99th centile → OR for VTE is 2.65
- **Hematocrit**: upper 20% of normal range → 1.5 times ↑ VTE risk
- **Reticulocyte count:** indication of blood turnover
- **Platelet count:** acute phase protein, high levels increase coagulability of blood
- **Prothrombin time:** <11 secs → increased coagulability of blood
- **Homocystein:** >15mcmol/L → RR of VTE is 1.5-2 (increases due to Vit B12, folate deficiency)

Methods

- LSAH database – medical and research data
- Post 2000, female short and long duration flights, not on HRT
- Repeat fliers counted as separate episodes

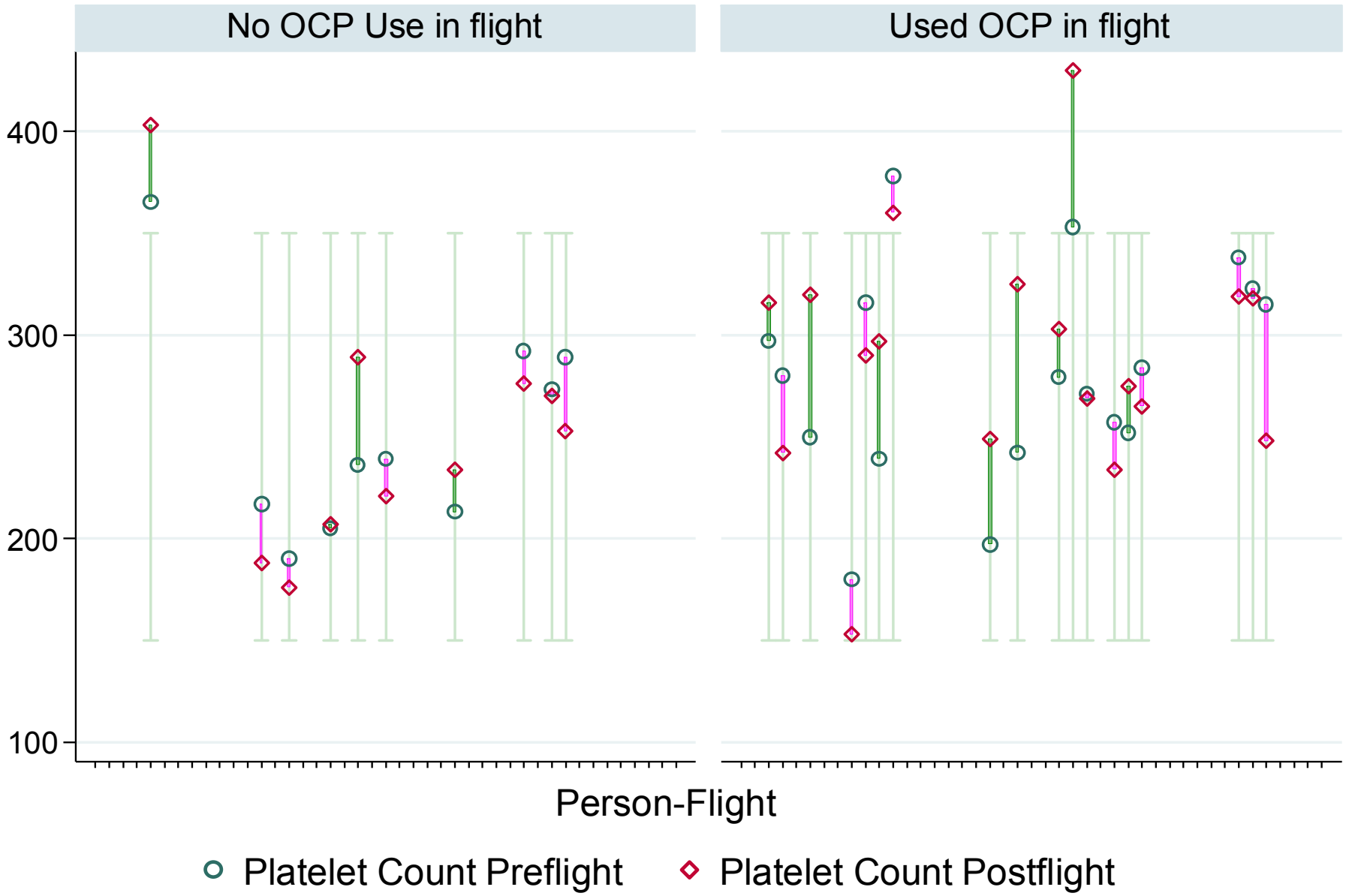
- Last pre-flight value and first post-flight value used to calculate:

1. Comparing post-flight data of dependent variables to normative high risk data from the literature.
2. Characterizing descriptively the changes between pre vs post-flight data of each dependent variable and determining if significant changes by using repeated measures t-test.

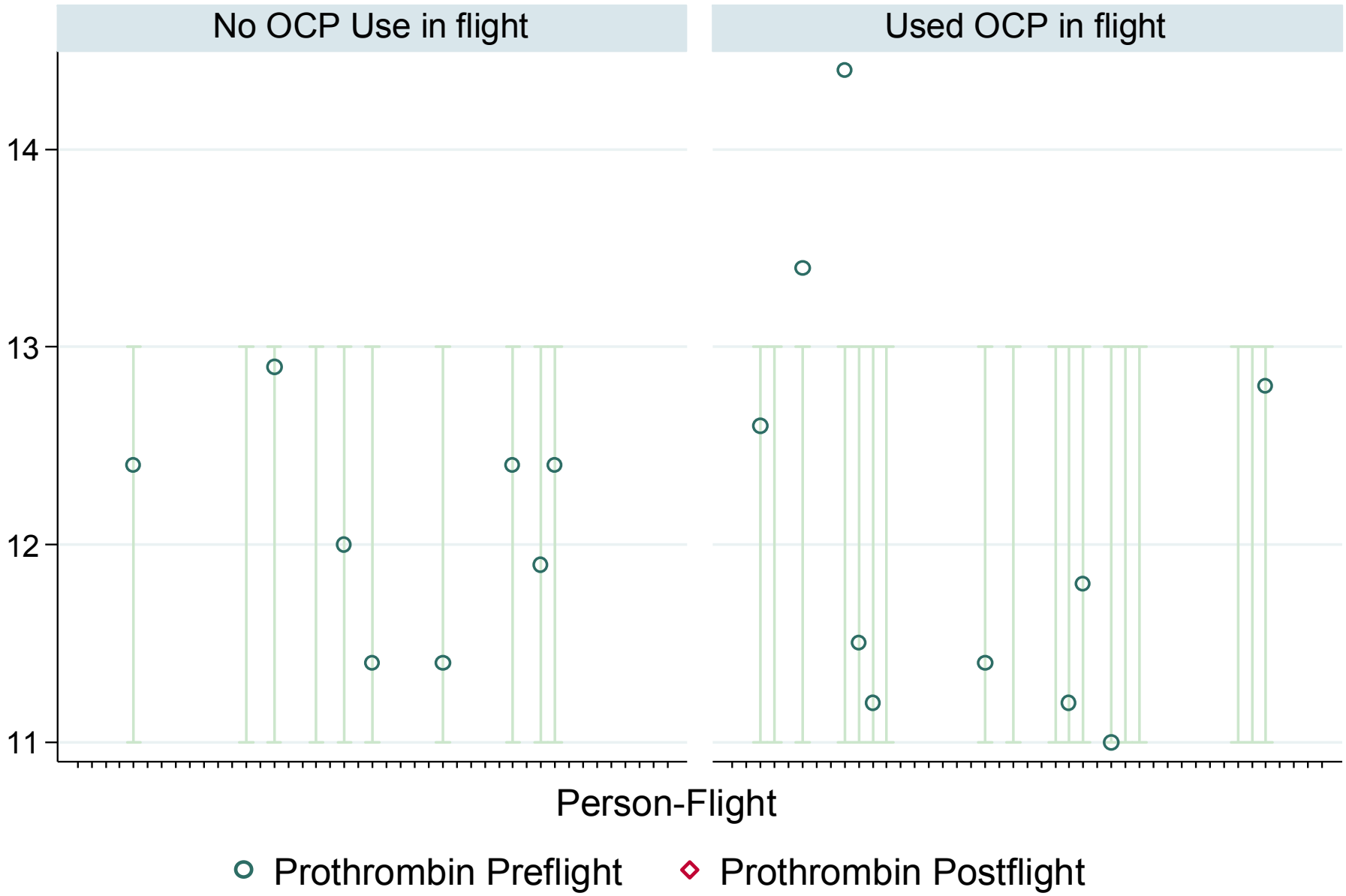
HYPOTHESIS: Predict spaceflight <u>does not</u> increase risk of VTE compared to terrestrial population

Results

First pass analysis of data suggests no obvious trend towards abnormality or increased risk of VTE, thus supporting hypothesis.



Green bars indicate increases post-flight relative to pre
Purple bars indicate decreases post-flight relative to pre



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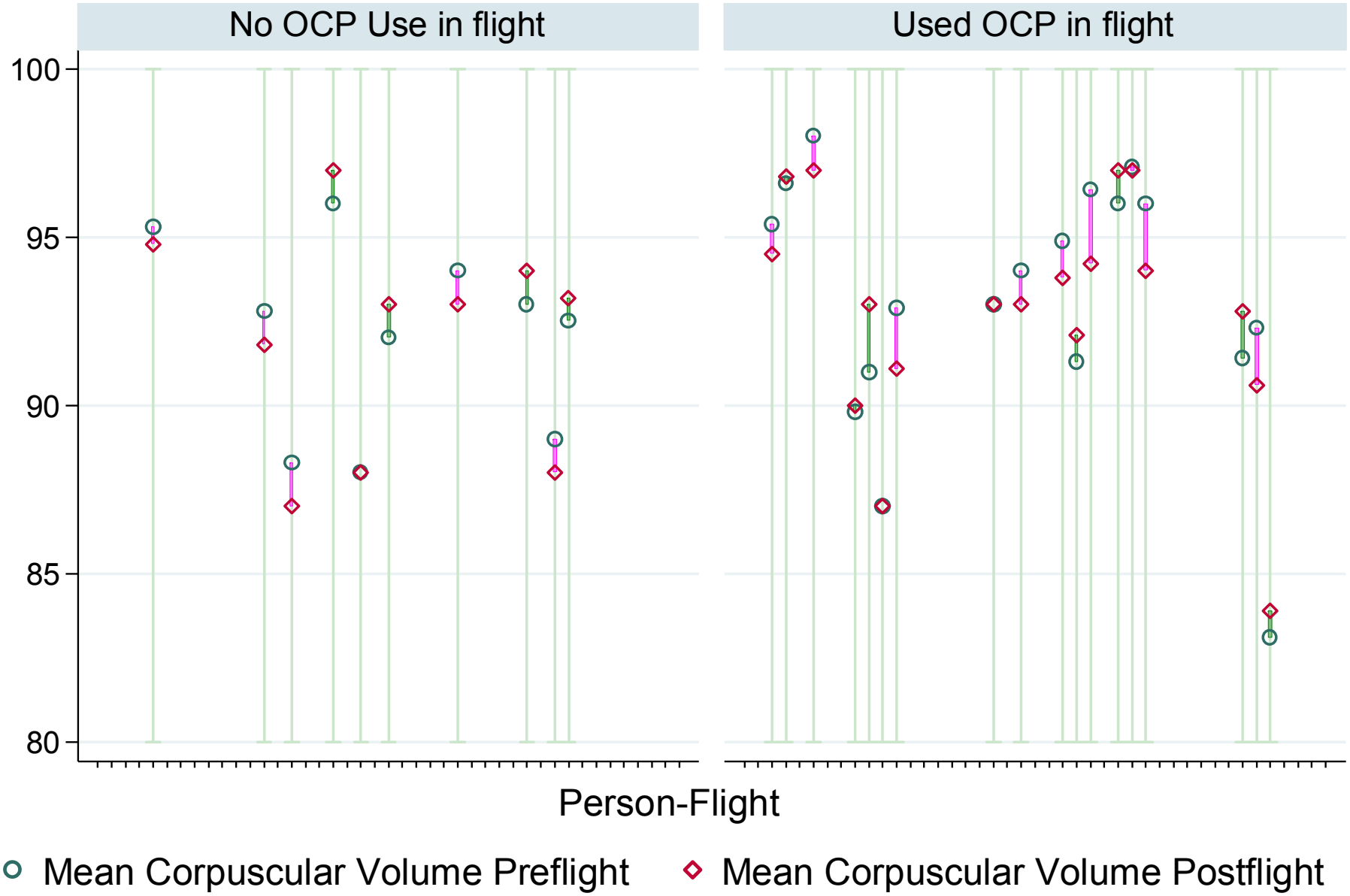

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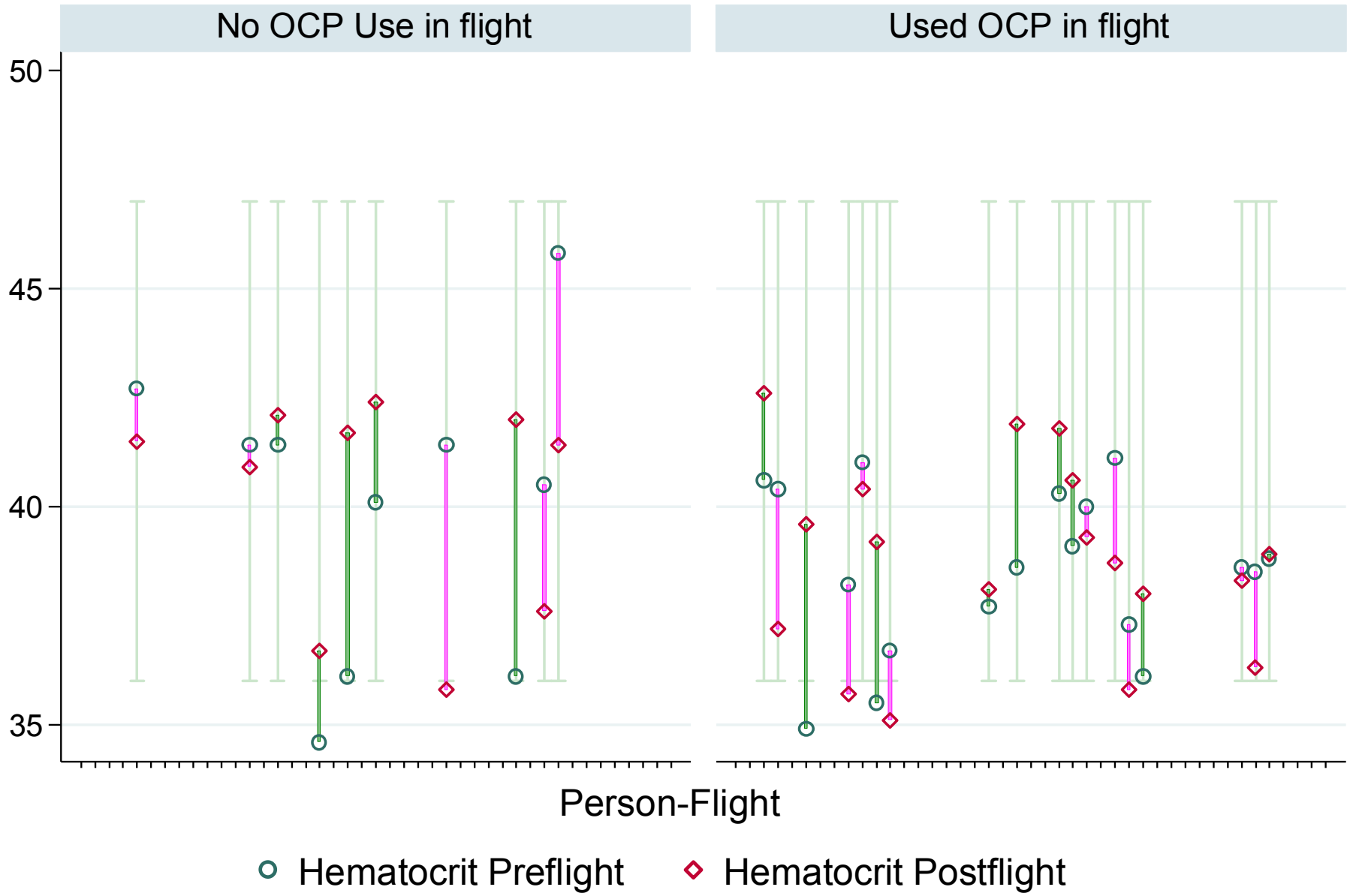

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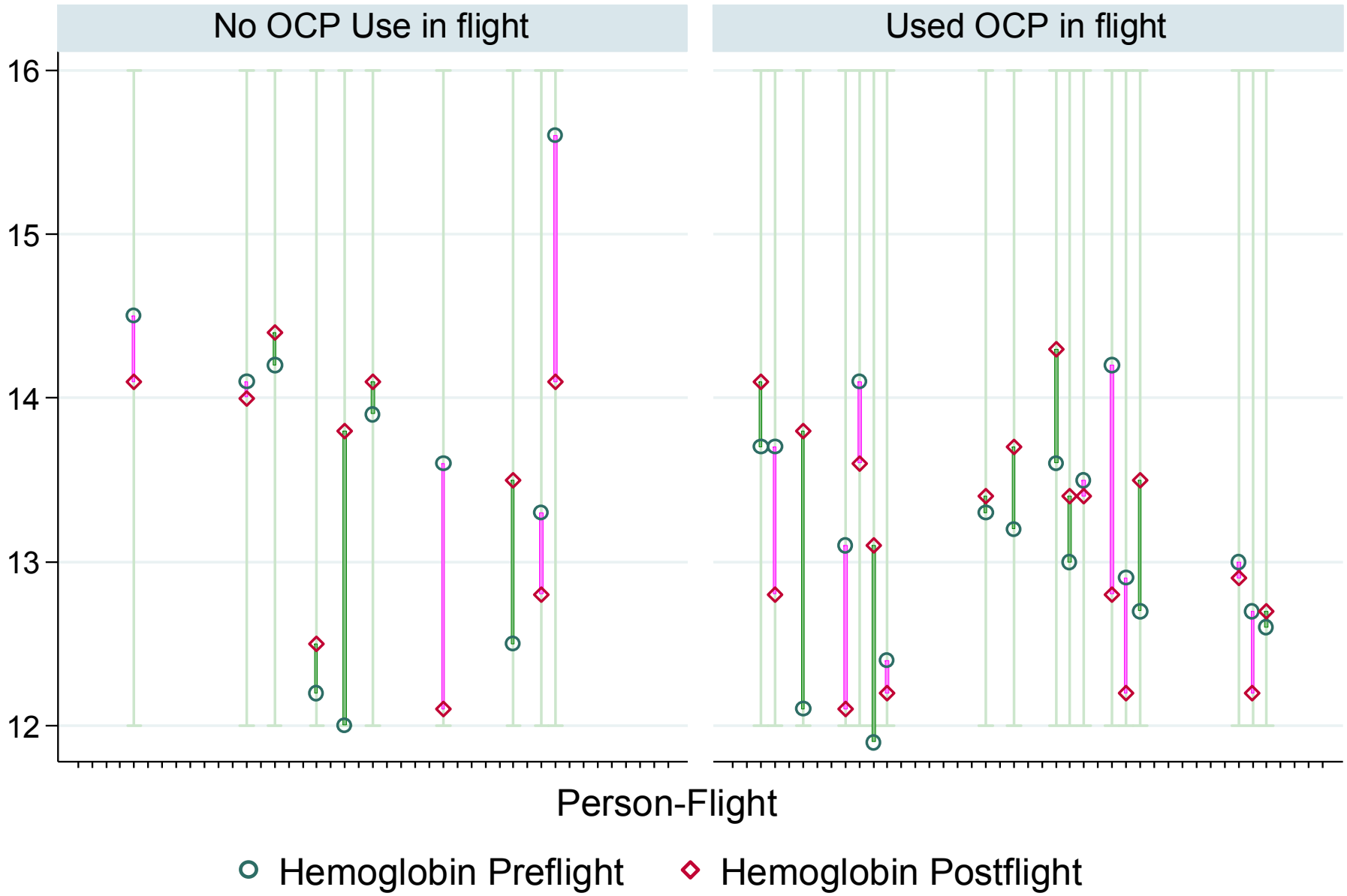

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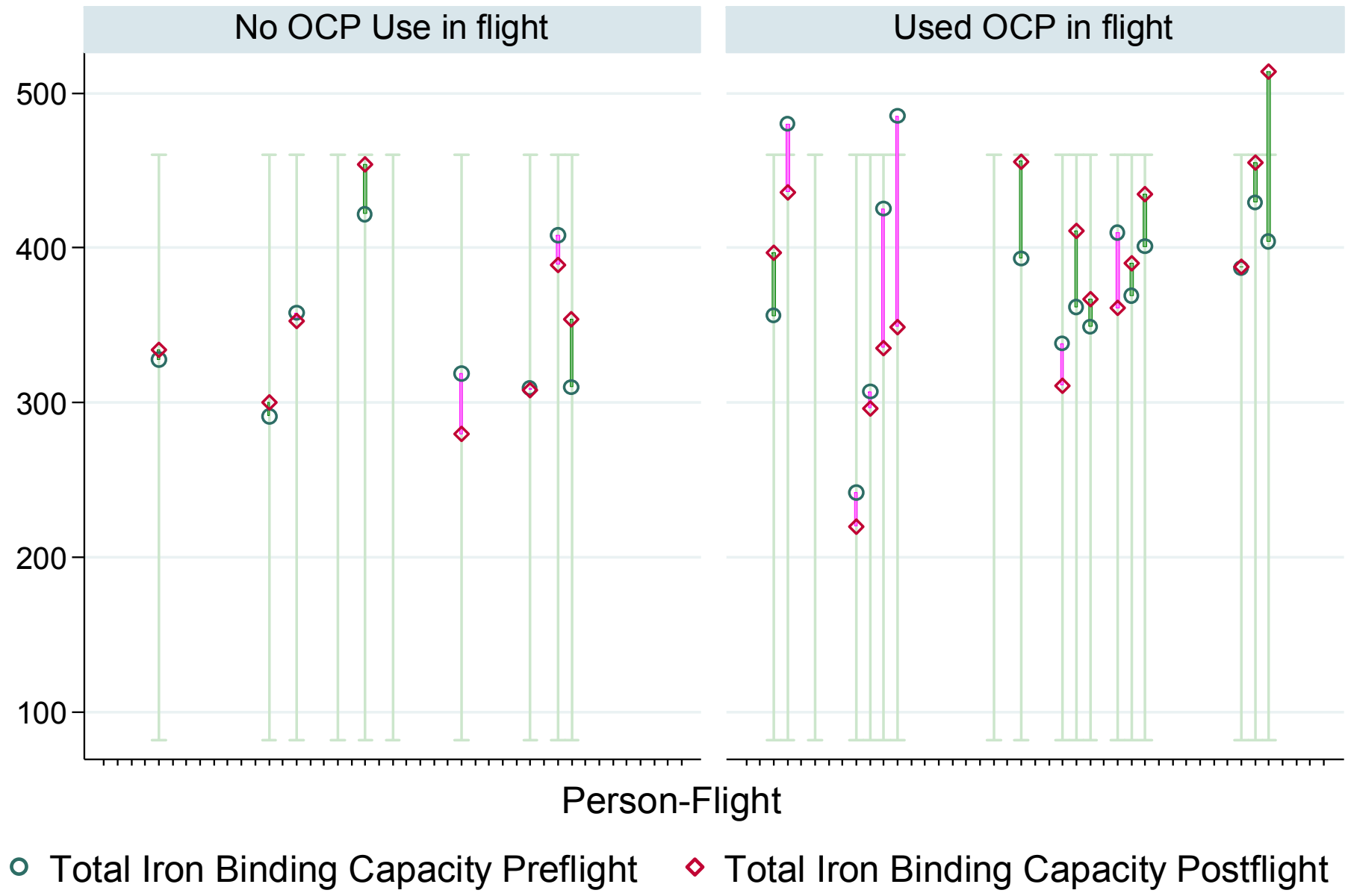

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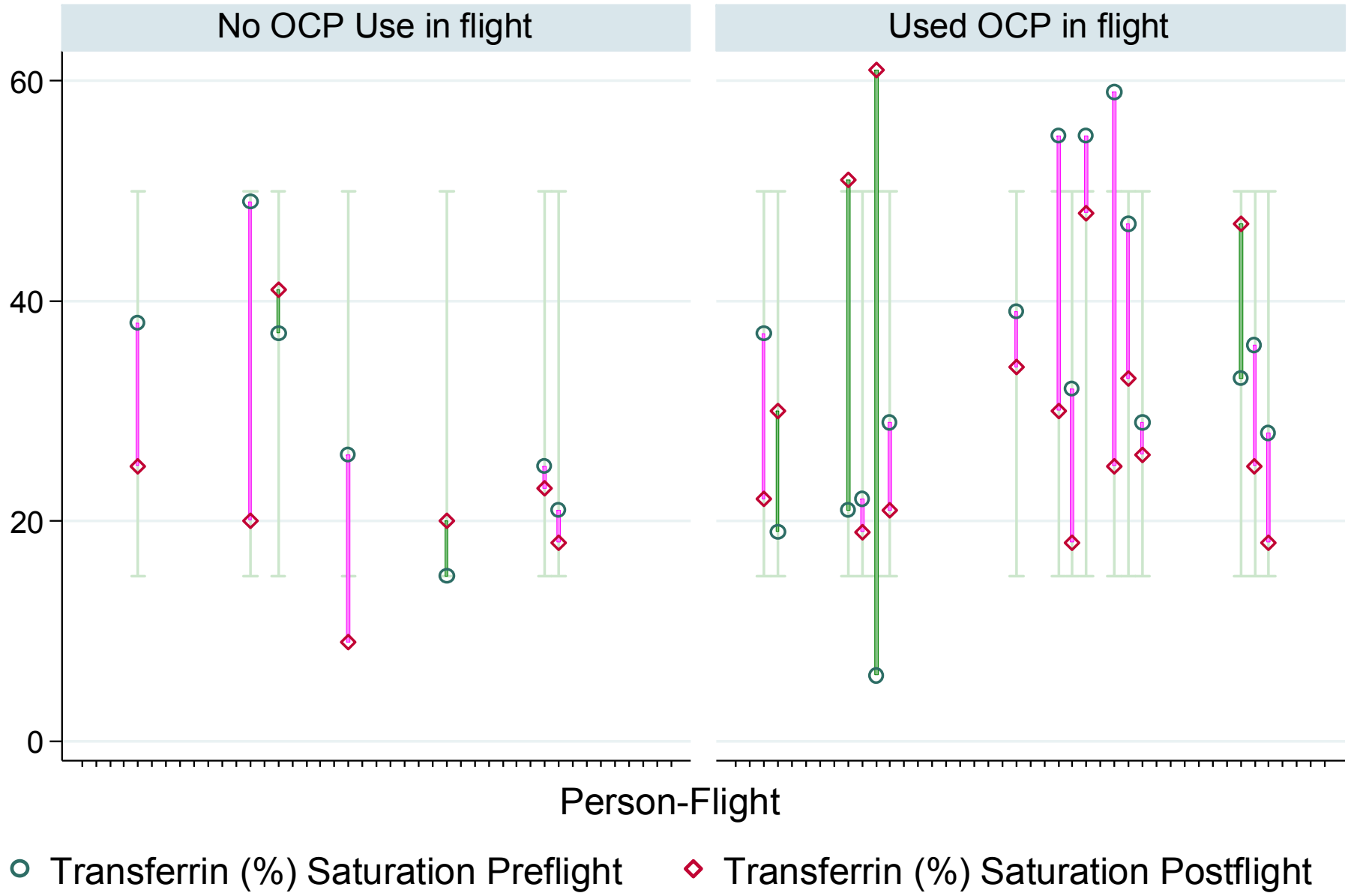

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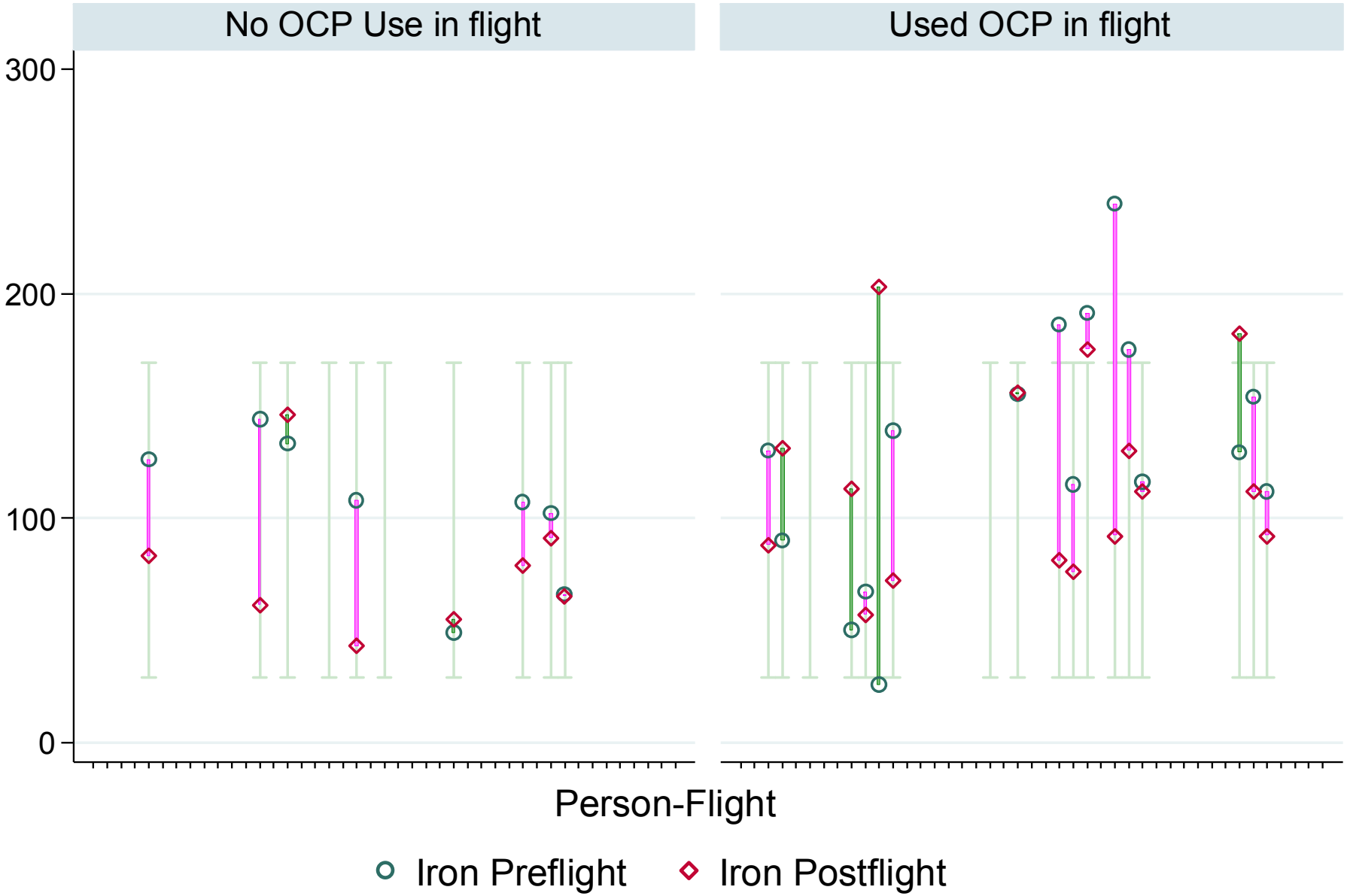

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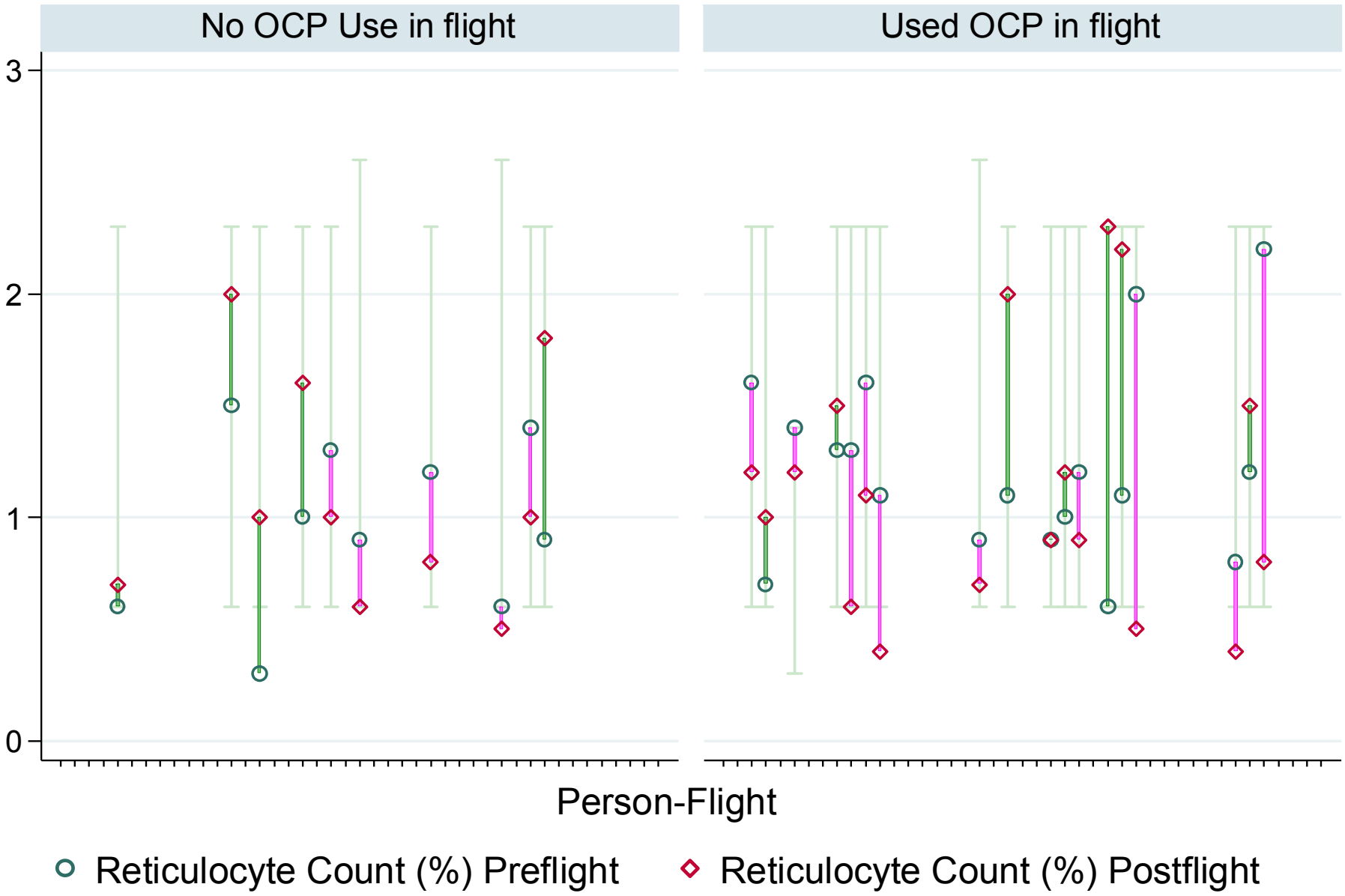

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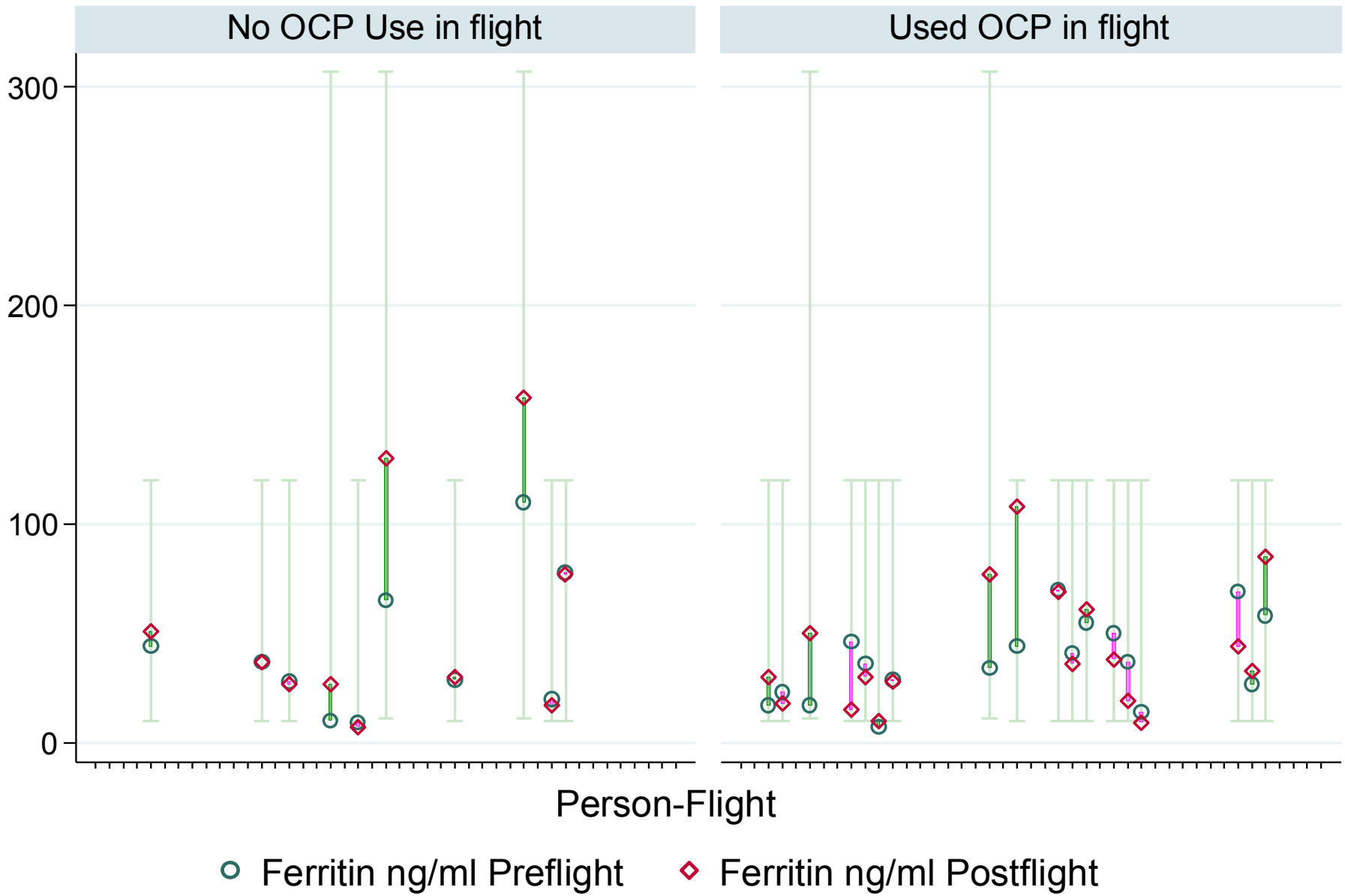

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Discussion

- Current menstrual suppression regimes could be adapted to LARC use +/- estrogen add-back
- Additional risk factors for astronaut population could include:
  - Lack of lower limb activity
  - Levels of dehydration and red cell lysis
  - Stress as an immunosuppressant
  - Radiation impacts
- Exercise mitigation strategies
- Compression stockings post-flight
- Longer duration missions and their impact

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COC Side Effects

Serious adverse reactions are arterial and venous thromboembolism.In addition, the following undesirable effects have been reported in users of COCs such as Microgynon 30, although the causal relationships have not been confirmed:

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Eye Disorders			Contact lens intolerance
Gastrointestinal Disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Immune System Disorders			Hypersensitivity
Investigations	Weight increased		Weight decreased
Metabolism and Nutrition Disorders		Fluid retention	
Nervous System Disorders	Headache	Migraine	
Psychiatric Disorders	Depressed mood, altered mood	Decreased libido	Increased libido
Reproductive System and Breast Disorders	Breast pain, breast tenderness	Breast hypertrophy	Vaginal discharge, breast discharge
Skin and Subcutaneous Tissue Disorders		Rash, urticaria	Erythema nodosum, erythema multiforme
Vascular disorders			Venous and arterial thromboembolic events **

** - Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives.

- 'Venous and arterial thromboembolic events' summarizes the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as hemorrhagic

Very Common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)

Mirena Side Effects

Table 1: Adverse reactions reported in clinical trials with MIRENA

System Organ Class	Very Common	Common	Uncommon	Rare
Psychiatric Disorders		Depressed mood Depression Nervousness Decreased libido	Altered mood	
Nervous System Disorders	Headache	Migraine		
Gastrointestinal Disorders	Abdominal /pelvic pain	Nausea	Abdominal distension	
Skin and Subcutaneous Tissue Disorders		Acne Hirsutism	Alopecia Pruritis Eczema	Rash Urticaria
Musculoskeletal, Connective Tissue and Bone Disorders		Back pain**		
Reproductive System and Breast Disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea Vulvovaginitis* Genital discharge*	Upper genital tract infection Ovarian cyst Dysmenorrhoea Breast tenderness Breast pain** Intra-uterine contraceptive device expulsion (complete and partial)	Cervicitis/ Papanicolaou smear normal, class II	Uterine perforation
General Disorders and Administration Site Conditions			Oedema	
Investigations		Weight increased		

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

* Endometrial prevention trials: "common"
** Endometrial prevention trials: "very common"

Very Common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)

Hormonal Implant Side Effects

System Organ Class	Adverse reaction in MedDRA Term1 Very Common > 1/10	Common < 1/10, ≥ 1/100	Uncommon <1/100, ≥ 1/1000
Infections and infestations	vaginal infection		pharyngitis, rhinitis, urinary tract infection
Immune system disorders			hypersensitivity
Metabolism and nutritional disorders		decreased appetite	
Psychiatric disorders		affect lability, depressed mood, nervousness, libido decreased	anxiety, insomnia
Nervous system disorders	headache	dizziness	migraine, somnolence
Vascular disorders		hot flush	
Gastrointestinal disorders		abdominal pain, nausea, flatulence	vomiting, constipation, diarrhoea
Skin and subcutaneous tissue disorders	acne	alopecia	hypertrichosis, rash, pruritus
Musculoskeletal and connective tissue disorders			back pain, arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders			dysuria
Reproductive system and breast disorders	~~breast tenderness~~, breast pain, menstruation irregular	dysmenorrhoea, ovarian cyst	genital discharge, vulvovaginal discomfort, galactorrhoea, hypertrophy breast, pruritus genital
General disorders and administration site condition		implant site pain, implant site reaction, fatigue influenza like illness, pain	pyrexia, oedema
Investigations	Weight increased	Weight decreased	

[1]The most appropriate MedDRA term (version 8.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

Very Common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)